Health-Related Quality of Life of Mothers and Children

Guannan Bai

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Health-Related Quality of Life of Mothers and Children

Gezondheidsgerelateerde Kwaliteit van Leven van Moeders en Kinderen

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To the Lord of Love and Life

To my aunt, Dr. Jiefen Yao, who defended her PhD thesis
on 22 September 1999, in Erasmus University Rotterdam

For the incredible bond between my family and Erasmus MC

MANUSCRIPTS THAT FORM THE BASIS OF THIS THESIS

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Xinye Fang, **Guannan Bai**, Dafna A Windhorst, David Feeny, Saroj Saigal, Liesbeth Duijts, Vincent WV Jaddoe, Shanlian Hu, Chunlin Jin, Hein Raat. Feasibility and validity of the Health Status Classification System-Preschool (HSCS-PS) in a large community sample: The Generation R Study. *Accepted by BMJ Open, Oct 2018*

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CHAPTER 1

General Introduction

This first chapter gives a brief overview on the concept of health-related quality of life (HRQOL), and of the literature regarding determinants of maternal HRQOL and children's HRQOL. Knowledge gaps are identified. The research questions and an outline of this thesis are presented at the end of the chapter.

The concept of health-related quality of life

Health-related quality of life (HRQOL) is a term referring to the health aspects of quality of life. HRQOL is considered as a measure of the value assigned to the duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy.(1) Thus, it is subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation.(2) The measurement of HRQOL can be added to traditional health outcome measures such as morbidity and mortality.(3) As Osoba and King argued, "the ultimate goal of health care is to restore or preserve functioning and well-being related to health, that is health-related quality of life".(4)

A conceptual model for health-related quality of life

There are many HRQOL models that have been applied cross various health and illness conditions, across the lifespan, and among diverse populations. The most frequently used HRQOL models are: Wilson and Cleary model, the revised Wilson and Cleary model by Ferrans and colleagues, and the World Health Organization model. (5) In 1995, Wilson and Cleary developed a conceptual model for health-related quality of life. (6) Wilson and Cleary have divided health outcomes into five levels: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. They also proposed specific relationships between these outcomes that link traditional clinical variables to measures of HRQOL. This model considers the interaction between individual characteristics and environmental characteristics. (6) Wilson and Cleary model contributes to the taxonomy of the variables used to measure HRQOL. In 2005, Ferrans et al. have revised and simplified this model (see Figure 1) in three ways: (a) adding the arrows to show that biological function is influenced by characteristics of both individuals and environments; (b) deleting nonmedical factors; and (c) deleting the factors on the arrows that show the relationship between individual or environmental characteristics and five levels of health outcomes.(7) The revised Cleary and Wilson model helps to clarify the critical elements of HRQOL and the casual relationship among them,(7) and appeared to have the greatest potential to guide future HRQOL research and practice. (5) Therefore, we applied the revised model in the thesis to guide the study design and the interpretation of our findings.

Measurements of health-related quality of life

Three types of measures are available to assess HRQOL: generic, disease-specific, and domain-specific. We applied generic measures in this thesis to assess HRQOL of mothers and children. Generic measures are designed to assess all areas of functioning deemed to

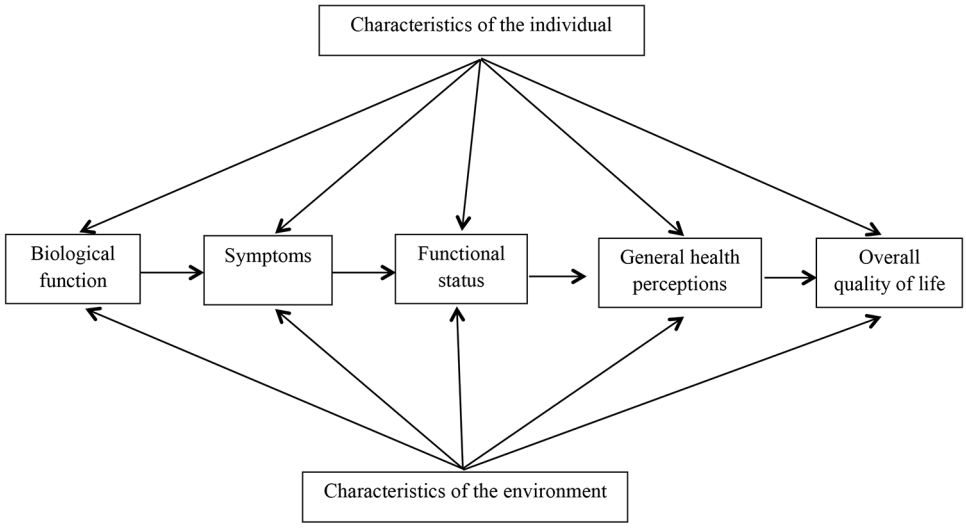

Figure 1. Revised Wilson and Cleary Model for health-related quality of life.
Reprint from "Conceptual Model of Health-Related Quality of Life" by Ferrans et al.. Copyright by Journal of Nursing Scholarship. Used with permission.

be directly affected by health conditions or treatments.(8) They are applicable to a wide range of population and allow comparison of HRQOL results across these populations. Generic HRQOL measures can be either health profiles or preference-based measures. (9) Health profiles originate from a psychometric tradition, and are designed to capture descriptive ratings across a wide range of areas of functioning likely to be affected by health conditions or treatments. Health profiles usually contains several items per scale. The individual items are not weighted. Preference-based measures originate from an economic tradition and have been increasingly used in health economic evaluations to calculate quality-adjusted life years (QALYs). Preference-based measure is a questionnaire with a scoring algorithm to weight the responses according to preferences for certain health conditions over others. These preference weights are based on surveying the general public's preferences for different combinations of health states. The index scores (sometimes called 'utilities') are calculated based on the selected scoring algorithms. The index scores or utilities usually range between 0 and 1, where 1 is usually taken to reflect a valuation of "perfect health" and 0 refers to valuation of "death". In some of these measures values below zero may be possible, representing health states perceived to be worse than death.(10)

In this thesis, we have applied several generic instruments to measure maternal and children's HRQOL. More specifically, we applied the 12-items Short Form Survey (SF-12) to assess maternal HRQOL in early, mid- and late pregnancy, and at two months

postpartum. SF-12 is a self-reported, health profile measure. To assess children's HRQOL we applied the Health Status Classification System-Preschool (HSCS-PS), a parent-reported, preference-based measure for preschoolers (aged three years in our study) and we applied the 28-items parent-reported Child Health Questionnaire (CHF-PF28), a health profile measure for school-aged (4-11 years) children.

Maternal health-related quality of life during pregnancy and postpartum

It is estimated that more than 200 million women get pregnant every year worldwide,(11) and 255 women give birth to a child every minute.(12) Maternal HRQOL is an essential issue during this transition period, and many factors may be associated with HRQOL. For instance, more than 70% of all the pregnant women report nausea, vomiting and fatigue in early pregnancy.(13-15) These symptoms may adversely influence women's day-to-day activities and HRQOL.(16-22) With pregnancy progressing, women's HRQOL may change. Physical functioning, for instance, tends to decrease during pregnancy.(23) However, this observation is based on a small body of studies. Mental health, on the other hand, was observed to be worst in early pregnancy.(24) Little was known with regard to the pattern of longitudinal development or trajectories of HRQOL during pregnancy.

After childbirth, mother's HRQOL is associated not only with the factors that were prevalent before delivery,(25-29) but also with factors that may occur during and after childbirth, such as fatigue, urinary incontinence, cesarean delivery and postpartum depression.(30-37)

Most of the above-mentioned studies on maternal HRQOL have a relatively small sample size, ranging from 19 to 2,161.(15-24, 26-28, 30-32, 34-37) Some studies were conducted within a sample of women with certain health conditions, such as depression and preeclampsia.(32, 34) By using data from a large prospective population-based mother- and child cohort (The Generation R Study), we aimed to investigate: a) the independent associations between nausea, vomiting, fatigue and HRQOL in early pregnancy; b) trajectories of HRQOL during pregnancy and their early predictors; and c) multiple determinants of postpartum HRQOL.

Maternal health-related quality of life during pregnancy and birth outcome

Preterm birth, small-for-gestational-age birth and low birth weight are primary indicators for newborn mortality and morbidity.(38-40) The above-mentioned birth outcomes are associated with maternal health, for example, maternal lifestyle-related factors (e.g. tobacco/alcohol use, body mass index) and medical conditions before or during pregnancy (e.g. preeclampsia, diabetes, depression).(41, 42) Given that HRQOL can be a marker or an indicator of women's overall health during pregnancy, we hypothesized

that maternal HRQOL during pregnancy may be associated with birth outcomes. To our best knowledge, there have been two relevant studies on this issue. One study in Austria shows that women who gave preterm birth reported worse physical HRQOL in late pregnancy than women who gave term birth.(43) The other study in Hong Kong, China, among 90 women shows that better physical and social health in late pregnancy were associated with a lower risk of preterm birth, and that better mental health of the mothers in late pregnancy was associated with a lower risk of low birth weight of their infants.(44) Given the low number of studies on this issue and the relatively small sample sizes in those studies, we aimed to enhance the understanding of the associations between maternal HRQOL during pregnancy and birth outcomes by using data from a large population-based mother- and child cohort study.

Children's health-related quality of life

Many factors may hamper good health in childhood; examples are low socioeconomic status, limited access to health care, and the presence of medical conditions.(45-51) In particular, chronic conditions in childhood may be an important factor for worse HRQOL of children.(51-60) In the Netherlands, the measure of HRQOL among school-aged children has been included in the annual health survey (Dutch Health Interview Survey, DHIS). The large, randomly selected sample is nationally representative, which provides us the opportunity to generate an overall understanding of potential determinants of children's HRQOL, and to investigate the pattern of impacts of the prevalent chronic conditions in childhood on children's HRQOL.

Measuring health-related quality of life in early childhood

Few comprehensive measures are available for assessing the overall health or HRQOL of preschool children.(61) As Grange and colleagues suggested, "there is a need to develop empirically robust and conceptually comprehensive health-related quality of life measures, particularly in the context of proxy-completion measures for very young children."(62) Saigal et al. have revised the existing system (Health Utilities Index, Marker 2 and 3)(63) for application to a preschool population, thus, a preference-based measure of HRQOL for preschoolers (Health Status Classification System-Preschool) has been developed.(61, 64) The reliability and validity of HSCS-PS has been evaluated in clinical populations, such as premature infants(61, 65, 66), children with cerebral palsy,(67) neonatal intensive care unit (NICU) survivors,(68) and preschool-aged patients with Wilms' tumor or advanced neuroblastoma(69, 70). The above-mentioned studies demonstrated that HSCS-PS is readily accepted, quick to complete, and can be used in various populations of preschool children in a consistent manner across different settings. To our best knowledge, there was no validation study of HSCS-PS in a community-dwelling setting. Therefore, we aimed to assess the feasibility and validity of HSCS-PS in a large general population sample of preschool children (aged three years).

Research questions

The overall aim of this thesis was to enhance the understanding of HRQOL of mothers and children. In four subsequent parts, the following study questions are addressed:

Part I: Assessing determinants of mother's health-related quality of life

1. To what extent are nausea, vomiting and fatigue in early pregnancy independently associated with maternal HRQOL? (Chapter 2)
2. What are trajectories of HRQOL during pregnancy and what are predictors of these trajectories? (Chapter 3)
3. What are the determinants of maternal HRQOL after childbirth? (Chapter 4)

Part II: Assessing the association between maternal health-related quality of life during pregnancy and birth outcomes

4. To what extent is maternal HRQOL during pregnancy associated with birth outcomes? (Chapter 5)

Part III: Assessing determinants of childhood health-related quality of life

5 What are the determinants of HRQOL among school-aged children in the Netherlands? (Chapter 6)
6. To what extent do prevalent chronic conditions in childhood impact HRQOL of school-aged children in the Netherlands? (Chapter 7)

Part IV: Measuring health-related quality of life in early childhood

7. What are the feasibility and validity of the Health Status Classification System-Preschool (HSCS-PS) in a large community-dwelling sample of preschool children? (Chapter 8)

We present the overview of all studies in this thesis in Table 1.

Data sources

Research questions 1 to 4 and research question 7 have been investigated within the Generation R Study, a prospective population-based mother- and child cohort study from fetal life until adulthood. The Generation R study is designed to detect early environmental and genetic determinants of normal and abnormal growth, development, and health.(71) Pregnant women with an expected delivery data between April 2002 and January 2006 in the Rotterdam area, the Netherlands, were invited to participate in the study. When Generation R was set up, the aim was to enroll women in early pregnancy (gestational age < 18 weeks). However, enrolment was possible until childbirth. 7069 mothers were enrolled in early pregnancy, 1594 mothers in mid-pregnancy (gestational age 18-25 weeks), 216 mothers in late pregnancy (gestational age ≥25 weeks) and 899 mothers after childbirth.(72)

Table 1. Overview of the studies included into this thesis

Chapter	Study design	Number	Main determinants	Main outcomes
2	Cross-sectional	5079	Nausea, vomiting and fatigue	HRQOL in early pregnancy
3	Longitudinal	3936	Multiple determinants	HRQOL during pregnancy
4	Cross-sectional	4259	Multiple determinants	Maternal HRQOL two month after childbirth
5	Longitudinal	6334; 6204; 6048	Maternal HRQOL in early, mid- and late pregnancy	Gestational age at birth and preterm birth; (low)birth weight; small size for gestational age
6	Cross-sectional	10651	Multiple exposure	HRQOL of children aged 4-11 years old
7	Cross-sectional	5301	Chronic conditions	HRQOL of children aged 4-11 years old
8	Cross-sectional	4546	n/a	n/a

Assessments included self-reported questionnaires, physical examinations, registration of pregnancy complications and outcomes, biological samples, and ultrasound examinations.(71, 72) With regard to research questions 1 to 4, we used data of maternal HRQOL measured in early, mid- and late pregnancy and data of maternal HRQOL measured two months after childbirth. With regard to research question 7, we used data of HRQOL of preschool children measured around 36 months after birth. Research questions 5 and 6 have been investigated in the Dutch Health Interview Survey (DHIS), conducted by Statistics Netherlands.(73) DHIS is a cross-sectional survey to measure health in the Dutch population living in non-institutionalized households. Each month, a stratified two-step-sample of persons is taken from the Dutch Municipal Personal Records. In this thesis, we included the survey data among school-aged (four-to-eleven-years-old) children. Regarding research question 5, we analyzed the survey data collected from January 2001 to December 2009. Regarding research question 6, we analyzed the survey data from January 2010 to December 2013.

REFERENCES

1. Kaplan RM. Quality of Life Measures: Measurement Strategies in Health Psychology. New York: John Wiley; 1985.
2. Schipper H, Clinch, JJ, Olweny CLM (1996) Quality of life studies: definitions and conceptual issues, In Spilker B (ed) Quality of Life and Pharmacoeconomics in Clinical Trials. Lippincott-Raven Publishers:Philadelphia. PP 11-23.
3. Centers for Disease C, Prevention. Health-related quality-of-life measures--United States, 1993. MMWR Morb Mortal Wkly Rep. 1995;44(11):195-200.
4. Osoba D, King M. Meaningful differences. Assessing quality of life in clinical trials. 2005;2:243-57.
5. Bakas T, McLennon SM, Carpenter JS, Buelow JM, Otte JL, Hanna KM, et al. Systematic review of health-related quality of life models. Health and Quality of Life Outcomes. 2012;10(1):134.
6. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Jama. 1995;273(1):59-65.
7. Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL. Conceptual model of health-related quality of life. J Nurs Scholarsh. 2005;37(4):336-42.
8. Spieth, L.E. (2002).Generic health-related quality of life measures for children and adolescents. In Quality of life in children and adolescent illness: concepts, methods, and findings. pp49. London: Routledge.
9. Mpundu-Kaambwa C, Chen G, Huynh E, Russo R, Ratcliffe J. A review of preference-based measures for the assessment of quality of life in children and adolescents with cerebral palsy. Qual Life Res. 2018;27(7):1781-99.
10. Preference-Based Measures [online]. (2016). York; York Health Economics Consortium; 2016. Retrived 15 August, 2018, from http://www.yhec.co.uk/glossary/preference-based-measures/
11. Sedgh G, Singh S, Hussain R. Intended and Unintended Pregnancies Worldwide in 2012 and Recent Trends. Studies in family planning. 2014;45(3):301-14.
12. Central Intelligence Agency. (2013 est). The World Factbook in birth rate. Retrieved 15 August, 2018, from https://www.cia.gov/library/publications/the-world-factbook/rankorder/2054rank.html.
13. Lee NM, Saha S. Nausea and Vomiting of Pregnancy. Gastroenterology clinics of North America. 2011;40(2):309-vii.
14. Bustos M, Venkataramanan R, Caritis S. Nausea and vomiting of pregnancy - What's new? Auton Neurosci. 2017;202:62-72.
15. Nazik E, Eryilmaz G. Incidence of pregnancy-related discomforts and management approaches to relieve them among pregnant women. Journal of Clinical Nursing. 2014;23(11-12):1736-50.
16. Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. J Nurs Scholarsh. 2003;35(2):119-25.
17. Tan A, Lowe S, Henry A. Nausea and vomiting of pregnancy: Effects on quality of life and day-to-day function. Aust N Z J Obstet Gynaecol. 2017.
18. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? Bjog. 2008;115(12):1484-93.
19. Heitmann K, Nordeng H, Havnen GC, Solheimsnes A, Holst L. The burden of nausea and vomiting during pregnancy: severe impacts on quality of life, daily life functioning and willingness to become pregnant again - results from a cross-sectional study. BMC Pregnancy Childbirth. 2017;17(1):75.
20. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol. 2011;31(1):10-20.

21. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol. 2000;40(4):397-401.
22. Swallow BL, Lindow SW, Masson EA, Hay DM. Women with nausea and vomiting in pregnancy demonstrate worse health and are adversely affected by odours. J Obstet Gynaecol. 2005;25(6):544-9.
23. Haas JS, Jackson RA, Fuentes-Afflick E, Stewart AL, Dean ML, Brawarsky P, et al. Changes in the Health Status of Women During and After Pregnancy. Journal of General Internal Medicine. 2005;20(1):45-51.
24. Chang SR, Chen KH, Lin Ming- I, Lin HH, Huang LH, Lin WA. A repeated measures study of changes in health-related quality of life during pregnancy and the relationship with obstetric factors. Journal of Advanced Nursing. 2014;70(10):2245-56.
25. Cheng CY, Li Q. Integrative review of research on general health status and prevalence of common physical health conditions of women after childbirth. Womens Health Issues. 2008;18(4):267-80.
26. Hoffenaar PJ, van Balen F, Hermanns J. The Impact of Having a Baby on the Level and Content of Women's Well-Being. Soc Indic Res. 2010;97(2):279-95.
27. Yeo JH, Chun N. [Influence of childbirth experience and postpartum depression on quality of life in women after birth]. J Korean Acad Nurs. 2013;43(1):11-9.
28. Zubaran C, Foresti K. Investigating quality of life and depressive symptoms in the postpartum period. Women Birth. 2011;24(1):10-6.
29. Symon A. A review of mothers' prenatal and postnatal quality of life. Health and Quality of Life Outcomes. 2003;1:38-.
30. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Steegers EA, et al. Poor health-related quality of life after severe preeclampsia. Birth. 2011;38(3):246-55.
31. Mortazavi F, Mousavi SA, Chaman R, Khosravi A. Maternal quality of life during the transition to motherhood. Iran Red Crescent Med J. 2014;16(5):e8443.
32. Prick BW, Bijlenga D, Jansen AJ, Boers KE, Scherjon SA, Koopmans CM, et al. Determinants of health-related quality of life in the postpartum period after obstetric complications. Eur J Obstet Gynecol Reprod Biol. 2015;185:88-95.
33. Van der Woude DA, Pijnenborg JM, de Vries J. Health status and quality of life in postpartum women: a systematic review of associated factors. Eur J Obstet Gynecol Reprod Biol. 2015;185:45-52.
34. Webster J, Nicholas C, Velacott C, Cridland N, Fawcett L. Quality of life and depression following childbirth: impact of social support. Midwifery. 2011;27(5):745-9.
35. Symon A, MacKay A, Ruta D. Postnatal quality of life: a pilot study using the Mother-Generated Index. Journal of Advanced Nursing. 2003;42(1):21-9.
36. Petrou S, Kim Sung W, McParland P, Boyle Elaine M. Mode of Delivery and Long-Term Health-Related Quality-of-Life Outcomes: A Prospective Population-Based Study. Birth. 2017;44(2):110-9.
37. Rezaei N, Azadi A, Zargousi R, Sadoughi Z, Tavalaee Z, Rezayati M. Maternal Health-Related Quality of Life and Its Predicting Factors in the Postpartum Period in Iran. Scientifica. 2016;2016:8542147.
38. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010;88(1):31-8.
39. Kristensen S, Salihu HM, Keith LG, Kirby RS, Fowler KB, Pass MA. SGA subtypes and mortality risk among singleton births. Early Hum Dev. 2007;83(2):99-105.
40. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1:S2.

41. Heaman M, Kingston D, Chalmers B, Sauve R, Lee L, Young D. Risk Factors for Preterm Birth and Small-for-gestational-age Births among Canadian Women. Paediatric and Perinatal Epidemiology. 2013;27(1):54-61.
42. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. Seminars in Fetal and Neonatal Medicine. 2016;21(2):68-73.
43. Mautner E, Greimel E, Trutnovsky G, Daghofer F, Egger JW, Lang U. Quality of life outcomes in pregnancy and postpartum complicated by hypertensive disorders, gestational diabetes, and preterm birth. J Psychosom Obstet Gynaecol. 2009;30(4):231-7.
44. Wang P, Liou SR, Cheng CY. Prediction of maternal quality of life on preterm birth and low birthweight: a longitudinal study. BMC Pregnancy Childbirth. 2013;13:124.
45. Mansour ME, Kotagal U, Rose B, Ho M, Brewer D, Roy-Chaudhury A, et al. Health-related quality of life in urban elementary schoolchildren. Pediatrics. 2003;111(6 Pt 1):1372-81.
46. Michel G, Bisegger C, Fuhr DC, Abel T, group K. Age and gender differences in health-related quality of life of children and adolescents in Europe: a multilevel analysis. Qual Life Res. 2009;18(9):1147-57.
47. Ravens-Sieberer U, Gosch A, Rajmil L, Erhart M, Bruil J, Power M, et al. The KIDSCREEN-52 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Value Health. 2008;11(4):645-58.
48. Simon AE, Chan KS, Forrest CB. Assessment of children's health-related quality of life in the United States with a multidimensional index. Pediatrics. 2008;121(1):e118-26.
49. von Rueden U, Gosch A, Rajmil L, Bisegger C, Ravens-Sieberer U. Socioeconomic determinants of health related quality of life in childhood and adolescence: results from a European study. J Epidemiol Community Health. 2006;60(2):130-5.
50. Wu XY, Ohinmaa A, Veugelers PJ. Sociodemographic and neighbourhood determinants of health-related quality of life among grade-five students in Canada. Qual Life Res. 2010;19(7):969-76.
51. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev. 2008;34(4):418-29.
52. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006;155(1):145-51.
53. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res. 1996;5(1):35-46.
54. Merikallio VJ, Mustalahti K, Remes ST, Valovirta EJ, Kaila M. Comparison of quality of life between asthmatic and healthy school children. Pediatr Allergy Immunol. 2005;16(4):332-40.
55. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract. 2006;60(8):984-92.
56. Klassen AF, Miller A, Fine S. Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder. Pediatrics. 2004;114(5):e541-7.
57. Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. Eur Respir J. 2013;41(4):952-9.
58. Lee SL, Cheung YF, Wong HSW, Leung TH, Lam TH, Lau YL. Chronic health problems and health-related quality of life in Chinese children and adolescents: a population-based study in Hong Kong. BMJ Open. 2013;3(1).
59. Sawyer MG, Whaites L, Rey JM, Hazell PL, Graetz BW, Baghurst P. Health-related quality of life of children and adolescents with mental disorders. J Am Acad Child Adolesc Psychiatry. 2002;41(5):530-7.
60. Sawyer MG, Reynolds KE, Couper JJ, French DJ, Kennedy D, Martin J, et al. Health-related quality of life of children and adolescents with chronic illness--a two year prospective study. Qual Life Res. 2004;13(7):1309-19.

61. Saigal S, Rosenbaum P, Stoskopf B, Hoult L, Furlong W, Feeny D, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Qual Life Res. 2005;14(1):243-57.
62. Grange A, Bekker H, Noyes J, Langley P. Adequacy of health-related quality of life measures in children under 5 years old: Systematic review. Journal of advanced nursing. 2007;59(3):197-220.
63. Feeny DH, Torrance GW. Incorporating utility-based quality-of-life assessment measures in clinical trials: two examples. Medical Care. 1989:S190-S204.
64. Saigal S, Stoskopf BL, Rosenbaum PL, Hoult LA, Furlong WJ, Feeny DH. Development Of A Multiattribute Pre-school Health Status Classification System † 1333. Pediatric Research. 1998;43:228.
65. Schiariti V, Klassen AF, Houbé JS, Synnes A, Lisonkova S, Lee SK. Perinatal characteristics and parents' perspective of health status of NICU graduates born at term. Journal of Perinatology. 2008;28(5):368.
66. Msall ME. Neurodevelopmental surveillance in the first 2 years after extremely preterm birth: evidence, challenges, and guidelines. Early Hum Dev. 2006;82(3):157-66.
67. Msall ME. Measuring functional skills in preschool children at risk for neurodevelopmental disabilities. Mental retardation and developmental disabilities research reviews. 2005;11(3):263-73.
68. Klassen AF, Lee SK, Raina P, Chan HW, Matthew D, Brabyn D. Health status and health-related quality of life in a population-based sample of neonatal intensive care unit graduates. Pediatrics. 2004;113(3 Pt 1):594-600.
69. Nathan PC, Furlong W, De Pauw S, Horsman J, Van Schaik C, Rolland M, et al. Health status of young children during therapy for advanced neuroblastoma. Pediatr Blood Cancer. 2004;43(6):659-67.
70. Nathan PC, Furlong W, Horsman J, Van Schaik C, Rolland M, Weitzman S, et al. Inter-observer agreement of a comprehensive health status classification system for pre-school children among patients with Wilms' tumor or advanced neuroblastoma. Qual Life Res. 2004;13(10):1707-14.
71. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004;18(1):61-72.
72. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
73. Health Survey, from 2010-2013. What does the survey comprise? Statistics Netherlands (CBS). Retrieved 15 August, 2018, from https://www.cbs.nl/en-gb/our-services/methods/surveys/korte-onderzoeksbeschrijvingen/health-survey-from-2010-2013

PART I

Assessing Determinants of Mother's Health-Related Quality of Life

CHAPTER 2

Associations between Nausea, Vomiting, Fatigue and Health-Related Quality of Life of Women in Early Pregnancy: The Generation R Study

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ABSTRACT

The objective of this study was to evaluate the independent associations between nausea, vomiting, fatigue and health-related quality of life of women in early pregnancy in the Generation R study, which is a prospective mother and child cohort. Analyses were based on 5079 women in early pregnancy in the Rotterdam area, the Netherlands. The information on nausea, vomiting and fatigue in the previous three months was measured in the questionnaire at enrollment, as well as potential confounders (i.e. maternal/gestational age, ethnic background, educational level, parity, marital status, body mass index, tobacco and alcohol use, chronic/infectious conditions, uro-genital conditions/symptoms, sleep quality, headache, anxiety, and depression). Health-related quality of life was assessed by the 12-item Short Form Health Survey and physical and mental component summary scores were calculated. Multivariate regression models were performed to evaluate the independent associations of the presence of nausea, vomiting and fatigue with health-related quality of life, adjusting for potential confounders. 33.6% of women experienced daily presence of nausea, 9.6% for vomiting and 44.4% for fatigue. Comparing with women who never reported nausea, vomiting and fatigue, women with daily presence of at least one of these symptoms had significantly lower scores of physical component summary and mental component summary, after adjusting for potential confounders. Our study shows how common nausea, vomiting and fatigue are among women in early pregnancy and how much each of these symptoms negatively impact on health-related quality of life. We call for awareness of this issue from health care professionals, pregnant women and their families.

INTRODUCTION

Nausea, vomiting and fatigue are the most common symptoms in early pregnancy; more than 70% of women have reported the presence of these symptoms in previous studies (1-3). Causes of nausea, vomiting and fatigue during pregnancy remains unknown; rising levels of hormone and stress might be risk factors (4, 5). Typically, nausea and vomiting begin around gestational weeks 5-8 with peak symptoms occurring around gestational weeks 9 and subsiding around week 12 (6, 7). Some studies show that fatigue increases over time throughout the whole pregnancy; other studies indicate that fatigue in the first trimester is worse than in the third trimester (8-10).

Nausea, vomiting and fatigue may affect the physiological, psychological and emotional aspects of women's lives, and may diminish women's quality of life (QOL) (3, 9, 11, 12). QOL reflects subjective perceptions of the individual's position in life in the context of the culture and value systems in which he or she lives, and in relation to the individual's goals, expectations, and concerns (13). QOL refers to holistic well-being, whereas health-related quality of life (HRQOL) focuses on health-related aspects of well-being (14). Recently, an increasing attention has been paid to associations between pregnancy-related symptoms and HRQOL (15-23). Some studies have indicated the relatively low score for many domains of HRQOL among women with presence of nausea and vomiting (15-20, 22, 23), for instance considering the 36 item Short Form Health Survey (SF-36) subscale scores on physical functioning (61.1 vs. 88.9), vitality (23.2 vs. 62.8) and social functioning (44.7 vs. 84.6) in comparison with the general population women aged 14-44 years (20). SF-36 is an often-used generic QOL measure. Lacasse et al. showed that the presence of nausea and vomiting of pregnancy in the first trimester was significantly associated with lower scores considering the 12 item Short Form Health Survey (SF-12) physical component summary scale ($p<0.0001$) and mental component summary score ($p=0.0066$) (17). SF-12 closely mirrors the SF-36 with a good reliability and validity (24). In two other studies, a negative association with the physical domain of HRQOL was observed (21, 25). The inconsistent findings may be due to differences in study design and the timing and mode of measurements, or it may be due to the small sample sizes. Little evidence is available regarding the HRQOL of women in early pregnancy in community samples. Data on associations between fatigue and HRQOL is scarce. Few studies applied multivariate regression models (17, 18), and many of the previous studies employed bivariate analysis (20-22).

In the present study, we present data of 5079 mothers participating in a population-based prospective mother and child cohort in the Netherlands. We aimed to evaluate the independent associations of nausea, vomiting and fatigue with HRQOL of women in early pregnancy.

METHODS

Data resources

This study was embedded within the Generation R study, a population-based prospective mother and child cohort study, designed to identify early environmental and genetic causes of normal and abnormal growth, development and health from fetal life until young adulthood. The Generation R study has been previously described in detail (26-29). In total, 9778 mothers with a delivery date from April 2002 until January 2006 were enrolled in pregnancy (n=8879) or at birth of their children (n=899) in the entire Generation R Study. This includes 7069 women, who were enrolled in early pregnancy (<18 weeks of gestation, median: 13 weeks). The overall response rate of the study was 61% (29). The assessments in prenatal phase were conducted using three questionnaires: Mother 1 Questionnaire in early pregnancy; Mother 3 Questionnaire in mid-pregnancy (18-25 weeks of gestation); Mother 4 Questionnaire in late pregnancy (gestational age ≥25 weeks) (27). Overall, mothers received four postal questionnaires during the prenatal phase; the three questionnaires that were just mentioned above plus Mother 2 Questionnaire regarding diet. The 25-page Mother 1 Questionnaire was used for the present study and assessed at around 12 weeks of gestation. It includes topics of medical history, family history, previous and current pregnancies, quality of life, life style habits, housing conditions, ethnicity and educational level (27). The study was conducted with the guideline proposed in the World Medical Association of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus Medical Center, University Medical Center Rotterdam. Written consent was obtained from all of the participating women (30).

Study population

Seven thousand and sixty-nine women were enrolled before 18 weeks of their gestation (26). The assessment by Mother 1 Questionnaire was planned at around 12 weeks of their pregnancy (median: 13 weeks). We excluded women who didn't respond to the questionnaire (n=497). Additionally, we excluded pregnancies with the following outcomes: twin pregnancies (n= 71), induced abortion (n=23), fetal deaths before 20 weeks of gestation (n=62), loss to follow up their pregnancy outcomes (n=23). Further, we excluded women with missing data on the symptoms (nausea, vomiting and fatigue) (n=158). Finally, we excluded women in case of lacking information on one or more items of the SF-12 (n=1156). Thus, the population for analysis comprised 5079 pregnant women (see Figure S1).

Measure of symptoms

The questions posed to pregnant women regarding to nausea, vomiting and fatigue are 'have you had nausea in the last three months', 'have you had vomiting in the last three

months' and 'have you had tiredness in the last three months'. The possible responses were 'daily, a few days a week, once per week, less than once per week and never'. 'The last three months' refers the latest three months before the subject completed the questionnaire. By using 'never' as the reference group, the other four categories were recoded as dummy variables for multiple regression analyses.

Health-related quality of life

Women's HRQOL in the past month was measured by SF-12 in the questionnaire at around 12 weeks of gestation (median: 13 weeks). SF-12 yields two component summaries: the physical component summary (PCS) and the mental component summary (MCS) (24, 31). The Cronbach's alpha for SF-12 in our study is 0.83. SF-12 includes 12 items regarding 8 scales: physical functioning (two items), role limitations due to physical problems (two items), bodily pain (one item), general health (one item), vitality (one item), social functioning (one item), role limitation due to emotional problems (two items) and perceived mental health (two items). Recoding for some items was conducted, so that a high value indicated the same type of response for each item. Then the raw scores were transformed to provide scale scores that ranged from 0 (the worst) and 100 (the best). We then calculated the raw physical component summary score and the raw mental component summary score by summing up all the scale scores weighted based on US general population survey. Finally the raw PCS and MCS scores were transformed into the standard scores based on the normalized algorithms from the US general population with the mean value of 50 (add 50) and the standard deviation of 10 (multiply by 10) (31). The standardization enables cross-cultural comparison (32).

Covariates

Based on previous studies of determinants of pregnant women's HRQOL, we considered the demographic characteristics, life-style related factors, and indicators of health status as potential confounders (9, 17, 18, 33, 34). Data on these variables were collected in self-reported questionnaires at enrollment. The demographic characteristics included maternal age, gestational age, ethnic background (native Dutch people, other Western immigrant and non-Western immigrant), educational level (low, mid-low, mid-high, high), parity, marital status. Maternal ethnic background and education level were defined according to the classification of Statistics Netherlands (35). Education was categorized into four subsequent levels based on the Dutch Standard Classification of Education: high (university degree), mid-high (higher vocational training, Bachelor's degree), mid-low (>3 years general secondary school, intermediate vocational training) and low (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school) (36).

Lifestyle-related factors included body mass index (BMI), tobacco and alcohol use; indicators of health status included chronic non-infectious conditions, infectious/ inflammatory conditions, uro-genital symptoms, sleep quality, headache, anxiety, and depression. Tobacco/alcohol use was measured by asking 'have you smoked in the past three months" and "have you drunk any alcohol in the past three months", respectively. The amount of alcohol use was also measured.

Women were asked whether in the past 12 months they had one or more of 14 chronic non-infectious conditions on the standard list of chronic conditions according to Statistics Netherlands (37), i.e. diabetes, high blood pressure, a heart condition, migraine, epilepsy, chronic eczema, intestinal disorder, a severe back disorder, arthritis, multiple sclerosis, a thyroid disorder, chronic bronchitis, asthma, nose allergy (such as hay fever). Women were asked whether in the past three months they had one or more infectious/inflammatory conditions, i.e. fever, flu, sore throat or throat infection, runny nose or cold, sinusitis, ear infection, pneumonia, eye infection, cold sore, mouth infection, rash, dermatitis, fungus infection of skin or feet, warts, shingles, diarrhea or enteritis, cystitis or pyelitis and jaundice. An open question followed by asking about other infectious or inflammatory condition not mentioned. Women were asked whether they had one or more of the 10 uro-genital conditions/symptoms in the past three months, i.e. urination/urethra: frequent need to urinate, pain, burning feeling, itching; vagina: discharge, burning feeling, itching; bleeding after sexual intercourse; non-painful ulceration of urethra or vagina; enlarged lymph glands in groin. We summed up the presence of chronic non-infectious conditions, infectious/inflammatory conditions or uro-genital conditions/symptoms respectively and categorized the results into three categories: none condition/symptom, one condition/symptom, two or more conditions/ symptoms. Frequency of 'sleep badly' and 'headache' were measured in the same way with the measurement of nausea, vomiting and fatigue, and were dichotomized as 'yes' or 'no'. Anxiety and depression were measured with two questions: "Have you ever had a period in which you were anxious or worried (for at least two consecutive weeks) and "Have you ever had a period in which you felt very down or depressed (for at least two consecutive weeks).

Statistical analysis

Descriptive analysis was applied to characterize the study population. Differences of mean scores in physical component summary and mental component summary among subgroups were compared using one-way ANOVA. Correlations between symptoms were assessed. The Spearman correlation coefficient between nausea and vomiting was 0.50 ($p<0.01$); the coefficient between nausea and fatigue was 0.32 ($p<0.01$); the coefficient between vomiting and fatigue was 0.14 ($p<0.01$). Cohen's effect sizes (d) were calculated by dividing the difference in mean scores among subgroups by largest

SD and interpreted as: 0.2≤d<0.5 small difference, 0.5≤d<0.8 moderate difference, d≥0.8 large difference (see S2 Table) (38). Multivariate linear regression was applied to assess the independent associations between nausea, vomiting, fatigue and scores of physical component summary and mental component summary by establishing a set of models. All models included the variable gestational age at enrollment. The crude model included three variables: frequency of nausea, vomiting and fatigue. In model 1, effect estimates were additionally adjusted by demographic characteristics. In model 2, effect estimates were additionally adjusted by the lifestyle-related factors. In model 3 (full model), we additionally adjusted by indicators of health status. Multicollinearity was checked and not serious. Multiple imputations were employed to account for the missing data in covariates. The imputed covariates were ethnic background, educational level, marital status, parity, smoking, alcohol use, headache, sleep badly, anxious or worried, feeling down and depressed, chronic non-infectious conditions, infectious/inflammatory conditions and uro-genital conditions/symptoms. Five imputed datasets were generated, based on which the pooled estimates were used to report betas and their 95% confidence intervals (CIs). Imputations were based on the relationships between all variables included in this study (39). We also applied the multivariate linear regression analyses using the non-imputed data. Differences between women who were included in the present study (n=5079) and women who were excluded (n=1990) were assessed using Chi-square tests, and independent-sample t tests. Sensitivity analysis was performed by splitting the population into two subgroups: less than 14 weeks of gestation and over 14 weeks of gestation, and then comparing their outcomes (see S4 Table).

All analyses were conducted with Statistical Package for Social Sciences (SPSS) version 21.0 for Windows (IBM Corp., Armonk, NY, USA). Significance differences were indicated at the level of p<0.05.

RESULTS

Table 1 shows the general characteristics of the study population. In this study sample, the mean maternal age was 30 years; gestational age was less than 14 weeks of gestation in 63.7% participants. The respective percentages of daily presence of nausea, vomiting and fatigue were 33.6%, 9.6% and 44.4%. The mean score of the physical component summary was 47.73 (SD 9.03) and the mean score of the mental component summary was 48.79 (SD 10.21).

Additionally, percentages of women with multiple symptoms are presented in Table 2. 42.1% of women reported the presence of three symptoms (42.1%). Only 0.9% women reported without any symptoms. The SF-12 physical component score in women with three symptoms was relatively low compared to women without any symptoms (45.60 vs. 53.74, effect size d=0.86).

Table 1. Characteristics of the study population (n=5079)

Characteristics	Value*
Maternal age(years)	
Mean (SD)	29.98 (4.97)
<30 years	2301 (45.3)
≥30 years	2778 (54.7)
Gestational age(weeks)	
Mean (SD)	13.50 (2.00)
<14 weeks	3235 (63.7)
≥ 14 weeks	1844 (36.3)
Ethnicity background	
Dutch	2838 (56.1)
Other western	656 (13.0)
Non-western	1567 (31.0)
Education level	
Low	1114 (22.2)
Mid-low	1525 (30.4)
Mid-high	1062 (21.2)
High	1311 (26.2)
Marital status	
Married and living together	4432 (88.0)
Single	606 (12.0)
Parity	
Nullipara	3027 (59.7)
Multipara	2046 (40.0)
Smoking during first trimester(% yes)	
Yes, until knowing pregnancy	657(13.1)
Yes, still doing so	602(12.0)
Alcohol use during first trimester(% yes)	
Yes, until knowing pregnancy	1561(31.0)
Yes, still doing so	888(17.6)
If yes, how many glasses did you drink?	
Less than 1 glass a week	1404(57.6)
1 to 3 glasses a week	701(28.8)
4-6 glasses a week	195(8.0)
1 glass a day	58(2.4)
1-3 glasses a day	70(2.9)
More than 3 glasses a day	8(0.3)
BMI	
Mean±SD	24.36±4.30
<25	3347(65.9)
≥25	1732(34.1)
Chronic non-infectious conditions	
None chronic condition	2723(56.0)
One chronic condition	1509(31.0)
Two or more chronic conditions	629(12.9)

Table 1. Continued

Characteristics	Value*
Infectious conditions	
None infectious condition	1186(23.4)
One infectious condition	1287(25.4)
Two or more infectious conditions	2591(51.2)
Uro-genital conditions/symptoms	
None condition/symptom	681(13.5)
One condition/symptom	1348(26.7)
Two or more conditions/symptoms	3027(59.9)
Headache(if yes)	3553 (71.2)
Sleep badly, (if yes)	3690 (73.6)
Anxious or worries (if yes)	1469 (29.3)
Feeling down or depressed(if yes)	1562 (31.1)
Nausea	
Daily	1708 (33.6)
A few days per week	1414(27.8)
Once per week	425(8.4)
Less than once per week	663(13.1)
Never	869 (17.1)
Vomiting	
Daily	486(9.6)
A few days per week	610(12.0)
Once per week	425(8.4)
Less than once per week	663(13.1)
Never	2876(56.6)
Fatigue	
Daily	2256(44.4)
A few days per week	2000(39.4)
Once per week	458(9.0)
Less than once per week	262(5.2)
Never	103(2.0)
Health-related quality of life (1-100)	
SF-12 Physical component summary	
Mean(SD)	47.73 (9.03)
Range	14.07 - 71.55
SF-12 Mental component summary	
Mean(SD)	48.79 (10.21)
Range	6.74 - 68.88

* Values are means, SD (standard deviation), and percentages for the whole study population.
High education corresponds to university degree; mid-high level corresponds to higher vocational training, Bachelor's degree; mid-low level corresponds to more than 3 years general secondary school, intermediate vocational training; low level corresponds to no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school. Data was missing for ethnicity background (n=18), education level (n=67), marital status (n=41), parity (n=18), smoking during first trimester (n=65), alcohol use during first trimester (n=42), uro-genital conditions/symptoms (n=23), chronic non-infectious conditions (n=218) and infectious conditions (n=15), headache (n=86), sleeping badly (n=65), being anxious or worried (n=61), feeling down or depressed (n=58).

Table 2. Women with the presence of multiple symptoms (nausea, vomiting and fatigue) (N=5079)

Symptom(s)	N (%)	Physical component summary		Mental component summary	
		mean (SD)	*d*	mean (SD)	*d*
with no nausea, vomiting nor fatigue					
	47 (0.9)	53.74 (7.91)	*reference*	54.15 (7.95)	*reference*
only one symptom:					
nausea	20 (0.3)	53.67 (5.42)	0.01	52.19 (7.83)	0.25[a]
vomiting	2 (0.04)	55.83 (5.58)	0.26[a]	49.60 (6.56)	0.57[b]
fatigue	792 (15.6)	50.94 (7.82)	0.35[a]	51.51 (8.59)	0.31[a]
Only two symptoms					
Nausea and vomiting	34 (0.6)	51.94 (9.24)	0.19	51.02 (8.86)	0.35[a]
Nausea and fatigue	2017 (39.7)	48.44 (8.45)*	0.63[b]	49.64 (9.72)*	0.46[a]
Vomiting and fatigue	28 (0.6)	48.41 (8.45)*	0.63[b]	51.62 (8.63)	0.29[a]
Three symptoms (nausea and vomiting and fatigue)					
	2139 (42.1)	45.60 (9.46)*	0.86[c]	46.76 (10.90)*	0.68[b]

d means effect size, which is highest minus lowest mean SF-12 score divided by the largest standard deviation. a means small difference when 0.2≤d<0.5 small difference; b means moderate difference when 0.5≤d<0.8; c means large difference when d≥0.8; for others that d was less than 0.2, we didn't mark them in our table. Subgroup with no nausea, vomiting nor fatigue is the reference group when we compared the difference between subgroups. *p<0.01.

Significant differences in physical and mental component summary scores were observed between subgroups of women who had reported the 'daily', 'a few days per week', 'once per week', 'less than once per week' or 'never' presence of symptoms (see S1 Table). Independent associations between nausea, vomiting, fatigue and physical / mental component summary scores are shown in Table 3.

Regarding to physical component summary (see Table 3), women with daily presence of nausea, vomiting and fatigue had lower scores than women without these symptoms (-3.05 [-3.84, -2.26]; -2.16 [-3.08, -1.23]; -5.19 [-6.87, -3.50]). Regarding to mental component summary, women with daily presence of nausea, vomiting and fatigue had lower scores than women without these symptoms (-1.81 [-2.72, -0.96]; -3.00 [-4.03, -1.98]; -3.00 [-4.87, -1.13]). Results based on the non-imputed data are presented in S2 Table. The profile of associations is very similar to that from the imputed data.

Non-response analyses

Compared with the participating women in the study (n=5079), the excluded women (n=1990) were more often with low education, non-Dutch, single and in their first pregnancy (p<0.05) and reported lower prevalence of infectious/inflammatory conditions and uro-genital conditions/symptoms (p<0.05) (see S3 Table). Given the

amount of missing data on covariates, we could not conclude that the study included healthier women, or the contrary, compared with the excluded women.

DISCUSSION

By far the most common pregnancy-related symptom in our study population was fatigue. Many pregnant women also reported the presence of nausea and vomiting in early pregnancy. This study shows that women with daily presence of nausea, vomiting and fatigue had lower HRQOL in both the physical and mental domains than women without these symptoms.

The average physical component summary score in our study population (47.73; SD 9.03) was below the average in a normative Dutch sample of women aged 30-39 years (53.37; SD 7.09) ($p<0.01$) (40). This may reflect the presence of pregnancy-related symptoms. In our study population the subgroup of women with no symptom of nausea, vomiting or fatigue reported an average score of physical component summary as 53.74 (SD 7.91), which is very similar to the normative data ($p>0.05$). The average mental component summary score in our study population (48.79; SD10.21) is similar to the average in a normative Dutch sample of women aged 30-39 years (48.67; SD 10.31) ($p>0.05$), while the subgroup of women with no symptom of nausea, vomiting nor fatigue reported an average score of mental component summary as 54.15 (SD 7.95), which is higher than the normative data ($p<0.01$).

In general, the impact on the physical domain is somewhat larger in comparison with the impact on the mental domain. In the present study, pregnant women with a combination of nausea, vomiting and fatigue reported a relatively low HRQOL in both physical and mental component summary scales; Cohen's effect sizes indicate large effects of these symptoms on the physical component summary scale and moderate effects on the mental component summary scale. Based on raw data, we calculated Cohen's effect sizes (S2 Table). These show the large effect of fatigue on the physical component summary scale ($d=0.90$) and moderate effects of nausea and vomiting on both physical and mental component summary scales.

Our multivariate regression analysis showed that nausea, vomiting and fatigue are each associated with HRQOL at a significant level ($p<0.05$). With regard to nausea and vomiting, the result patterns are consistent with those of previous studies (9, 15, 17, 18, 41). We also found the independent association of fatigue and HRQOL, which has not been assessed in previous studies. Specifically, daily presence of fatigue is associated with a relatively low score on the physical component summary score. Fatigue is highly prevalent, and is combined with nausea and/or vomiting in most of the study population

Table 3. Multiple regression analyses for associations between nausea, vomiting, fatigue and SF-12 scores (N = 5079).

	SF-12 Physical Component Score			
	Crude model β(95%CI)	**Model 1 β(95%CI)**	**Model 2 β(95%CI)**	**Model 3 β(95%CI)**
Nausea				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.21	-0.24	-0.28	0.01
	(-1.07, 0.65)	(-1.10, 0.11)	(-1.15, 0.59)	(-0.88, 0.89)
Once a week	-0.52	-0.60	-0.72	-0.41
	(-1.51, 0.46)	(-1.60, 0.39)	(-1.72, 0.28)	(-1.44, 0.61)
Few days a week	**-1.13**	**-1.25**	**-1.24**	**-0.91**
	(-1.88, -0.37)	**(-2.00, -0.49)**	**(-2.00, -0.48)**	**(-1.69, -0.12)**
Daily	**-3.33**	**-3.44**	**-3.38**	**-2.95**
	(-4.13, -2.52)	**(-4.25, -2.64)**	**(-4.19, -2.56)**	**(-3.79, -2.12)**
Vomiting				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.66	-0.60	-0.63	-0.43
	(-1.34, 0.02)	(-1.28, 0.08)	(-1.31, 0.06)	(-1.13, 0.27)
Once a week	**-2.03**	**-1.81**	**-1.78**	**-1.55**
	(-3.02,-1.03)	**(-2.82, -0.80)**	**(-2.78, -0.77)**	**(-2.58, -0.52)**
Few days a week	**-2.40**	**-2.09**	**-2.08**	**-1.79**
	(-3.19, -1.62)	**(-2.89, -1.29)**	**(-2.88, -1.27)**	**(-2.62, -0.97)**
Daily	**-2.67**	**-2.35**	**-2.29**	**-2.08**
	(-3.58, -1.76)	**(-3.29, -1.40)**	**(-3.25, -1.34)**	**(-3.08, -1.09)**
Fatigue				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	0.40	-0.55	-0.53	0.33
	(-2.29, 1.50)	(-2.48, 1.38)	(-2.17, 1.41)	(-1.67, 2.33)
Once a week	-0.83	-1.14	-1.03	0.33
	(-2.61, 0.95)	(-2.96, 0.69)	(-2.87, 0.81)	(-1.57, 0.84)
Few days a week	**-3.73**	**-3.94**	**-3.92**	**-2.35**
	(-5.47, -0.30)	**(-5.64, -2.25)**	**(-5.63, -2.20)**	**(-4.14, -0.56)**
Daily	**-7.13**	**-7.44**	**-7.42**	**-5.48**
	(-8.78, -5.47)	**(-9.14, -5.74)**	**(-9.13, -5.70)**	**(-7.28, -3.68)**
R square	0.16	0.17	0.17	0.20

Table 3 is based on imputed dataset. Bold print indicates statistical significance ($p<0.05$). Values represent betas and 95% confidence intervals derived from multiple linear regression analyses. All models were adjusted by the gestational age at measurement. Model 1 was adjusted by demographic characteristics (i.e. maternal age, ethnicity background, education level, parity and marital status). Model 2 was additionally adjusted by life-style related factors (i.e. smoking, alcohol use and BMI). Model 3 was additionally adjusted by symptoms and indicators of health status, including (i.e. headache, sleep badly, feel anxious or worried, feel down or depressed, uro-genital conditions/symptoms, chronic non-infectious conditions and infectious conditions).

Table 3. Continued

	SF-12 Mental Component Score			
	Crude model β(95%CI)	**Model 1 β(95%CI)**	**Model 2 β(95%CI)**	**Model 3 β(95%CI)**
Nausea				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.79	-0.89	**-1.02**	-0.80
	(-1.80, 0.22)	(-1.89, 0.11)	**(-2.02, -0.02)**	(-1.78, 0.19)
Once a week	-0.53	-0.80	-0.80	-0.12
	(-1.70, 0.63)	(-1.95, 0.36)	(-1.96, 0.36)	(-1.26, 1.02)
Few days a week	**-1.16**	**-1.40**	**-1.59**	-0.79
	(-2.05, -0.28)	**(-2.27, -0.52)**	**(-2.47,-0.71)**	(-1.66, 0.08)
Daily	**-2.20**	**-2.51**	**-2.85**	**-1.74**
	(-3.14, -1.26)	**(-3.45, -1.58)**	**(-3.79, -1.91)**	**(-2.67, -0.80)**
Vomiting				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	**-1.18**	-0.85	-0.85	-0.56
	(-1.97, -0.38)	(-1.64, -0.06)	(-1.64, -0.06)	(-1.34, 0.21)
Once a week	**-1.28**	-0.92	-0.86	-1.09
	(-2.45, -0.11)	(-2.09, 0.24)	(-2.02, 0.30)	(-2.24, 0.06)
Few days a week	**-1.79**	-0.71	-0.67	**-0.92**
	(-2.71, -0.87)	(-1.64, 0.21)	(-1.60, 0.25)	**(-1.84, -0.01)**
Daily	**-4.80**	**-3.08**	**-3.01**	**-3.39**
	(-5.86, -3.73)	**(-4.18, -1.98)**	**(-4.11, -1.91)**	**(-4.50, -2.29)**
Fatigue				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	0.64	-0.46	-0.53	1.24
	(-1.59, 2.86)	(-2.70, 1.78)	(-2.78, 1.71)	(-0.98, 3.46)
Once a week	-1.05	-2.31	**-2.35**	-0.10
	(-3.15, 1.05)	(-4.42, -0.20)	**(-4.47, -0.23)**	(-2.22, 2.02)
Few days a week	**-2.25**	**-3.47**	**-3.53**	-0.75
	(-4.19, -0.30)	**(-5.43, -1.51)**	**(-5.50, -1.56)**	(-2.74, 1.23)
Daily	**-5.25**	**-6.36**	**-6.34**	**-2.92**
	(-7.20, -3.30)	**(-8.33, -4.39)**	**(-8.32, -4.36)**	**(-4.92, -0.92)**
R square	0.09	0.13	0.14	0.21

in the present study. Chou et al. showed that women with nausea and vomiting were more likely to show fatigue in early pregnancy (41). In the present study, pregnant women with a combination of nausea, vomiting and fatigue reported a relative low HRQOL in both the physical and mental domains; Cohen's effect sizes were large and moderate, respectively.

The presence of symptoms and the impact on HRQOL may affect the ability of women in early pregnancy to cope with demands in the workplace and other daily activities. Gadsby et al. found each year around 8.6 million hours of paid employment and 5.8 million hours of housework being lost via nausea and vomiting in the United Kingdom (6). According to the study by Vellacott et al., about 25% women with nausea and vomiting during pregnancy reported markedly impaired job efficiency (42).

Chou et al. reported that nausea, vomiting and fatigue in early pregnancy may be associated with depressive symptoms (9), which may be an explanation for the relatively low scores in the mental domain of women with these symptoms in our study. They also suggested that this association may be mediated by the level of social support (9, 41). So, attention for organizing social support for women experiencing these symptoms might be part of future intervention approaches (41, 43).

A recent study showed that women with nausea and vomiting during pregnancy felt their distress was trivialized by the general practitioners (44). Health care professionals should not underestimate the presence of nausea, vomiting and fatigue in early pregnancy just because that 'morning sickness' is common during pregnancy. This is included into the recently published Pregnancy Nausea/Vomiting Treatment Guidelines from the American College of Obstetricians and Gynecologists (11). Evsen et al. found that almost half of women in early pregnancy did nothing at all or 'non-evidence based' actions to manage nausea, vomiting or fatigue (2). Chou et al. and O'Brien et al. also indicated that only few women with nausea and vomiting seek medical treatments (7, 19). These findings highlight the need to be aware of negative impacts of these symptoms on HRQOL by health care professionals and pregnant women as well as their families, and accordingly necessary symptom managements should be taken under the supervision of health professionals. Since fatigue is often combined with the presence of nausea and vomiting, Donna et al. suggested that controlling fatigue may be an effective approach to manage nausea and vomiting (45). With regard to employed women, flexible work schedule including breaks in daily life and assistance from families with daily duties in the household may help to relieve fatigue (45) and may consequently help to relieve nausea and vomiting, and improve HRQOL in these women.

Strengths and limitations

A strength of this study is the large sample size compared to earlier studies (15, 17-21, 45). Information regarding a comprehensive set of potential confounders was available. Some limitations should be taken into account. Causation could not be evaluated with the current cross-sectional analyses. We recommend that future studies evaluate time trajectories of nausea, vomiting, fatigue and HRQOL during pregnancy. Women who were included in the present study were younger, higher educated, more often of Dutch origin and more frequently had infectious/inflammatory conditions and uro-genital conditions/symptoms than women excluded from the sample for analysis. Given the amount of missing data on the covariates in the excluded population, we could not conclude that the excluded population was healthier or more morbid. The selection bias may have occurred; for example, if the excluded women with nausea, vomiting and fatigue provided higher (or lower) HRQOL scores than the included women with these symptoms. Furthermore, the women in this study may not fully represent the general population in the Netherlands, as all of them resided in Rotterdam. We asked women to think about the frequency of their symptoms in the previous three months, while for the most SF12 items we only asked them to recall within past month. Although we included many potential confounders in the models, remaining unmeasured confounders, such as work status (17), therapeutic approaches to relieve nausea, vomiting and fatigue, could also explain associations between nausea, vomiting, fatigue and HRQOL. Regarding the measurement of covariates in the present study, we acknowledge that the anxiety and depression were not measured by either a psychometric instrument or a diagnostic interview. The questions were unspecific, which did not capture the information of severity. Misclassification may not be ruled out.

In our study, generic HRQOL was measured. For future studies, we recommend to include both generic measures of HRQOL and specific measures such as the 'health-related quality of life for nausea and vomiting during pregnancy' (NVPQOL) (16). Munch et al. showed that the NVPQOL was more sensitive to measure the impact of pregnancy-related symptoms on HRQOL compared to the SF-36 (18). Previous studies indicated that the degree of the negative impacts of nausea and vomiting may be associated with the severity of these symptoms (17, 19). In the present study, we measured the frequency rather than the severity of the symptoms. Women's interpretation of the question and the framing of frequencies may have influenced the results. It is controversial that women never presented with fatigue in early pregnancy. We recommend to measure the severity by symptom-specific instruments such as the Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system (46) or the Multidimensional Assessment of Fatigue (MAF) scale (47).

CONCLUSION

In this population-based study, daily presence of nausea, vomiting and fatigue was strongly associated with decreased HRQOL. This confirms the importance of paying attention by health care professionals to the presence of these symptoms and the consequences for the woman in early pregnancy. Also, social and practical support from family, relatives and friends, and adaptations with regard to work in dialogue with the employer may lead to more effective management of the impact of these pregnancy-related symptoms in early pregnancy.

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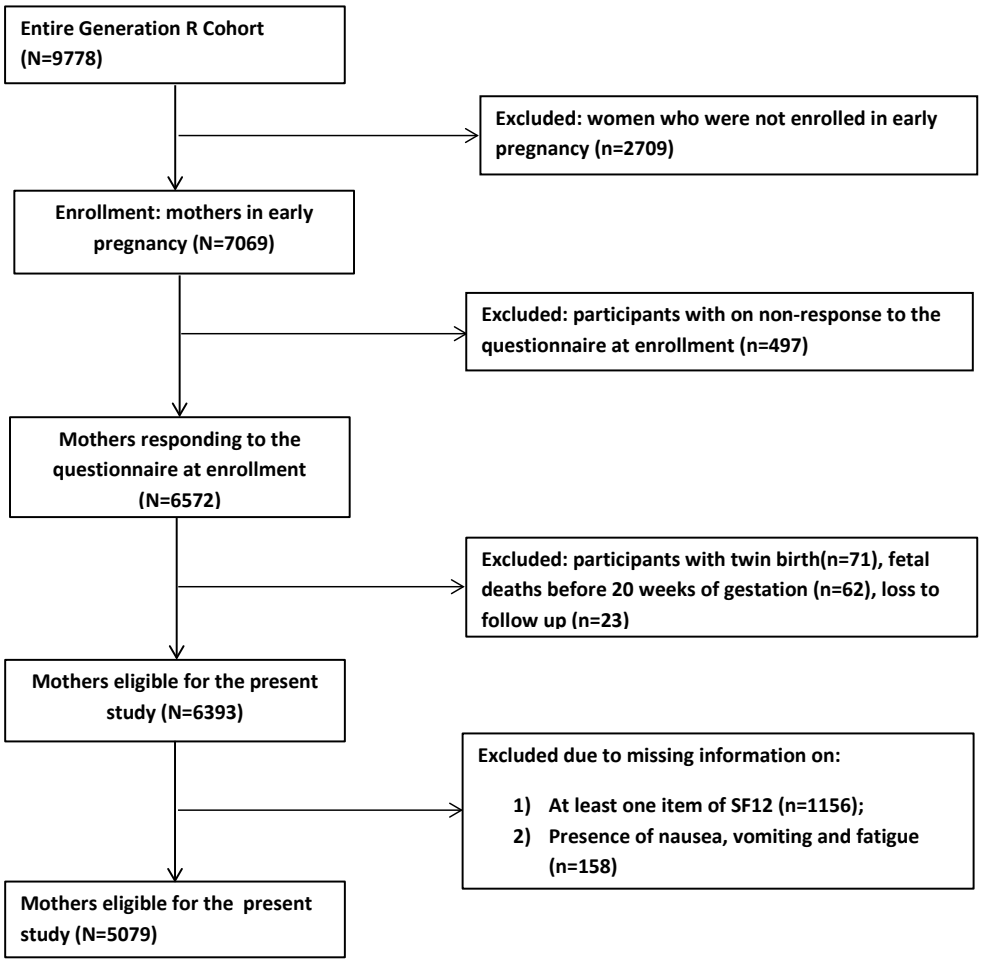
REFERENCES

1. Lee NM, Saha S. Nausea and Vomiting of Pregnancy. Gastroenterology clinics of North America. 2011;40(2):309-34.
2. Nazik E, Eryilmaz G. Incidence of pregnancy-related discomforts and management approaches to relieve them among pregnant women. J Clin Nurs. 2014;23(11-12):1736-50.
3. Davis M. Nausea and vomiting of pregnancy: an evidence-based review. J Perinat Neonatal Nurs. 2004;18(4):312-28.
4. Matthews A, Haas DM, O'Mathuna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2015(9):CD007575.
5. Isbir GG, Mete S. Experiences with nausea and vomiting during pregnancy in Turkish women based on roy adaptation model: a content analysis. Asian Nurs Res (Korean Soc Nurs Sci). 2013;7(4):175-81.
6. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract. 1993;43(371):245-8.
7. Chou FH, Chen CH, Kuo SH, Tzeng YL. Experience of Taiwanese women living with nausea and vomiting during pregnancy. J Midwifery Womens Health. 2006;51(5):370-5.
8. Pugh LC, Milligan RA. Patterns of fatigue during childbearing. Appl Nurs Res. 1995;8(3):140-3.
9. Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. J Nurs Scholarsh. 2003;35(2):119-25.
10. Affonso DD, Lovett S, Paul SM, Sheptak S. A standardized interview that differentiates pregnancy and postpartum symptoms from perinatal clinical depression. Birth. 1990;17(3):121-30.
11. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126(3):e12-24.
12. Miller F. Nausea and vomiting in pregnancy: the problem of perception--is it really a disease? Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S182-3.
13. Canavarro MC, Serra AV, Simoes MR, Rijo D, Pereira M, Gameiro S, et al. Development and psychometric properties of the World Health Organization Quality of Life Assessment Instrument (WHOQOL-100) in Portugal. Int J Behav Med. 2009;16(2):116-24.
14. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9.
15. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S220-7.
16. Lacasse A, Berard A. Validation of the nausea and vomiting of pregnancy specific health related quality of life questionnaire. Health Qual Life Outcomes. 2008;6:32.
17. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? Bjog. 2008;115(12):1484-93.
18. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol. 2011;31(1):10-20.
19. O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. Birth. 1992;19(3):138-43.
20. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol. 2000;40(4):397-401.
21. Kugahara T, Ohashi K. Characteristics of nausea and vomiting in pregnant Japanese women. Nurs Health Sci. 2006;8(3):179-84.
22. Swallow BL, Lindow SW, Masson EA, Hay DM. Women with nausea and vomiting in pregnancy demonstrate worse health and are adversely affected by odours. J Obstet Gynaecol. 2005;25(6):544-9.

23. Otchet F, Carey MS, Adam L. General health and psychological symptom status in pregnancy and the puerperium: what is normal? Obstet Gynecol. 1999;94(6):935-41.
24. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.
25. Hueston WJ, Kasik-Miller S. Changes in functional health status during normal pregnancy. J Fam Pract. 1998;47(3):209-12.
26. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. Eur J Epidemiol. 2012;27(9):739-56.
27. Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, et al. The Generation R Study: design and cohort update until the age of 4 years. Eur J Epidemiol. 2008;23(12):801-11.
28. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004;18(1):61-72.
29. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
30. World Medical Association I. Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Indian Med Assoc. 2009;107(6):403-5.
31. Ware JE, Kosinski M, Keller SD. SF-12: How to score the SF-12 physical and mental health summary scales: Health Institute, New England Medical Center; 1995.
32. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol. 1998;51(11):1171-8.
33. Neri A, Levavi H, Ovadia J. Nausea and vomiting in pregnancy: a review of the problem with particular regard to psychological and social aspects. Br J Obstet Gynaecol. 1995;102(8):671.
34. Chou FH, Kuo SH, Wang RH. A longitudinal study of nausea and vomiting, fatigue and perceived stress in, and social support for, pregnant women through the three trimesters. Kaohsiung J Med Sci. 2008;24(6):306-14.
35. Statistics Netherlands. Migrants in the Netherlands 2004 (Allochtnen in Nederland 2004). Voorburg/Heelen, the Netherlands: Centraal Bureau voor de Statistiek; 2004.
36. Statistics Netherlands. The Dutch Standard Classification of Education, SOI 2006. Voorburg/Heerlen; 2008
37. Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der Zee J. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. The European Journal of Public Health. 2005;15(1):59-65.
38. Houben-van Herten M, Bai G, Hafkamp E, Landgraf JM, Raat H. Determinants of health-related quality of life in school-aged children: a general population study in the Netherlands. PLoS One. 2015;10(5):e0125083.
39. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol. 1995;142(12):1255-64.
40. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. Qual Life Res. 2009;18(4):403-14.
41. Chou FH, Avant KC, Kuo SH, Fetzer SJ. Relationships between nausea and vomiting, perceived stress, social support, pregnancy planning, and psychosocial adaptation in a sample of mothers: a questionnaire survey. Int J Nurs Stud. 2008;45(8):1185-91.
42. Vellacott ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. Int J Gynaecol Obstet. 1988;27(1):57-62.
43. Liu MC, Kuo SH, Lin CP, Yang YM, Chou FH, Yang YH. Effects of professional support on nausea, vomiting, and quality of life during early pregnancy. Biol Res Nurs. 2014;16(4):378-86.

44. Heitmann K, Svendsen HC, Sporsheim IH, Holst L. Nausea in pregnancy: attitudes among pregnant women and general practitioners on treatment and pregnancy care. Scand J Prim Health Care. 2016;34(1):13-20.
45. van Lier D, Manteuffel B, Dilorio C, Stalcup M. Nausea and fatigue during early pregnancy. Birth. 1993;20(4):193-7.
46. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S228-31.
47. Fairbrother N, Hutton EK, Stoll K, Hall W, Kluka S. Psychometric evaluation of the Multidimensional Assessment of Fatigue scale for use with pregnant and postpartum women. Psychol Assess. 2008;20(2):150-8.

SUPPLEMENTARY



Supplementary Figure S1. Flow chart of population for analysis in this study

Table S1. Univariate analysis of SF-12 scores between subgroups according to demographic characteristics, lifestyle-related factors, indicators for health status and symptoms (n=5079)#

	SF-12 Physical Component Score			SF-12 Mental Component Score		
	Mean (SD)	P value	Effect size	Mean (SD)	P value	Effect size
Age		<0.001	0.09		<0.001	0.22[a]
<30 years	47.28 (9.23)			47.46 (10.78)		
≥30 years	48.10 (8.84)			49.89 (9.58)		
Gestational age		0.332	0.03		0.02	0.07
<14 weeks	47.64 (9.00)			49.05 (10.01)		
≥14 weeks	47.89 (9.10)			48.34 (10.54)		
Ethnicity		<0.001	0.21[a]		<0.001	0.43[a]
Dutch	48.40 (8.54)			50.60 (8.76)		
Other western	48.12 (8.96)			48.71 (10.61)		
Non-western	46.36 (9.72)			45.64 (11.53)		
Education		<0.001	0.19		<0.001	0.33[a]
Low	47.44 (9.07)			46.94 (10.94)		
Mid-low	47.00 (9.21)			48.09 (10.60)		
Mid-high	47.84 (9.12)			49.66 (9.80)		
High	48.74 (8.58)			50.58 (9.00)		
Marital status		0.22	0.0		<0.001	0.4[a]
Married or living together	47.67 (9.00)			49.29 (9.92)		
No partner	48.15 (9.25)			45.21 (11.49)		
Parity		0.39	0.05		0.29	0.03
Nullipara	47.65 (9.00)			48.7 (10.2)		
Multipara	47.87 (8.90)			49.0 (10.2)		
Smoking in past three months		<0.001	0.13		<0.001	0.25[a]
No	47.43 (9.04)			49.51 (9.76)		
Yes	48.63 (8.90)			46.70 (11.29)		
Alcohol use in past three months		<0.001	0.10		<0.001	0.12
No	47.59 (9.27)			48.18 (10.52)		
Yes	48.53 (8.68)			49.45 (9.83)		
Body mass index		0.005	0.08		0.46	0.02
<25	47.98 (9.05)			48.87 (10.22)		
≥25	47.24 (8.97)			48.64 (10.20)		
Headache		<0.001	0.33[a]		<0.001	0.27[a]
Yes	46.86 (9.26)			48.03 (10.50)		
No	49.91 (8.01)			50.84 (9.08)		
Sleep badly		<0.001	0.29[a]		<0.001	0.36[a]
Yes	47.02 (9.20)			47.75 (10.64)		
No	49.68 (8.24)			51.55 (8.42)		
Anxious or worried		<0.001	0.23[a]		<0.001	0.48[a]
Yes	46.13 (9.73)			44.73 (11.95)		
No	48.40 (8.65)			50.49 (8.86)		
Feel down or depressed		<0.001	0.24[a]		<0.001	0.52[b]
Yes	46.12 (9.71)			44.50 (11.95)		
No	48.48 (8.61)			50.76 (8.65)		

Table S1. Continued

	SF-12 Physical Component Score			SF-12 Mental Component Score		
	Mean (SD)	P value	Effect size	Mean (SD)	P value	Effect size
Uro-genital symptoms		<0.001	0.21[a]		<0.001	0.27[a]
Yes	47.48 (9.07)			48.42 (10.36)		
No	49.41 (8.52)			51.20 (8.71)		
Chronic non-infectious conditions		<0.001	0.30[a]		<0.001	0.17
Yes	46.74 (9.22)			48.20 (10.56)		
No	49.51 (8.35)			50.04 (9.25)		
Infectious conditions		<0.001	0.21[a]		<0.001	0.19
Yes	47.30 (9.11)			48.33 (10.42)		
No	49.22 (8.56)			50.27 (9.37)		
Nausea		<0.001	0.71[b]		<0.001	0.50[b]
Never	51.02 (7.87)			51.65 (8.56)		
Less than once per week	50.32 (7.90)			50.38 (9.26)		
Once per week	49.53 (7.66)			50.28 (9.16)		
A few days per week	48.12 (8.64)			49.18 (9.98)		
Daily	44.28 (9.45)			46.07 (11.09)		
Vomiting		<0.001	0.60[b]		<0.001	0.61[b]
Never	49.25 (9.03)			50.25 (9.43)		
Less than once per week	47.83 (8.65)			48.44 (9.78)		
Once per week	45.91 (9.60)			48.11 (10.51)		
A few days per week	45.01 (9.41)			47.18 (11.13)		
Daily	43.18 (10.05)			43.21 (11.57)		
Fatigue		<0.001	0.93c		<0.001	0.57[b]
Never	53.17 (7.90)			52.65 (8.24)		
Less than once per week	53.00 (6.55)			50.08 (9.18)		
Once per week	52.60 (6.86)			51.76 (8.55)		
A few days per week	49.05 (8.10)			53.44 (8.08)		
Daily	44.28 (9.45)			46.32 (11.04)		

Analysis is based on non-imputed database. Effect sizes are highest minus lowest mean SF-12 score divided by the largest standard deviation. a= small difference, b=moderate difference; c= largest difference; for others that d was less than 0.2, we didn't mark them in our table.

Table S2. Multiple regression analyses for associations between nausea, vomiting, fatigue and SF-12 scores using non-imputed data

	SF-12 Physical Component Score			
	Crude model (N=5079) β(95%CI)	Model 1 (N=4981) β(95%CI)	Model 2 (N=4919) β(95%CI)	Model 3 (N=4557) β(95%CI)
Nausea				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.21 (-1.07, 0.65)	-0.24 (-1.10, 0.62)	-0.26 (-1.12, 0.61)	0.04 (-0.84, 0.92)
Once a week	-0.52 (-1.51, 0.46)	-0.60 (-1.60, 0.39)	-0.70 (-1.70, 0.30)	-0.38 (-1.40, 0.65)
Few days a week	**-1.13 (-1.88, -0.37)**	**-1.25 (-2.01, -0.49)**	**-1.22 (-1.98, -0.45)**	**-0.88 (-1.66, -0.09)**
Daily	**-3.33 (-4.13, -2.52)**	**-3.44 (-4.25, -2.64)**	**-3.35 (-4.16, -2.53)**	**-2.92 (-3.76, -2.08)**
Vomiting				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.66 (-1.34, 0.02)	-0.60 (-1.28, 0.08)	-0.64 (-1.32, 0.05)	-0.43 (-1.13, 0.27)
Once a week	**-2.03 (-3.02,-1.03)**	**-1.81 (-2.82, -0.80)**	**-1.78 (-2.79, -0.77)**	**-1.55 (-2.58, -0.52)**
Few days a week	**-2.40 (-3.19, -1.62)**	**-2.09 (-2.89, -1.29)**	**-2.07 (-2.88, -1.27)**	**-1.79 (-2.61, -0.96)**
Daily	**-2.67 (-3.58, -1.76)**	**-2.35 (-3.29, -1.40)**	**-2.29 (-3.24, -1.34)**	**-2.08 (-3.08, -1.08)**
Fatigue				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	0.40 (-2.29, 1.50)	-0.55 (-2.48, 1.38)	-0.56 (-2.50, 1.38)	0.31 (-1.68, 2.31)
Once a week	-0.83 (-2.61, 0.95)	-1.14 (-2.96, 0.69)	-1.07 (-2.90, 0.77)	0.30 (-1.61, 2.21)
Few days a week	**-3.73 (-5.47, -0.30)**	**-3.94 (-5.64, -2.25)**	**-3.92 (-5.63, -2.21)**	**-2.34 (-4.13, -0.55)**
Daily	**-7.13 (-8.78, -5.47)**	**-7.44 (-9.14, -5.74)**	**-7.42 (-9.14, -5.71)**	**-5.47 (-7.27, -3.67)**
R square	0.16	0.17	0.17	0.20

Table is based on non-imputed dataset. Bold print indicates statistical significance (p<0,05). Values represent betas (95% confidence intervals) and R squares derived from multiple linear regression analyses. All models are adjusted by gestational age at measurement. Model 1 was adjusted by demographic characteristics (i.e. maternal age, ethnicity background, education level, parity and marital status); Model 2 was additionally adjusted by life-style related factors (i.e. smoking, alcohol use and BMI); Model 3 was additionally adjusted by symptoms and indicators of health status, including(i.e. headache, sleep badly, feel anxious or worried, feel down or depressed, uro-genital symptoms, chronic non-infectious conditions and infectious conditions).

Table S2. Continued

	SF-12 Mental Component Score			
	Crude model (N=5079) β(95%CI)	**Model 1 (N=4981) β(95%CI)**	**Model 2 (N=4919) β(95%CI)**	**Model 3 (N=4557) β(95%CI)**
Nausea				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.79 (-1.80, 0.22)	-0.89 (-1.89, 0.11)	**-1.06 (-2.05, -0.06)**	-0.83 (-1.81, 0.15)
Once a week	-0.53 (-1.70, 0.63)	-0.80 (-1.95, 0.36)	-0.84 (-2.01, 0.31)	-0.16 (-1.30, 0.97)
Few days a week	**-1.16 (-2.05, -0.28)**	**-1.40 (-2.27, -0.52)**	**-1.62 (-2.50,-0.74)**	-0.81 (-1.69, 0.06)
Daily	**-2.20 (-3.14, -1.26)**	**-2.51 (-3.45, -1.58)**	**-2.85 (-3.84, -1.95)**	**-1.77 (-2.70, -0.84)**
Vomiting				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	**-1.18 (-1.97, -0.38)**	**-0.85 (-1.64, -0.06)**	**-0.84 (-1.62, -0.05)**	-0.56 (-1.34, 0.22)
Once a week	**-1.28 (-2.45, -0.11)**	-0.92 (-2.09, 0.24)	-0.87 (-2.03, 0.30)	-1.09 (-2.23, 0.05)
Few days a week	**-1.79 (-2.71, -0.87)**	-0.71 (-1.64, 0.21)	-0.68 (-1.60, 0.25)	**-0.93 (-1.85, -0.02)**
Daily	**-4.80 (-5.86, -3.73)**	**-3.08 (-4.18, -1.98)**	**-3.02 (-4.12, -1.92)**	**-3.41 (-4.51, -2.30)**
Fatigue				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	0.64 (-1.59, 2.86)	-0.46 (-2.70, 1.78)	-0.46 (-2.71, 1.78)	1.28 (-0.94, 3.51)
Once a week	-1.05 (-3.15, 1.05)	**-2.31 (-4.42, -0.20)**	**-2.29 (-4.47, -0.34)**	-0.05 (-2.17, 2.07)
Few days a week	**-2.25 (-4.19, -0.30)**	**-3.47 (-5.43, -1.51)**	**-3.52 (-5.50, -1.55)**	-0.76 (-2.74, 1.23)
Daily	**-5.25 (-7.20, -3.30)**	**-6.36 (-8.33, -4.39)**	**-6.34 (-8.31, -4.35)**	**-2.92 (-4.92, -0.92)**
R square	0.09	0.13	0.14	0.21

Table S3. Non-response analyses (n=7069)

Characteristics	population for analysis (n=5079)*	Excluded population (n=1990)**	P value&
Maternal age(years)			
Mean(SD)	29.98 (4.97)	29.13 (5.44)	<0.001
Range	15.27-46.34	15.50-43.98	
<30 years	2301 (45.3)	1053 (52.9)	<0.001
≥30 years	2778 (54.7)	937 (47.1)	
Gestational age(weeks)			
Mean(SD)	13.21(10.50-17.21) (2.00)	13.36(10.36-17.36)	0.027
Range	4.50-17.98	5.70-17.93	
<14 weeks	3235 (63.7)	1191 (59.8)	0.003
≥ 14 weeks	1844 (36.3)	799 (40.2)	
Ethnicity background			<0.001
Dutch	2838 (56.1)	652 (38.3)	
Other western	656 (13.0)	163 (9.6)	
Non-western	1567 (31.0)	887 (52.1)	
Education level			<0.001
Low	1114 (22.2)	516 (33.8)	
Mid-low	1525 (30.4)	482 (31.6)	
Mid-high	1062 (21.2)	264 (17.3)	
High	1311 (26.2)	263 (17.2)	
Marital status			<0.001
Married and living together	4432 (88.0)	1200 (81.6)	
Single	606 (12.0)	270 (18.4)	
Parity			<0.001
Nullipara	2046 (51.4)	961 (66.2)	
Multipara	3027 (48.6)	961 (33.8)	
Smoking in past three months(%)			0.20
No	3755 (74.9)	836 (74.0)	
Yes, until knowing pregnancy	657 (13.1)	137 (12.1)	
Yes, still doing so	602 (12.0)	156 (13.8)	
Alcohol use in past three months(%)			<0.001
No	2588 (51.4)	756 (38.0)	
Yes, until knowing pregnancy	1561 (31.0)	265 (23.2)	
Yes, still doing so	888 (17.6)	121 (10.6)	
Body mass index			
Mean±SD	24.36 (4.30)	25.17 (4.80)	<0.001
Range	15.60-50.61	15.70-49.10	
<25	3347 (65.9)	1125 (56.5)	<0.001
≥25	1732 (34.1)	865 (43.5)	
Uro-genital symptoms			<0.001
None symptom	681 (13.5)	555 (37.6)	
One symptom	1348 (26.7)	292 (19.8)	
Two or more symptoms	3027 (59.9)	630 (42.7)	

Table S3. Continued

Characteristics	population for analysis (n=5079)*	Excluded population (n=1990)**	P value&
Chronic non-infectious conditions			0.27
None condition	2603 (55.6)	477 (52.7)	
One condition	1276 (27.3)	260 (28.7)	
Two or more conditions	802 (17.1)	168 (18.6)	
Infectious/inflammatory conditions			<0.001
None condition	1186 (23.4)	685 (46.2)	
One condition	1287 (25.4)	253 (17.0)	
Two or more conditions	2591 (51.2)	546 (36.8)	
Headache(if yes)	3553 (71.2)	798 (78.8)	<0.001
Sleep badly, (if yes)	3690 (73.6)	768 (76.6)	0.05
Anxious or worries (if yes)	1469 (29.3)	312 (28.2)	0.48
Feeling down or depressed(if yes)	1562 (31.1)	337 (30.3)	0.61

Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continues variables. * Data was missing for ethnicity background (n=18), education level (n=67), marital status (n=41), parity (n=18), smoking during first trimester (n=65), alcohol use during first trimester (n=42), uro-genital symptoms (n=23), chronic non-infectious conditions (n=398) and infectious/ inflammatory conditions (n=15), headache (n=86), sleep badly (n=65), anxious or worried (n=61), feeling down or depressed (n=58). **Data was missing for ethnicity background (n=288), education level (n=465), marital status (n=520), parity (n=69), smoking in past three months(n=861), alcohol use in past three months (n=848), headache (n=977), sleep badly (n=987), anxious or worried (n=884), feeling down or depressed (n=879), uro-genital symptoms (n=513), chronic non-infectious conditions (n=1085) and infectious/ inflammatory conditions (n=506). &Independent-sample t tests for continuous variables and Chi-square tests for categorical variables.

Table S4. Sensitivity analysis (n=5079)

	SF-12 Physical Component Score		SF-12 Mental Component Score	
	<14 weeks	**≥14 weeks**	**<14 weeks**	**≥14 weeks**
Nausea				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	0.17 (-0.94, 1.28)	-0.49 (-1.98, 1.01)	-1.22 (-2.44, 0.01)	-0.10 (-1.79, 1.59)
Once a week	-0.05 (-1.36, 1.25)	-0.98 (-2.65, 0.68)	-0.50 (-1.93, 0.94)	0.30 (-1.58, 2.19)
Few days a week	-0.90 (-1.88, 0.08)	-0.93 (-2.21, 0.39)	**-1.12 (-2.20, -0.04)**	-0.38 (-1.88, 1.12)
Daily	**-2.97 (-4.03, -1.90)**	**-2.83 (-4.21, -1.44)**	**-2.11 (-3.28, -0.94)**	-1.31 (-2.87, 0.26)
Vomiting				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	-0.38 (-1.24, 0.48)	-0.44 (-1.64, 0.77)	-0.41 (-1.36, 0.54)	-0.97 (-2.24, 0.39)
Once a week	**-1.99 (-3.24, -0.74)**	-0.87 (-2.70, 0.97)	-1.02 (-2.40, 0.36)	-1.24 (-3.31, 0.84)
Few days a week	**-1.87 (-2.92, -0.82)**	**-1.59 (-2.94, -0.23)**	**-1.25 (-2.41, -0.10)**	-0.49 (-2.02, 1.04)
Daily	**-1.78 (-3.05, -0.53)**	**-2.45 (-4.06, -0.84)**	**-3.78 (-5.17, -2.38)**	**-2.92 (-4.74, -1.09)**
Fatigue				
Never	(Ref)	(Ref)	(Ref)	(Ref)
Less than once a week	1.96 (-0.56, 4.47)	-1.77 (-5.09, 1.56)	1.11 (-1.66, 3.88)	1.63 (-2.14, 5.39)
Once a week	1.70 (-0.71, 4.10)	-1.90 (-5.04, 1.25)	-0.17 (-2.82, 2.48)	-0.04 (-3.60, 3.58)
Few days a week	-0.63 (-2.88, 1.62)	**-5.01 (-7.97, -2.05)**	-1.08 (-3.56, 1.41)	-0.28 (-3.62, 3.07)
Daily	**-3.76 (-6.04, -1.49)**	**-8.09 (-11.07, -5.11)**	**-3.29 (-5.80, -0.79)**	-2.28 (-5.64, 1.09)
R square	0.21	0.20	0.22	0.23

Data was based on the non-imputed dataset. Bold print indicates statistical significance (p<0,05). Values represent betas (95% confidence intervals) and R squares derived from multiple linear regression analyses. The results are based on full models adjusted by all covariates (i.e. maternal age, gestational age, ethnicity background, education level, parity and marital status, smoking, alcohol use and BMI, headache, sleep badly, feel anxious or worried, feel down or depressed, uro-genital symptoms, chronic non-infectious conditions and infectious conditions).

CHAPTER 3

Trajectories and Predictors of Women's Health-Related Quality of Life during Pregnancy: A Large Longitudinal Cohort Study

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ABSTRACT

The objective of this study was to identify distinct trajectories and their predictors of health- related quality of life (HRQOL) of women during pregnancy in a prospective mother and child cohort. Analyses were based on 3936 Dutch pregnant women in Rotterdam area, the Netherlands. Information on potential predictors was collected in early pregnancy by questionnaire. Latent Class Mixture Modelling and Multinomial Logistic Regression were applied to assess the trajectory and predictors of HRQOL during pregnancy. HRQOL was measured by SF-12 in early, mid- and late pregnancy; physical and mental component summary (PCS-12/MCS-12) scores were calculated. Four physical HRQOL trajectories were identified: a healthy trajectory ('healthy') in 63.3%, consistently low ('vulnerable') in 10.8%; a small increase ('recovering') in 12.8% and a large decrease ('at risk') in 13.1%. Three mental HRQOL trajectories were identified: a healthy trajectory ('healthy') in 86.1%; a large increase ('recovering') in 7.5%; and a large decrease ('at risk') in 6.4%. Compared with healthy trajectories, the likelihood of following the 'vulnerable' physical HRQOL trajectory rather than a healthy trajectory was increased by daily fatigue(OR: 4.82[2.76, 8.40]), pelvic pain (OR:4.76[2.91, 7.78]) and back pain (OR:5.29[3.21, 8.70]); pregnancy-specific anxiety increased the likelihood of following the 'at risk' mental HRQOL trajectory (OR:7.95[4.84, 13.05]). Healthy physical and mental HRQOL trajectories during pregnancy were most common. Predictors indicative of poor HRQOL trajectories included pregnancy-related symptoms and anxiety.

INTRODUCTION

Health-related quality of life (HRQOL) is a multidimensional term referring to the health aspects of quality of life, encompassing physical and occupational functions, psychological state, social interaction and somatic sensation.[1] Women's HRQOL is acknowledged as a critical concept in the childbearing period.[2, 3] It provides a broad view of women's experience during pregnancy.

Many studies have demonstrated associated factors of HRQOL in pregnancy. For instance, young maternal age, low education, financial dissatisfaction, unplanned pregnancy, pregnancy-related symptoms, depression and domestic violence may be associated with low HRQOL;[4–9] while participation in physical activities and social support may be associated with high HRQOL.[10, 11] However, most study designs are cross-sectional, providing limited insights into HRQOL trajectories during pregnancy.

Two studies have reported changes of HRQOL during pregnancy.[12, 13] Haas et al. reported a decrease of physical functioning during pregnancy but did not conduct longitudinal analysis to identify predictors of the trend.[12] Chang et al. found that physical functioning was poorest in late pregnancy whereas mental health was poorest in early pregnancy; longitudinal analysis demonstrated that stage of pregnancy, parity, previous infertility, assisted reproduction, unplanned pregnancy and medical conditions were predictors of HRQOL during pregnancy.[13] Other longitudinal studies relevant to women's HRQOL in perinatal period only measured HRQOL in late pregnancy and then after delivery.[3, 14–16]

A population may include different subgroups of individuals sharing a common, underlying pattern of HRQOL change over time (latent class). There is very limited data on the distinct trajectories of HRQOL during pregnancy. Identifying the potential distinct trajectories of HRQOL during pregnancy and their predictors may be of benefit to health professionals and pregnant women, as well as to policy makers, so that women more likely to have greater need of healthcare services can be identified and interventions can be targeted at more specific risk factors for the poor HRQOL trajectory. To help reduce this knowledge gap, we conducted the present study by analysing data from a large, population-based prospective mother and child cohort in the Netherlands, aiming to identify distinct trajectories of HRQOL from early to late pregnancy and to assess predictors of poor HRQOL trajectories in the early phase of pregnancy. We used a latent class approach, assuming that a population of pregnant women may include different subgroups of individuals sharing a common, underlying pattern of HRQOL change over time.

METHODS

Data source

Data were obtained from the Generation R Study, a prospective population-based mother and child cohort from fetal life until adulthood. The Generation R Study has been described previ- ously in detail.[17–20] Briefly, the cohort includes 9778 (response rate 61%) mothers with a delivery date from April 2002 until January 2006 and their children, living in the Rotterdam area, the Netherlands. [19] Although when Generation R was being set up the aim was to enrol women in early pregnancy (gestational age < 18 weeks), enrolment was possible until parturi- tion. 7069 mothers were enrolled in early pregnancy, 1594 mothers in mid-pregnancy (gestational age 18–25 weeks), 216 mothers in late pregnancy (gestational age ≥ 25 weeks) and 899 mothers at parturition. Physical examinations and four postal questionnaires were planned in early, mid- and late pregnancy. The study was conducted in accordance with the World Medical Association's Helsinki guidelines and was approved by the Medical Ethical Committee of the Erasmus Medical Center, University Medical Center Rotterdam.[21] Written consent had been obtained from all of the participating women.[21]

Study population

Of the 8879 mothers enrolled in prenatal phase, we excluded pregnancies with the following outcomes: twin birth (n = 97), induced abortion (n = 29), fetal deaths before 20 weeks of gestation (n = 75), loss to follow-up pregnancy outcomes (n = 45). Additionally, we excluded mothers who were not Dutch (n = 4163) and mothers for whom data on ethnic background was missing (n = 473). Finally, we excluded mothers with missing data for three measurements of SF-12 (n = 61). This left 3936 mothers with at least one measurement of SF-12 in early, mid- and/or late pregnancy, who were eligible for analysis in the present study (see S1 Fig).

Health-related quality of life

HRQOL was measured using the SF-12 questionnaire at three waves: early, mid- and late preg- nancy. SF-12 includes 12 items regarding eight scales: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems and perceived mental health. SF-12 is a reliable and well-validated instrument to measure HRQOL and is widely used in studies with large sample sizes.[22] Some items were recoded and the raw score of each scale was transformed into 0 (the worst) to 100 (the best) before we calculated the raw Physical Component Summary (PCS-12) score and the raw Mental Component Summary (MCS-12) score. Finally the raw PCS-12and MCS-12 scores were transformed into the standard scores based on the normalised algorithms from the United States general population with the mean value of 50 and the standard deviation of 10.[23]

Potential predictors

We measured 18 variables in early pregnancy as potential predictors of women's HRQOL trajectory during pregnancy, including maternal/gestational age, education, marital status, household income, parity, planned pregnancy, body mass index (BMI), maternal smoking and drinking, pregnancy-related physical symptoms (i.e. headache, fatigue, sleeping badly, pelvic pain, back pain, nausea, vomiting) and pregnancy-specific anxiety. Information on all variables was collected by the questionnaire at intake. Education was categorised into four successive levels based on the Dutch Standard Classification of Education: high (Master's degree or PhD), mid-high (higher vocational training, Bachelor's degree), mid- low (>3 years general secondary school, intermediate vocational training) and low (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school).[24] Household income was coded as low (< 2200 euros per month) and high (≥2200 euros per month). BMI was based on women's height and weight measured at intake. Maternal smoking and alcohol use were measured with three options 'non-smokers/teetotal', 'stopped when pregnancy was known' and 'continued to smoke/drink during pregnancy'. The frequency of pregnancy-related physical symptoms (i.e. fatigue, pelvic pain, back pain, sleeping badly, nausea, vomiting, headache) was measured in early pregnancy on a five-point Likert scale: 'daily', 'a few days a week', 'once per week', 'less than once per week' or 'never'. In the multinomial logistic regression models, we lumped the frequency of symptoms into three or two categories to avoid extremely small subgroups. Pregnancy-specific anxiety was assessed by an adapted version of the Pregnancy Outcome Questionnaire in early pregnancy.[25] This version consisted of 13 items that were rated on four-point scales ranging from '0' (almost never) to '3' (almost always). Total scores were calculated by summing the item scores and dividing by the number of endorsed items.[26] In the present study, the inter- nal consistency was $\alpha = 0.67$.

Statistical analyses

We applied Latent Class Mixture Modelling (LCMM) to assess the distinct trajectories of women's HRQOL during pregnancy.[27, 28] First, a preliminary LCMM analysis was con- ducted in R Studio (R x64 3.3.2) without covariates, to identify the optimal number of latent classes (distinct trajectories) for PCS-12 scores and MCS-12 scores. A distinct trajectory consists of a group of individuals who share a common underlying pattern of HRQOL change over time.[29] First we tried one latent class, then two latent classes, and so on. The optimal number of latent classes was evaluated by model fit statistics, i.e. the Akaike information criterion (AIC) and Bayes information criterion (BIC). Lower values indicate a better-fitting model. The optimal number of latent classes is achieved if adding one latent class fails to produce a better model fit.[27]

Next, we performed a descriptive analysis of the characteristics of the study population. The chi square test for categorical variables and one-way ANOVA for continuous variables were applied to describe differences in covariates across latent classes.
Finally, all significant predictors identified in the second step were incorporated into the final model, using multinomial logistic regression. We have only included the cases with complete data on these predictor variables for regression analyses (n = 2852 and n = 2803, respectively). The optimal latent classes of PCS-12 and MCS-12, identified in the first step, were regarded as outcome variables. To explore the potential bias that may result from only including women with complete data on predictor variables, we assessed differences of characteristics between women who were included in the regression analyses and women who were excluded from the regression analyses using two independent t-tests and Chi Square tests. Additionally, we evaluated whether the HRQOL trajectories differed between the women included in the regression analyses and those excluded from the analyses using Chi Square tests.

All the analyses were conducted in SPSS 21.0 (IBM Corp., Armonk, NY, USA). Significance was indicated at $p < 0.05$.

RESULTS

The mean age of women at intake was 31 years; mean gestational age at intake was around 14 weeks. 59.8% women were in their first pregnancy; 18.7% reported unplanned pregnancy. S1 Table presents the general characteristics of the study population.

Determining the latent classes

As indicated by the model fit indices (see Table 1), four latent classes (distinct trajectories) of PCS-12 and three latent classes of MCS-12 were identified as the optimal numbers of latent classes by LCMM. S2 Table presents the means of PCS-12 and MCS-12 scores across the latent classes.

Table 1. Fit indices used to identify number of latent classes.

	Physical Component Summary		Mental Component Summary	
Number of latent class	**AIC**	**BIC**	**AIC**	**BIC**
1	71538.75	71570.14	70648.4	70679.79
2	71055.89	71112.39	69589.75	69646.25
3	70972.31	71053.92	68467.27	68548.88
4	70710.32	70817.05	68475.27	68581.99
5	70718.32	70850.16		

Figure 1 illustrates these distinct trajectories. Regarding PCS-12, the first trajectory contained more than half of the women (n = 2491, 63.3%) and represented a healthy trajectory of physical HRQOL during pregnancy (termed 'healthy'); the second trajectory, termed 'recovering', contained 505 women (12.8%) and represented an increase in physical HRQOL during pregnancy; the third trajectory (n = 516, 13.1%), termed 'at risk', was characterised by a significant decline in physical HRQOL; the fourth trajectory (n = 424, 10.8%), termed 'vulnerable', was characterised by consistently low mean scores of PCS-12 during pregnancy. Regarding MCS-12, the first trajectory contained the majority of women (n = 3388, 86.1%), representing a consistent and slight increase in means during pregnancy (termed 'healthy'); the second trajectory (n = 295, 7.5%), termed 'recovering', was characterised by a significant increase in mean scores over time; the third trajectory (n = 253, 6.4%), termed 'at risk', was characterised by a significant decrease in mean scores over time.

Predictors of the trajectory of HRQOL during pregnancy

S3 and S4 Tables show the distribution of covariates across latent classes of PCS-12 and MCS- 12 during pregnancy. Significant covariates were included in the multinomial logistic regression models by using the healthy trajectories of PCS-12 and MCS-12 as the reference. Tables 2 and 3 present Odds Ratios (ORs) for all the predictors of PCS-12 and MCS-12, respectively.

Physical HRQOL trajectories

Vulnerable trajectory vs. healthy trajectory

Women who were enrolled in the study at later gestational stage and who had higher body weights or higher levels of pregnancy-specific anxiety were more likely to follow the 'vulnerable' trajectory than those who were enrolled earlier, had lower body weight, or lower levels of anxiety. Those with more than two chronic conditions or with pregnancy-related physical symptoms (i.e. headache, fatigue, pelvic pain, back pain and nausea) also had higher odds of following a 'vulnerable' trajectory. Dose effects were observed for chronic condition, fatigue, back pain and nausea. Women who continued to smoke even though they were aware of their pregnancy were less likely to follow the 'vulnerable' trajectory (OR:0.45, 95% CI: 0.27, 0.74).

At risk trajectory vs. healthy trajectory

The odds of following the 'at risk' trajectory of physical HRQOL were significantly higher in women with one or more chronic conditions, fatigue, pelvic pain, back pain and nausea than in women without these conditions or symptoms. Higher BMI also increased this likelihood (OR:1.06, 95%CI:1.03, 1.10). However, being pregnant for the first time decreased this likelihood (OR: 0.71, 95%CI: 0.56, 0.90).

Fig.1a Means of Physical Component Summary scores during pregnancy

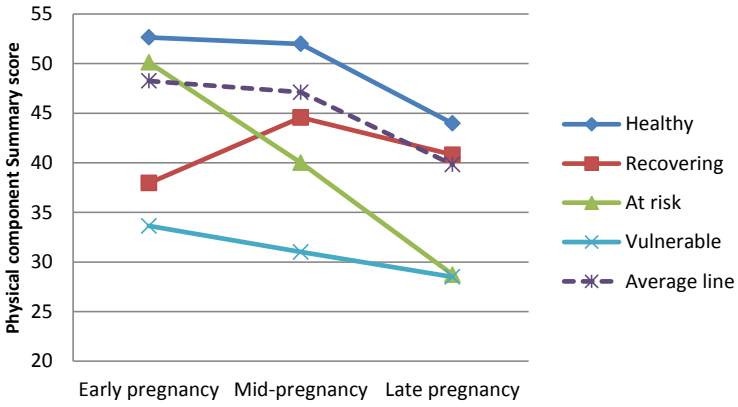

Fig. 1b Patterns of Mental Component Summary scores during pregnancy

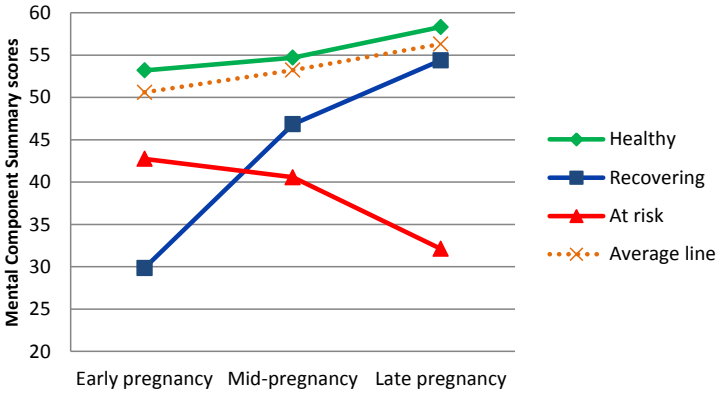

Figure 1. Trajectories of Physical/Mental Component Summary scores during pregnancy

Recovering trajectory vs. healthy trajectory

Women who continued to smoke even though they were aware of the pregnancy were less likely to follow the 'recovering' trajectory (OR:0.42, 95% CI: 0.24, 0.69). Women who were in their first pregnancy, or had pregnancy- related physical symptoms (i.e. headache, fatigue, pelvic pain, back pain and nausea) and pregnancy-specific anxiety were more likely to follow a 'recovery' trajectory.

Mental HRQOL trajectories

At risk trajectory vs. healthy trajectory

Women who were older and had higher anxiety levels were more likely to follow the 'at risk' trajectory than the 'healthy' trajectory. The most notable finding was that a one-

point change in the pregnancy-specific anxiety measure resulted in a 7.95-fold increase (OR: 7.95, 95% CI: 4.84, 13.05) in the odds of classification into the 'at risk' trajectory. Women who had a low household income, unplanned pregnancy, nausea, were sleeping badly or continued to smoke even though they were aware of their pregnancy were also more likely to follow the 'at risk' trajectory.

Recovering vs. healthy
The odds of falling into the 'recovering' trajectory were significantly higher among women who were older, stopped smoking when the pregnancy was known, presented with nausea and sleeping badly, and had higher anxiety levels. When women stopped smoking because of the awareness of pregnancy, the odds of following the recovering trajectory increased significantly (OR: 2.18, 95% CI: 1.50, 3.18).

S5 and S6 Tables show that the excluded women were younger, more often single, more often with lower educational level, lower household income, higher BMI, and they more often reported smoking during pregnancy, having chronic condition(s), having pregnancy-related physical symptoms (such as headache, fatigue, nausea, vomiting, sleeping difficulty, pelvic pain and back pain) and reported a higher pregnancy-specific anxiety ($p<0.05$). Additionally, S7 and S8 Tables demonstrated that there were no significant differences with regard to the distribution of both physical and mental HRQOL trajectories between the women included in the analyses and those excluded from the analyses ($p>0.05$).

DISCUSSION

This study identified distinct trajectories of physical and mental HRQOL during pregnancy in a large community sample of pregnant Dutch women. More than 60% of the women had a healthy physical HRQOL level, and the majority of women (86%) had healthy levels of mental HRQOL during the entire pregnancy, which is a positive finding. However, by comparison with women following the healthy trajectory, women with poor HRQOLtrajectories were found to have different patterns of characteristics. Therefore, assisting them to modify the factors leading to worse HRQOL may prevent the deterioration of HRQOL in pregnancy.

Trajectories of physical HRQOL

Nausea and fatigue are the most common somatic symptoms in early pregnancy and they may be associated with lower physical HRQOL in early pregnancy.[5, 30] So far, little is known about the long-term impact of fatigue and nausea on physical HRQOL during pregnancy. Our study showed that daily presence of fatigue and nausea in early

Table 2. Significant predictors of trajectories of Physical Component Summary scores during pregnancy (n = 2852).

Predictors	OR (95% CI)		
	Vulnerable	At risk	Recovering
Gestational age at intake	1.07 (1,03, 1,10)**	1.00 (0.97, 1.04)	1.03 (0.99, 1.06)
Maternal educational level			
High	reference	reference	reference
Mid-high	1.02 (0.70, 1.49)	1.34 (0.99, 1.82)	1.11 (0.83, 1.48)
Mid-low	1.29 (0.89, 1.87)	1.28 (0.93, 1.75)	0.94 (0.68, 1.28)
low	0.80 (0.50, 1.29)	0.69 (0.45, 1.06)	0.64 (0.41, 1.00)
Parity			
Multiparity	Reference	reference	reference
Null parity	0.87 (0.65, 1.16)	0.71 (0.56, 0,90)**	1.35 (1.05, 1.74)*
BMI at intake	1.06 (1.03, 1.10)**	1.06 (1.03, 1,10)**	1.01 (0.98, 1.04)
Maternal smoking in early pregnancy			
Non-smoker	reference	reference	reference
Smoked until pregnancy confirmed	0.82 (0.52, 1.29)	1.38 (0.98, 1.93)	0.86 (0.57, 1.31)
Continued smoking during pregnancy	0.45 (0.27, 0,74)**	1.25 (0.86, 1.82)	0.42 (0.24, 0.69)**
Chronic conditions in previous year			
None	reference	reference	reference
One	1.33 (0.98, 1.80)	1.36 (1.06, 1.76)*	0.94 (0.73, 1.22)
≥Two	1.64 (1.09, 2.48)*	1.89 (1.34, 2.69)**	1.20 (0.83, 1.74)
Headache in early pregnancy			
≤Once a week	reference	reference	reference
Daily/few days a week	2.64 (1.83, 3.80)**	1.33 (0.91, 1.94)	1.64 (1.13, 2.36)**
Fatigue in early pregnancy			
≤Once a week	reference	reference	reference
A few days a week	1.82 (1.03, 3.21)*	1.55 (1.06, 2.28)*	2.20 (1.40, 3.45)**
Daily	4.82 (2.76, 8.40)**	2.61 (1.77, 3.85)**	3.71 (2.36, 5.84)**
Pelvic pain in early pregnancy			
≤Once a week	reference	reference	reference
Daily/ a few days a week	4.76 (2.91, 7.78)**	2.86 (1.74, 4.71)**	1.82 (1.02, 3.22)*
Back pain in early pregnancy			
≤Once a week	reference	reference	reference
A few days a week	2.04 (1.40, 2.95)**	1.98 (1.44, 2.72)**	1.61 (1.14, 2.26)**
Daily	5.29 (3.21, 8.70)**	1.52 (0.85, 2.73)	3.11 (1.82, 5.30)**
Nausea in early pregnancy			
≤Once a week	reference	reference	reference
A few days a week	1.13 (0.79, 1.63)	1.07 (0.85, 1,41)	1.98 (1.46, 2.68)**
Daily	2.26 (1.62, 3.18)**	1.44 (1.08, 1.93)*	3.33 (2.46, 4.51)**
Pregnancy-specific anxiety	2.10 (1.34, 3.29)**	1.27 (0.85, 1.87)	1.64 (1.10, 2.43)*

Values are presented as ORs using the healthy trajectory as a reference category. *p<0.05, **p<0.01

Table 3. Significant predictors of trajectories of Mental Component Summary scores during pregnancy (n=2803)

Predictors	OR (95% CI)	
	At risk	Recovering
Maternal age at intake	1.06 (1.02, 1.10)**	1.06(1.02, 1.09)**
Monthly household income (€)		
>2200	reference	reference
≤2200	2.06 (1.45, 2.94)**	1.39 (0.99, 1.94)
Planned pregnancy		
Yes	reference	reference
No	2.60 (1.80, 3.74)**	1.39 (0.96, 2.02)
Maternal smoking during pregnancy		
Non-smoker	reference	reference
Smoked until pregnancy confirmed	1.40 (0.86, 2.24)	2.18 (1.50, 3.18)**
Continued to smoke during pregnancy	2.08 (1.37, 3.18)**	1.32 (0.82, 2.11)
Nausea in early pregnancy		
≤Once a week	reference	reference
A few days a week	1.32 (0.89, 1.96)	1.62 (1.12, 2.32)*
Daily	1.67(1.13, 2.46)*	2.10 (1.48, 2.99)**
Sleeping badly in early pregnancy		
≤Once a week	reference	reference
A few days a week	1.88 (1.32, 2.68)**	1.27 (0.91, 1.77)
Daily	2.52 (1.51, 4.21)**	2.06 (1.26, 3.37)**
Pregnancy-specific anxiety	7.95 (4.84, 13.05)**	5.33 (3.36, 8.43)**

Values are presented as ORs using the healthy trajectory as a reference category. *p<0.05, **p<0.01

pregnancy may be associated with experiencing a suboptimal physical HRQOL during pregnancy. Even though pelvic/back pain is not as common in early pregnancy as nausea and fatigue, their impact on physical HRQOL trajectory is significant. Therefore, management of these pregnancy-related physical symptoms from early pregnancy is warranted and may prevent physical HRQOL decreasing over time in pregnancy.

Additionally, our study indicated that higher BMI may be associated with a decrease of physical HRQOL during pregnancy. A longitudinal study in Finland yielded a similar finding: the decrease of HRQOL during pregnancy was significantly larger in the obese group.[14] Not being pregnant for the first time and presence of chronic conditions increased the likelihood of following the 'at risk' trajectory. It has been suggested that women with higher parity status may have lower physical HRQOL.[31] So far, little is known about the impact of chronic conditions during pregnancy on HRQOL. The existing studies focus on specific conditions, such as gestational diabetes, showing that pregnant women with chronic conditions may have worse HRQOL in both the short and long term.[32] Chronic conditions in pregnancy, such as high blood pressure, diabetes

and heart disease may put women at higher risk of pregnancy complications.[33] Our findings suggest that pregnancy-specific anxiety may have impacted on how women perceive their physical quality of life during pregnancy. Women with high levels of trait anxiety may be hypervigilant during pregnancy and inclined to interpret ambiguous stimuli such as inconclusive test results or bodily sensations like cramp as threatening.[34]

Unexpectedly, we found that women who continued to smoke when they were aware of the pregnancy were less likely to follow a trajectory of suboptimal physical HRQOL during pregnancy. We cannot explain this finding. We stress that in our study, physical HRQOL refers to the perceived physical quality of life rather than measured physical health. There is no doubt that smoking negatively affects mother's physical health and also fetal health.[35] We recommend further research on the association between maternal smoking and HRQOL.

Trajectories of mental HRQOL

Our study showed that various factors may predict the decrease of mental HRQOL during pregnancy, such as low household income, unplanned pregnancy, continuation with smoking and presence of nausea, sleeping badly and pregnancy-specific anxiety. Nilna et al. reported that women in early pregnancy who were financially insecure tended to have lower HRQOL than women who were financially secure, and this may influence the later health or wellbeing of mothers.[4] Unplanned pregnancy has been found to be a significant risk factor for women's mental health.[36, 37] Furthermore, the suggestion that unplanned pregnancy may affect women's mental health more than their physical health [37] is supported by our results. Our finding that nausea and sleeping badly were also associated with the decreasing of mental HRQOL is consistent with findings of previous studies.[5, 6, 30, 38] Disrupted sleep is related to peripartum mood disorders and these are associated with a significant reduction in HRQOL.[7] The most notable factor affecting mental HRQOL in our study was pregnancy-specific anxiety. It can be thought of as the interaction between a woman's general predisposition to anxious emotional states and the conditions of her pregnancy, including medically risky conditions and psychosocial factors.[34] Pregnancy-specific anxiety is related to previous negative pregnancy experience and may be associated with other psychosocial variables such as depressive symptoms, stress and low self-esteem.[39] Guardino et al. have suggested that regardless of its origin, anxiety during pregnancy poses a greater risk than medical conditions and traditional risk factors.[34]

Women who stopped smoking when they were aware of the pregnancy were also more likely to have an improving mental HRQOL during pregnancy; and women who continued smoking even though they were aware of their pregnancy were more likely to have a decreasing mental HRQOL during pregnancy. This finding is consistent with previous

studies on maternal smoking during pregnancy and women's mental health: women who smoked during pregnancy were more likely to have worse mental health and to have received treatment for mental disorders.[40, 41]

The present study has identified various patterns of predictors for physical and mental HRQOL trajectories during pregnancy which health professionals could take into account when developing targeted interventions. Two aspects in particular that should be targeted in health promotion strategies are management of pregnancy-related physical symptoms and alleviating pregnancy-specific anxiety.

Strengths and limitations

To our knowledge, this is the first study to apply LCMM to the study of HRQOL trajectories during pregnancy in a large community sample. Usually, the entire population is analysed and the average trajectory identified, which is likely to be similar to the trajectory of the majority. However, in a heterogeneous and diverse population, different trajectories may exist. LCMM enables the identification of the distinct underlying trajectories. A second strength is that the present study is a prospective study in a large population-based community sample of 3936 women, and information was available on a comprehensive set of covariates. This enabled the identification of clearly distinct trajectories and of predictors for each trajectory.

Several limitations should be taken into account. As is to be expected in a prospective cohort study, there are several bias should be considered. The overall response rate in the entire Generation R Study was 61%.[19] Differences between women who accepted the invitation to participate and those who did not may lead to non-response bias. In general, the women participating in the Generation R Study are relatively healthier than the women in the source population.[20] Moreover, to assess the predictors of suboptimal HRQOL trajectories, we excluded study participants with missing values on the potential predicting variables from regression analyses. Compared with the included women, the excluded women were younger, more often single, more often with lower educational level, lower household income, higher BMI, and they more often reported smoking during pregnancy, having chronic condition(s), having pregnancy-related physical symptoms and reported a higher level of pregnancy-specific anxiety. Therefore, our results should be interpreted with caution. There were no significant differences regarding physical and mental HRQOL trajectories between the included women and the excluded women. In the present study, we only included women with a Dutch ethnic background in the analyses since we aimed for a more homogenous population to assess the trajectories of HRQOL for the first time. Therefore, the results in non-Dutch populations are unknown. Now that we are able to identify trajectories, we recommend repeating this study in large study populations with heterogeneous backgrounds to confirm or reject our findings.

CONCLUSIONS

Physical and mental HRQOL trajectories during pregnancy differ, with the most common being healthy trajectories. The predictors we identified as being indicative of poor HRQOL trajectories included pregnancy-related symptoms and anxiety. Clinicians and other health professionals should recognise the predictors of adverse HRQOL trajectories during pregnancy, and collaborate across disciplines to address them in an early stage to prevent disparities in HRQOL becoming established.

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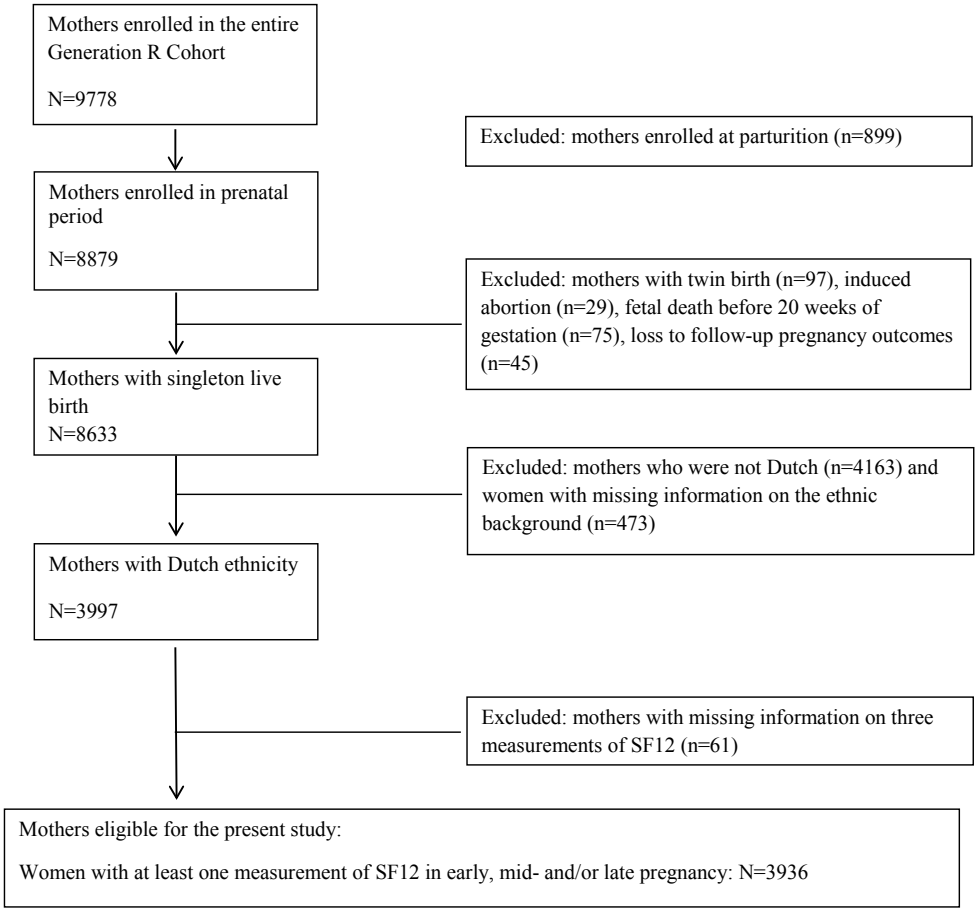
REFERENCES

1. Schipper H, Clinch JJ, Olweny CLM (1996) Quality of life studies: definitions and conceptual issues, In Spilker B (ed) Quality of Life and Pharmacoeconomics in Clinical Trials. Lippincott-Raven Publishers: Philadelphia. PP 11–23.
2. Jomeen J, Martin C. Perinatal quality of life: is it important for childbearing women? Pract Midwife. 2012; 15(4):30–4. PMID: 22662538.
3. Emmanuel EN, Sun J. Health related quality of life across the perinatal period among Australian women. Journal of clinical nursing. 2014; 23(11–12):1611–9. https://doi.org/10.1111/jocn.12265 PMID: 23750859
4. Calou CGP, Pinheiro AKB, Castro RCMB, de Oliveira MF, de Souza Aquino P, Antezana FJ. Health related quality of life of pregnant women and associated factors: An integrative review. Health. 2014; 6 (18):2375.
5. Bai G, Korfage IJ, Hafkamp-de Groen E, Jaddoe VWV, Mautner E, Raat H. Associations between Nausea, Vomiting, Fatigue and Health-Related Quality of Life of Women in Early Pregnancy: The Generation R Study. PloS one. 2016; 11(11):e0166133. https://doi.org/10.1371/journal.pone.0166133 PMID: 27814390
6. Tsai S-Y, Lee P-L, Lin J-W, Lee C-N. Cross-sectional and longitudinal associations between sleep and health-related quality of life in pregnant women: a prospective observational study. International journal of nursing studies. 2016; 56:45–53. https://doi.org/10.1016/j.ijnurstu.2016.01.001 PMID: 26803171
7. Da Costa D, Dritsa M, Verreault N, Balaa C, Kudzman J, Khalife S. Sleep problems and depressed mood negatively impact health-related quality of life during pregnancy. Arch Womens Ment Health. 2010; 13(3):249–57. https://doi.org/10.1007/s00737-009-0104-3 PMID: 19728037.
8. Tavoli Z, Tavoli A, Amirpour R, Hosseini R, Montazeri A. Quality of life in women who were exposed to domestic violence during pregnancy. BMC Pregnancy Childbirth. 2016; 16:19. https://doi.org/10.1186/ s12884-016-0810-6 PMID: 26813894.
9. Coban A, Arslan GG, Colakfakioglu A, Sirlan A. Impact on quality of life and physical ability of preg- nancy-related back pain in the third trimester of pregnancy. J Pak Med Assoc. 2011; 61(11):1122–4. PMID: 22125993.
10. Kolu P, Raitanen J, Luoto R. Physical activity and health-related quality of life during pregnancy: a secondary analysis of a cluster-randomised trial. Matern Child Health J. 2014; 18(9):2098–105. https://doi. org/10.1007/s10995-014-1457-4 PMID: 24585400.
11. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol. 2011; 31 (1):10–20. https://doi.org/10.1038/jp.2010.54 PMID: 20410906.
12. Haas JS, Jackson RA, Fuentes-Afflick E, Stewart AL, Dean ML, Brawarsky P, et al. Changes in the health status of women during and after pregnancy. Journal of general internal medicine. 2005; 20 (1):45–51. https://doi.org/10.1111/j.1525-1497.2004.40097.x PMID: 15693927
13. Chang SR, Chen KH, Lin MI, Lin HH, Huang LH, Lin WA. A repeated measures study of changes in health-related quality of life during pregnancy and the relationship with obstetric factors. Journal of advanced nursing. 2014; 70(10):2245–56. https://doi.org/10.1111/jan.12374 PMID: 24617652
14. Sahrakorpi N, Koivusalo SB, Stach-Lempinen B, Eriksson JG, Kautiainen H, Roine R. " The Burden of Pregnancy"; heavier for the heaviest? The changes in Health Related Quality of Life (HRQoL) assessed by the 15D-instrument during pregnancy and postpartum in different body mass index groups: a longitu- dinal survey. Acta obstetricia et gynecologica Scandinavica. 2016.
15. Setse R, Grogan R, Pham L, Cooper LA, Strobino D, Powe NR, et al. Longitudinal Study of Depressive Symptoms and Health-Related Quality of Life During Pregnancy and After

Delivery: The Health Status in Pregnancy (HIP) Study. Maternal and Child Health Journal. 2009; 13(5):577–87. https://doi.org/10. 1007/s10995-008-0392-7 PMID: 18931832
16. Dalfrà MG, Nicolucci A, Bisson T, Bonsembiante B, Lapolla A. Quality of life in pregnancy and post-partum: a study in diabetic patients. Quality of Life Research. 2012; 21(2):291–8. https://doi.org/10.1007/ s11136-011-9940-5 PMID: 21633879
17. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. Eur J Epidemiol. 2012; 27(9):739–56. https:// doi.org/10.1007/s10654-012-9735-1 PMID: 23086283.
18. Jaddoe VW, Bakker R, van Duijn CM, van der Heijden AJ, Lindemans J, Mackenbach JP, et al. The Generation R Study Biobank: a resource for epidemiological studies in children and their parents. Eur J Epidemiol. 2007; 22(12):917–23. https://doi.org/10.1007/s10654-007-9209-z PMID: 18095172.
19. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006; 21(6):475–84. https:// doi.org/10.1007/s10654- 006-9022-0 PMID: 16826450.
20. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004; 18(1):61–72. PMID: 14738548.
21. General Assembly of the World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent. 2014; 81(3):14–8. PMID: 25951678.
22. Ware J Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and pre- liminary tests of reliability and validity. Med Care. 1996; 34(3):220–33. PMID: 8628042.
23. Ware JE, Kosinski M, Keller SD, QualityMetric I, New England Medical Center H, Health Assessment L. SF-12: how to score the SF-12 physical and mental health summary scales. Lincoln, R.I.; Boston, Mass.: QualityMetric Inc.; Health Assessment Lab; 2002.
24. Statistics Netherlands. The Dutch Standard Classification of Education, SOI 2006. Voorburg/ Heerlen; 2008
25. Trautman PD, Meyer-Bahlburg HF, Postelnek J, New MI. Effects of early prenatal dexamethasone on the cognitive and behavioral development of young children: results of a pilot study. Psychoneuroendo- crinology. 1995; 20(4):439–49. PMID: 8532827.
26. Henrichs J, Schenk JJ, Schmidt HG, Velders FP, Hofman A, Jaddoe VWV, et al. Maternal pre- and post- natal anxiety and infant temperament. The generation R study. Infant and Child Development. 2009; 18 (6):556–72.
27. Nylund KL, Asparouhov T, Muthe´n BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Structural equation modeling. 2007; 14 (4):535–69.
28. Ram N, Grimm KJ. Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. International journal of behavioral development. 2009; 33 (6):565–76. https://doi.org/10.1177/0165025409343765 PMC3718544. PMID: 23885133
29. Muthe´n BO. Latent variable analysis: growth mixture modeling and related techniques for longitudinal data. In: Kaplan D, ed. Handbook of quantitative methodology for the social science. Newbury Park, CA: Sage; 2004.p. 345–68.
30. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? BJOG: An International Journal of Obstetrics & Gynaecology. 2008; 115(12):1484–93.
31. Singh S, Kaur R, Singh S. Relationship of Parity and Health Related Quality of Life among women. 2015.

32. Marchetti D, Carrozzino D, Fraticelli F, Fulcheri M, Vitacolonna E. Quality of Life in Women with Gestational Diabetes Mellitus: A Systematic Review. J Diabetes Res. 2017; 2017:7058082. https://doi.org/10. 1155/2017/7058082 PMID: 28326332.
33. Maternal Health. Centers for Disease Control and Prevention. Centers for Disease Control and Preven- tion; 2016. Available: https://www.cdc.gov/chronicdisease/resources/publications/aag/maternal.htm
34. Guardino CM, Schetter CD. Understanding Pregnancy Anxiety: Concepts, Correlates, and Conse- quences. Zero to Three. 2014; 34(4):12–21.
35. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal charac- teristics, and pregnancy outcomes. Nicotine Tob Res. 2004; 6 Suppl 2:S125–40. https://doi.org/10. 1080/14622200410001669187 PMID: 15203816.
36. Lau Y, Yin L. Maternal, obstetric variables, perceived stress and health-related quality of life among pregnant women in Macao, China. Midwifery. 2011; 27(5):668–73. https://doi.org/10.1016/j.midw.2010. 02.008 PMID: 20466467.
37. Ali A. Relationship between Unwanted Pregnancy and Health-Related Quality of Life in Pregnant Women. Journal of the College of Physicians and Surgeons—Pakistan: JCPSP. 2016; 26(6):507. PMID: 27353990
38. Effati-Daryani F, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S, Shiri-Sarand F, Zarei S. Sleep quality and its relationship with quality of life in Iranian pregnant women. Int J Nurs Pract. 2017. https://doi.org/10.1111/ijn.12518 PMID: 28120358.
39. Nilsson C, Lundgren I, Karlstro¨ m A, Hildingsson I. Self reported fear of childbirth and its association with women's birth experience and mode of delivery: A longitudinal population-based study. Women and Birth. 2012; 25(3):114–21. https://doi.org/10.1016/j.wombi.2011.06.001 PMID: 21764400
40. Oskarsdottir GN, Sigurdsson H, Gudmundsson KG. Smoking during pregnancy: A population-based study. Scand J Public Health. 2017; 45(1):10–5. https://doi.org/10.1177/1403494816676034 PMID: 27799421.
41. Holtrop JS, Meghea C, Raffo JE, Biery L, Chartkoff SB, Roman L. Smoking among pregnant women with Medicaid insurance: are mental health factors related? Matern Child Health J. 2010; 14(6):971–7. https://doi.org/10.1007/s10995-009-0530-x PMID: 19838777.

SUPPLEMENTARY



S1 Figure. Flow chart of the study population

S1 Table. Characteristics of the study population (n=3936)

Characteristics	values
Maternal age at intake	31.29±4.50
Gestational age at intake	14.50±3.72
Maternal educational level	
High	1285 (32.6)
Mid-high	962 (24.4)
Mid-low	1004 (25.5)
Low	637 (16.2)
missing	48
Marital status	
Married/cohabiting	3542 (92.5)
Single	287 (7.5)
missing	107
Parity	
Nullpara	2344 (59.8)
Multipara	1581 (40.3)
missing	11
Monthly household income (€)	
≤2200	927 (26.6)
>2200	2563 (73.4)
missing	446
Planned pregnancy	
No	690 (18.7)
Yes	3002 (81.3)
missing	244
BMI at intake	24.33±4.14
missing	18
Maternal smoking in early pregnancy	
Non-smoker	2666 (74.6)
Smoked until pregnancy confirmed	452 (12.5)
Continued smoking in pregnancy	467 (12.9)
missing	318
Maternal drinking in early pregnancy	
Teetotal during pregnancy	1496 (41.2)
Drank until pregnancy confirmed	1262 (32.1)
Continued drinking in pregnancy	870 (24.0)
missing	308
Chronic conditions in the previous year	
None	1950 (55.7)
One	1102 (31.5)
≥ Two	449 (12.8)
missing	435
Headache	
Daily/ Few days a week	428 (12.0)
≤ Once a week	3140 (88.0)
missing	368

S1 Table. Continued

Characteristics	values
Fatigue	
Daily	1517 (42.1)
Few days a week	1497 (41.6)
≤ Once a week	588 (16.3)
missing	334
Sleeping badly	
Daily	254 (7.1)
Few days a week	861 (24.1)
≤ Once a week	2457 (68.8)
missing	364
Pelvic pain	
Daily/ Few days a week	209 (6.1)
≤ Once a week	3379 (94.2)
missing	348
Back pain	
Daily	221 (6.1)
Few days a week	525 (14.6)
≤ Once a week	2853 (79.3)
missing	337
Nausea	
Daily	1008 (28.0)
Few days a week	1022 (28.3)
≤ Once a week	1576 (43.7)
Missing	330
Vomiting	
Daily	178 (5.0)
Few days a week	335 (9.3)
≤ Once a week	3076 (85.7)
missing	347
Pregnancy-specific anxiety	0.76±0.32
missing	371

*Values in this table are means, standard deviations, numbers and percentages.

S2 Table. Comparisons of the mean scores of PCS-12 and MCS-12 in early, mid- and late pregnancy across trajectories

	early pregnancy (n=3391)	mid-pregnancy (n=3429)	late pregnancy (n=3368)	P value (early vs. mid-)	P value (mid- vs. late)
PCS-12					
Healthy	52.64 (5.09)	51.99 (5.27)	43.97 (5.80)	<0.001	<0.001
Number (%)	2127 (62.7)	2149 (62.7)	2118 (62.9)		
Recovering	37.96 (3.87)	44.56 (6.32)	40.81 (6.21)	<0.001	<0.001
Number(%)	478 (14.1)	439 (12.8)	426 (12.6)		
At risk	50.12 (5.18)	40.01 (6.88)	28.72 (5.81)	<0.001	<0.001
Number(%)	430 (12.7)	462 (13.5)	475 (14.1)		
Vulnerable	33.63 (6.26)	31.01 (5.69)	28.50 (6.42)	0.76	<0.001
Number(%)	356 (10.5)	379 (11.5)	349 (10.4)		
MCS-12					
Healthy	53.19 (5.32)	54.69 (5.72)	58.31 (5.19)	<0.001	<0.001
Number(%)	2897 (85.4)	2972 (86.7)	2910 (86.4)		
Recovering	29.85 (5.73)	46.83 (11.29)	54.39 (6.93)	<0.001	<0.001
Number(%)	282 (8.3)	231 (6.7)	234 (6.9)		
At risk	47.74 (11.56)	40.56 (11.65)	32.12 (5.97)	<0.001	<0.001
Number(%)	212 (6.2)	226 (6.6)	224 (6.6)		

S3 Table. Comparisons of the characteristics of women across physical HRQOL trajectories

	Healthy	Recovering	At risk	Vulnerable	P value
Maternal age at intake (years)	31.45±4.39	31.13±4.57	30.85±4.71	31.03±4.75	0.016
Gestational age at intake (weeks)	14.40±3.59	14.53±3.66	14.34±3.52	15.22±4.60	<0.001
Maternal educational level					<0.001
High	879 (35.7)	170 (33.7)	135 (26.5)	101 (24.3)	
Mid-high	602 (24.5)	135 (26.8)	135 (26.5)	90 (21.6)	
Mid-low	576 (23.4)	124 (24.6)	161 (31.6)	143 (34.4)	
Low	402 (16.3)	75 (14.9)	78 (15.3)	82 (19.7)	
Marital status					0.09
married/cohabiting	2229 (92.2)	467 (93.6)	472 (94.6)	374 (90.6)	
Single	189 (7.8)	32 (6.4)	27 (5.4)	39 (9.4)	
Parity					<0.001
nullpara	1503 (60.5)	332 (65.9)	285 (55.3)	224 (53.0)	
multipara	980 (39.50)	172 (34.1)	230 (44.7)	199 (47.0)	
Monthly household income (€)					<0.001
≤2200	521 (23.6)	113 (25.5)	149 (31.4)	144 (39.7)	
>2200	1688 (76.4)	330 (74.5)	326 (68.6)	219 (60.3)	
Planned pregnancy					0.27
No	425 (18.3)	83 (16.8)	99 (20.6)	83 (21.0)	
Yes	1898 (81.7)	410 (83.2)	382 (79.4)	312 (79.0)	
BMI at intake	23.98±3.81	24.27±4.25	25.16±4.38	25.49±5.11	<0.001
Maternal smoking in early pregnancy					0.003
Non-smoker	1690 (74.1)	395 (81.3)	324 (69.8)	290 (74.9)	
Smoked until pregnancy confirmed	286 (12.5)	50 (10.3)	73 (15.7)	43 (11.1)	
Continued smoking in pregnancy	305 (13.4)	41 (8.4)	67 (14.4)	54 (14.0)	
Maternal drinking during pregnancy					<0.001
Teetotal	870 (38.0)	227 (46.7)	207 (44.4)	192 (49.5)	
Drank until pregnancy confirmed	814 (35.6)	169 (34.8)	151 (32.4)	128 (33.0)	
Continued drinking in pregnancy	604 (26.4)	90 (18.5)	108 (23.2)	68 (17.5)	
Chronic conditions in previous year					<0.001
None	1336 (60.4)	250 (53.1)	212 (47.3)	152 (41.2)	
One	660 (29.8)	151 (32.1)	156 (34.8)	135 (36.6)	
≥ two	217 (9.8)	70 (14.9)	80 (17.9)	82 (22.2)	
Headache					<0.001
Daily/ a few days a week	191 (8.5)	76 (15.8)	63 (13.8)	98 (25.7)	
≤ once a week	2059 (91.5)	405 (84.2)	393 (86.2)	283 (74.3)	
Sleeping badly					<0.001
Daily	108 (4.8)	42 (8.8)	35 (7.6)	69 (17.9)	
A few days a week	478 (21.3)	136 (28.6)	126 (27.3)	121 (31.4)	
≤ once a week	1663 (73.9)	298 (62.6)	301 (65.2)	195 (50.6)	
Fatigue					<0.001
Daily	743 (32.7)	279 (57.6)	236 (51.1)	259 (66.9)	
A few days a week	1039 (45.8)	175 (36.2)	179 (38.7)	104 (26.9)	
≤ once a week	487 (21.5)	30 (6.2)	487 (21.5)	47 (10.2)	

S3 Table. Continued

	Healthy	Recovering	At risk	Vulnerable	P value
Pelvic pain					<0.001
Daily/ a few days a week	57 (2.5)	30 (6.2)	47 (10.2)	75 (19.9)	
≤ once a week	2211 (97.5)	451 (93.8)	418 (89.8)	302 (80.1)	
Back pain					<0.001
Daily	70 (3.1)	43 (8.9)	27 (5.8)	81 (21.1)	
A few days a week	245 (10.8)	88 (18.2)	105 (22.7)	87 (22.7)	
≤ once a week	1956 (86.1)	352 (72.9)	330 (71.4)	215 (56.1)	
Nausea					
Daily	476 (21.0)	215 (44.3)	142 (30.7)	175 (45.1)	
A few days a week	645 (28.4)	146 (30.1)	134 (29.0)	97 (25.0)	
≤ once a week	1150 (50.6)	124 (25.6)	186 (40.3)	116 (29.9)	
Vomiting					<0.001
Daily	75 (3.3)	40 (8.2)	21 (4.6)	42 (11.0)	
A few days a week	173 (7.6)	70 (14.4)	40 (8.8)	52 (13.6)	
≤ once a week	2019 (89.1)	375 (77.4)	394 (86.6)	288 (75.4)	
Pregnancy-specific anxiety	0.73±0.32	0.81±0.32	0.78±0.31	0.86±0.33	<0.001

S4 Table. Comparisons of the characteristics of women across mental HRQOL trajectories

	Healthy	Recovering	At risk	P value
Maternal age at intake (years)	31.35±4.41	30.85±4.66	30.85±5.35	0.05
Gestational age at intake (weeks)	14.50±3.74	14.38±3.72	14.71±3.64	0.56
Maternal educational level				<0.001
High	1161 (34.7)	79 (26.8)	45 (18.1)	
Mid-high	818 (24.5)	82 (27.8)	62 (25.0)	
Mid-low	858 (25.7)	78 (26.4)	68 (27.4)	
Low	508 (15.2)	56 (19.0)	73 (29.4)	
Marital status				<0.001
Married/cohabiting	3093 (94.0)	256 (87.4)	193 (79.1)	
Single	199 (6.0)	37 (12.6)	51 (20.9)	
Parity				0.12
Nullpara	2001 (59.2)	193 (65.4)	150 (59.5)	
Multipara	1377 (40.8)	102 (34.6)	102 (40.5)	
Monthly household income (€)				<0.001
≤2200	724 (24.0)	87 (35.1)	116 (51.1)	
>2200	2291 (76.0)	161 (64.9)	111 (48.9)	
Planned pregnancy				<0.001
No	516 (16.3)	80 (27.8)	94 (39.7)	
Yes	2651 (83.7)	208 (72.2)	143 (60.3)	
BMI at intake	24.29±4.09	24.49±4.44	24.75±4.40	0.20
Maternal smoking in early pregnancy				<0.001
Non-smoker	2392 (77.2)	175 (60.6)	132 (57.6)	
Smoked until pregnancy confirmed	360 (11.6)	61 (21.1)	31 (13.5)	
Continued smoking in pregnancy	348 (11.2)	53 (18.3)	66 (28.8)	
Maternal drinking in early pregnancy				0.40
Teetotal	1290 (41.5)	105 (36.2)	101 (43.7)	
Drank until pregnancy confirmed	1073 (34.5)	113 (39.0)	76 (32.9)	
Continued drinking in pregnancy	744 (23.9)	72 (24.8)	54 (23.4)	
Chronic conditions				0.003
None	1706 (56.8)	137 (49.8)	107 (47.8)	
One	927 (30.9)	101 (36.7)	74 (33.0)	
≥ Two	369 (12.3)	37 (13.5)	43 (19.2)	
Headache				<0.001
Daily/a few days a week	319 (10.4)	57 (20.2)	52 (22.6)	
≤ Once a week	2737 (89.6)	225 (79.8)	178 (77.4)	
Fatigue				<0.001
Daily	1219 (39.5)	162 (56.6)	136 (59.4)	
Few days a week	1334 (43.2)	94 (32.9)	69 (30.1)	
≤ once a week	534 (17.3)	30 (10.5)	24 (10.5)	
sleeping badly				<0.001
Daily	171 (5.6)	44 (7.1)	39 (17.1)	
Few days a week	695 (22.7)	87 (30.4)	79 (34.6)	
≤ Once a week	2192 (71.7)	155 (54.2)	110 (48.2)	
Pelvic pain				0.024
Daily/a few days a week	167 (5.4)	20 (7.0)	22 (9.6)	
≤ Once a week	2905 (94.6)	266 (93.0)	208 (90.4)	

S4 Table. Continued

	Healthy	Recovering	At risk	P value
Back pain				<0.001
Daily	160 (5.2)	25 (8.7)	36 (15.7)	
Few days a week	431 (14.0)	49 (17.0)	45 (19.7)	
≤ Once a week	2491 (80.8)	214 (74.3)	148 (64.6)	
Nausea				<0.001
Daily	806 (26.1)	117 (40.8)	85 (37.0)	
Few days a week	880 (28.5)	80 (27.9)	65 (27.0)	
≤ Once a week	1403 (45.4)	90 (31.4)	83 (36.1)	
Vomiting				<0.001
Daily	132 (4.3)	23 (8.0)	23 (10.0)	
Few days a week	267 (8.7)	40 (14.0)	28 (12.2)	
≤ Once a week	2675 (87.0)	223 (78.0)	178 (77.7)	
Pregnancy-specific anxiety	0.73 ±0.30	0.93 ±0.38	0.96 ±0.35	<0.001

S5 Table. Comparisons of the characteristics of women included in analyses (n=2852) and women excluded from analyses regarding predictors for physical HRQOL trajectories (n=1084)

	Women included in analyses (n=2852)	Women excluded from analyses (n=1084)	P value
Maternal age at intake	31.5 (4.3)	30.8 (5.0)	<0.001
Gestational age at intake	14.5 (3.7)	14.4 (3.8)	0.45
Maternal educational level			
High	1023 (35.9)	262 (25.3)	<0.001
Mid-high	760 (26.6)	202 (19.5)	
Mid-low	701 (24.6)	302 (29.2)	
Low	368 (12.9)	269 (26.0)	
missing	0	48	
Parity			
Nullpara	1710 (60.0)	634(59.1)	0.62
Multipara	1142 (40.0)	439 (40.9)	
missing	0	11	
Monthly household income (€)			
≤2200	723 (25.4)	204 (32.0)	0.006
>2200	2129 (74.6)	434 (68.0)	
missing	0	446	
BMI at intake	24.21 (3.95)	24.68 (4.60)	0.002
missing	0	18	
Maternal smoking in early pregnancy			
Non-smoker	2205 (77.3)	494 (64.5)	<0.001
Smoked until pregnancy confirmed	336 (11.8)	116 (15.1)	
Continued smoking in pregnancy	311 (10.9)	156 (20.4)	
missing	0	318	
Maternal drinking in early pregnancy			
Teetotal during pregnancy	1110 (38.9)	386 (49.7)	<0.001
Drank until pregnancy confirmed	1008 (35.6)	254 (32.7)	
Continued drinking in pregnancy	734 (25.7)	136 (17.5)	
Missing	0	308	

S5 Table. Continued

	Women included in analyses (n=2852)	Women excluded from analyses (n=1084)	P value
Chronic conditions in the previous year			
None	1593 (55.9)	357 (55.0)	<0.001
One	922 (32.3)	180 (27.7)	
≥ Two	337 (11.8)	112 (17.3)	
missing	0	435	
Headache			
Daily/ Few days a week	310 (10.9)	118 (16.5)	<0.001
≤ Once a week	2542 (89.1)	598 (83.5)	
missing	0	368	
Fatigue			
Daily	1172 (41.1)	345(46.0)	0.02
Few days a week	1194 (41.9)	303 (40.4)	
≤ Once a week	486 (17.0)	102 (13.6)	
missing	0	334	
Sleeping badly			
Daily	171 (6.0)	83 (11.5)	<0.001
Few days a week	670 (23.5)	191 (26.5)	
≤ Once a week	2011 (70.5)	446 (61.9)	
missing	0	364	
Pelvic pain			
Daily/ Few days a week	160 (5.6)	49 (6.7)	0.28
≤ Once a week	2692 (94.4)	687 (93.3)	
missing	0	348	
Back pain			
Daily	156 (5.5)	65 (8.7)	<0.001
Few days a week	378 (13.3)	147 (19.7)	
≤ Once a week	2318 (81.3)	535 (71.6)	
missing	0	337	
Nausea			
Daily	760 (26.6)	248 (32.9)	<0.001
Few days a week	828 (29.0)	194 (25.7)	
≤ Once a week	1264 (44.3)	312 (41.4)	
missing	0	330	
Vomiting			
Daily	115 (4.0)	63 (8.5)	<0.001
Few days a week	259 (9.1)	76 (10.3)	
≤ Once a week	2478 (86.9)	598 (81.1)	
missing	0	347	
Pregnancy-specific anxiety	0.75 (0.31)	0.81 (0.35)	<0.001
missing	0	371	

S6 Table. Comparisons of the characteristics of women included in analyses (n=2803) and women excluded from analyses regarding predictors for mental HRQOL trajectories (n=1133)

	Women included in analyses (n=2803)	Women excluded from analyses (n=1133)	P value
Maternal age at intake	31.5 (4.3)	30.9 (4.9)	<0.001
Maternal educational level			
High	1010 (36.0)	276 (25.4)	<0.001
Mid-high	741 (26.4)	313 (28.8)	
Mid-low	691 (24.7)	221 (20.4)	
Low	361 (12.9)	275 (25.3)	
missing	0	48	
Marital status			
Married/cohabiting	2625 (93.6)	917 (89.4)	<0.001
Single	178 (6.4)	109 (10.6)	
missing	0	107	
Monthly household income (€)			
≤2200	711(25.4)	216 (31.4)	0.001
>2200	2092 (74.6)	471 (68.6)	
missing	0	446	
Planned pregnancy			
No	474 (16.9)	216 (24.3)	0.002
Yes	2329 (83.1)	673 (75.7)	
missing	0	244	
Maternal smoking in early pregnancy			
Non-smoker	2435 (86.9)	533 (65.4)	<0.001
Smoked until pregnancy confirmed	332 (11.8)	120 (14.7)	
Continued smoking in pregnancy	305 (10.9)	162 (19.9)	
missing	0	318	
Chronic conditions in the previous year			
None	1568 (55.9)	382 (33.7)	0.004
One	901 (32.1)	201 (28.8)	
≥ Two	334 (11.9)	115 (16.5)	
missing	0	435	
Headache			
Daily/ Few days a week	302 (10.8)	126 (16.5)	<0.001
≤ Once a week	2501 (89.2)	639 (83.5)	
missing	0	368	
Fatigue			
Daily	1152 (41.1)	365 (45.7)	0.04
Few days a week	1176 (42.0)	321 (40.2)	
≤ Once a week	475 (16.9)	113 (14.1)	
missing	0	334	
Sleeping badly			
Daily	167 (6.0)	87 (11.3)	<0.001
Few days a week	659 (23.5)	202 (26.3)	
≤ Once a week	1977 (70.5)	480 (62.4)	
missing	0	364	

S6 Table. Continued

	Women included in analyses (n=2803)	Women excluded from analyses (n=1133)	P value
Pelvic pain			
Daily/ Few days a week	157 (5.6)	52 (6.6)	0.28
≤ Once a week	2646 (94.4)	733 (93.4)	
missing	0	348	
Back pain			
Daily	155 (5.5)	66 (8.3)	<0.001
Few days a week	374 (13.3)	151 (19.0)	
≤ Once a week	2274 (81.1)	579 (72.7)	
missing	0	337	
Nausea			
Daily	752 (26.8)	256 (31.9)	0.01
Few days a week	816 (29.1)	206 (25.7)	
≤ Once a week	1235 (44.1)	341 (42.5)	
missing	0	330	
Vomiting			
Daily	114 (4.1)	64 (8.1)	<0.001
Few days a week	254 (9.1)	81 (10.3)	
≤ Once a week	2435 (86.8)	641 (81.6)	
missing	0	347	
Pregnancy-specific anxiety	0.75 (0.31)	0.80 (0.34)	<0.001
missing	0	371	

S7 Table. Numbers and percentages of physical HRQOL among women included in the analyses (n=2852) and women excluded from analyses (n=1084) regarding predictors of physical HRQOL trajectories

Physical HRQOL trajectories	Women included in analyses (n=2852)	Women excluded from analyses (n=1084)	P value
Healthy	1813 (63.6)	678 (62.5)	0.18
Recovering	375 (13.1)	130 (12.0)	
At risk	375 (13.1)	141 (13.0)	
Vulnerable	289 (10.1)	135 (12.5)	

S8 Table. Numbers and percentages of mental HRQOL among women included in the analyses (n=2803) and women excluded from analyses (n=1133) regarding predictors of physical HRQOL trajectories

Mental HRQOL trajectories	Women included in analyses (n=2803)	Women excluded in analyses (n=1133)	P value
Healthy	2406 (85.8)	982 (86.7)	0.80
Recovering	214 (7.6)	81 (7.1)	
At risk	183 (6.5)	70 (6.2)	

CHAPTER 4

Determinants of Maternal Postpartum Health-Related Quality of Life: The Generation R Study

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ABSTRACT

Aims

Having good health-related quality of life (HRQOL) is essential, also for women after delivery. However, little is known about its determinants. We aimed to identify the determinants of postpartum HRQOL in a large community sample in the Netherlands.

Methods

4312 women were included in the present study. At two months postpartum HRQOL was assessed by 12-item Short Form Survey (SF-12); Physical (PCS-12) and Mental Component Summary (MCS-12) scores were calculated. Information on 27 potential determinants was collected through questionnaires and medical records. Multivariate linear regression models were applied to assess significant determinants of PCS-12 and MCS-12.

Results

The multivariate regression models showed that older maternal age, shorter time after delivery, elective/emergency cesarean delivery, loss of energy, maternal psychopathology, and the hospital admission of the baby were significantly associated with worse physical HRQOL ($p<0.05$); older maternal age, non-western background, low household income, loss of energy and maternal psychopathology were significantly associated with worse mental HRQOL($p<0.05$).

Conclusions

After assessing an extensive set of determinants of maternal postpartum HRQOL in a large general population in the Netherlands. We found multiple factors to be associated with postpartum physical and mental HRQOL. In particular, maternal psychopathology was profoundly associated with postpartum mental HRQOL. These women may need support. We therefore call for awareness among health care professionals.

INTRODUCTION

Every minute about 255 infants born are born worldwide.(1) The birth of a child may impact women's physical, psychological and social health. In the past decades, the focus of maternity care in the developed countries has expanded from the traditional goal of reducing mortality and morbidity to broader aims, such as improving health-related quality of life (HRQOL).(2) HRQOL is a multidimensional concept that incorporates physical, psychological and social domains of health,(3) which is in accordance with the definition of health by the World Health Organization as 'not merely the absence of disease or infirmity but a state of complete physical, mental and social well-being'.

Many factors have been found to be associated with impaired maternal HRQOL after delivery, such as urinary incontinence and being HIV positive,(4) multiparity, more gestational weight gain, (5) severe preeclampsia,(6) difficulties in breastfeeding, postpartum psychological disorders, low social support,(7) fatigue,(8, 9) less personal time,(9) gestational hypertension, delivery in an academic hospital and neonatal admission.(10) Most findings mentioned above were based on a relatively small sample size, and most studies focused on limited numbers of determinants. One study reported findings based on a relatively big sample size (n=2310), but these findings considered women with pregnancy complications.(10) Therefore, our study aimed to assess an extensive set of potential determinants of maternal HRQOL around two months postpartum in a large community sample.

METHODS

Data Source

The present study was embedded in the Generation R Study, a prospective population-based mother- and child cohort study from fetal life until adulthood. The Generation R Study has been described in detail elsewhere.(11-13) Briefly, the cohort study includes 9778 (response rate 61%) mothers and their children born between April 2002 and January 2006 in the Rotterdam area, the Netherlands.(13) The study was conducted in accordance with the World Medical Association's Helsinki guidelines,(14) and was approved by the Medical Ethical Committee of the Erasmus MC-University Medical Center Rotterdam. Written consent had been obtained from all participating women.

Study population

Of the 9778 mothers enrolled in the entire Generation R Study, we excluded mothers who did not give consents in the postpartum phase (n=1983) and mothers who gave restricted consent for use of data (n=588). Thus, it left 7027 mothers who gave full consents in the postpartum phase. We also excluded mothers who did not respond to the questionnaire that was sent around two months postpartum (n=2130). Further, we

excluded mothers with missing data on at least one item of 12-item Short Form Survey (SF-12) (n=765). Thus, 4312 mothers were eligible for analyses in the present study (see supplementary Figure S1). 776 (18%) mothers had multiple pregnancies or births included in the Generation R Study. In the present study, we selected the information related to the first pregnancy and the first child per mother.

Health-related Quality of Life

SF-12 was used to assess maternal HRQOL at two months postpartum. SF-12 includes 12 items asking women to recall within the past one month. There are eight scales: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems and perceived mental health.(15) Following the user manual, the score of each scale was transformed into 0 (the worst) to 100 (the best). Based on the scores of all scales, the raw Physical Component Summary (PCS-12) score and the raw Mental Component Summary (MCS-12) score were calculated. Then the raw scores were transformed into the standard scores based on the normalized algorithms from the general population in United States with the mean value of 50 and the standard deviation of 10.(16) A higher score indicates a better HRQOL.

Potential determinants

Based on the literature, we selected the following variables as the potential determinants of maternal postpartum HRQOL.

Mother and infant -demographic characteristics

Maternal age at enrollment, educational level, ethnic background, marital status and *household income* were measured by the questionnaire when women were enrolled in the Generation R Study. *Maternal ethnic background* and *educational level* were defined according to the classifications of Statistics Netherlands.(17)(18) *Education* was categorized into four successive levels based on the Dutch Standard Classification of Education: high (Master's degree or PhD), mid-high (higher vocational training, Bachelor's degree), mid-low (>3 years general secondary school, intermediate vocational training) and low (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school). *Ethnic background* was categorized into three categories: native Dutch, other western immigrant and non-Western immigrants. Marital status was coded as single and married/living together. *Household income* was coded as low (< 2200 euros per month) and high (≥2200 euros per month).

Time after delivery (in months) was reported by mothers when they filled in the postpartum questionnaire. *Infant's gender* was based on the hospital and midwives registries.

Characteristics of this pregnancy

Parity was coded as 'nullipara' and 'multipara'. *Twin birth* was based the medical records. Unplanned pregnancy was reported by women by the questionnaire in early pregnancy (<18 gestational weeks). *Hospitalization during pregnancy* was measured by the questionnaire in late pregnancy (>25 gestational weeks) by one question: "During this pregnancy, have you been admitted to a hospital for more than 24 hours?"

Gestational weight gain. At enrollment, we measured maternal height and obtained the information on weight before pregnancy by questionnaire. Pre-pregnancy Body Mass Index (BMI) was calculated and categorized into four categories (underweight, normal weight, overweight, and obese). Information on the maximum weight during pregnancy was obtained through the two months postpartum questionnaire. In accordance with the Institute of Medicine (IOM) guidelines, we defined inadequate, adequate and excessive gestational weight gain depending on pre-pregnancy BMI categories.(19)

Information on pregnancy complications was based on medical records. *Pregnancy-induced hypertension* was diagnosed if previously normotensive women had a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation; *preeclampsia* was diagnosed if these women additionally had proteinuria (≥ 300 mg/24 hour).(20) *Gestational diabetes* was diagnosed following Dutch midwifery and obstetric guidelines: random glucose level > 11.1 mmol/Liter/ or a glucose level > 7.0 mmol/Liter after fasting, both in the absence of previously diagnosed diabetes.(20)

Delivery characteristics

Mode of delivery was divided into four categories; (1) spontaneous vaginal delivery; (2) induced vaginal delivery (including expression, forceps, and vacuum extraction); (3) elective cesarean delivery; (4) emergency cesarean delivery. *Location of delivery* was categorized into three categories: (1) at home; (2) at hospital; and (3) at child birth clinic or other places.

Maternal postpartum health-related factors

Loss of energy and *headache* were measured with two items in the postpartum questionnaire: 'In the first two weeks after the birth I was troubled by reduced energy levels'; 'In the first two weeks after the birth I was troubled by headache'. The answer options were 'yes' and 'no'. *Maternal psychopathology* (score in tertile) was assessed at two months postpartum using the Global Severity Index (GSI) of the Brief Symptom Inventory (BSI). BSI is a validated self-report questionnaire with 53 items that cover a broad spectrum of psychiatric symptoms in the last seven days.(21) The item scores were summed up to get a total score of GSI (range 0-200). GSI is used as a general measure of maternal psychopathological symptoms. Higher score indicates more psychopathological symptoms. (22) The total GSI score was divided into tertiles using 3 and 10 as cut-off points.(23)

Infant health-related factors

Information on *meconium-stained amniotic fluid* (yes, no), *Apgar score* at 5 minutes after delivery (below seven; eight or higher), *birth weight* of the infant (<2500gram, ≥2500 gram), and *intrauterine growth restriction* (IUGR) was obtained from routine midwife and hospital registry records. Gestational age was determined by fetal ultrasound examination in our research center.(24) *Preterm birth* was defined as the birth of an infant before 37.0 weeks of gestation.(25) In this study, *small for gestational age (SGA)* was defined as a birth weight below the 10th percentile for gestational age and based on standard deviation curves derived from the Generation R birth cohort.(24) *Hospital admission of the baby* in the first week after birth was reported by mothers in the postpartum questionnaire.

Statistical Analyses

Descriptive analyses were applied to characterize the population for analyses (n=4312). The differences in the average SF-12 summary scores (PCS-12 and MCS-12) across categories of potential determinants were assessed by two independent sample t-tests and one-way ANOVA. The variables that were found significant in the above step were then included in the final regression models, as well as maternal age at enrollment and time after delivery. Multivariate linear regression was applied to assess the significant determinants of postpartum physical and mental HRQOL. Multiple imputations were applied to deal with the missing data. Imputations were based on the relationships between all variables.(26) Five imputed datasets were generated. Additionally, we also conducted multivariate linear regression analysis using the non-imputed data. The clinical relevance was assessed by effect size (Cohen's *d*). Cohen's *d* was calculated by dividing the difference in mean scores between subgroups by the largest standard deviation and interpreted as: $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate difference, and $d \geq 0.8$ large difference.(27)

All analyses were conducted in SPSS 21.0 (IBM Corp., Armonk, NY, USA). Significance was indicated at $p < 0.05$.

RESULTS

The mean maternal age at enrollment was 31.0 (4.7) years (see Table 1); the median of time after delivery was 2.8 (Interquartile range: 2.3-3.5) months. 2692 (63.4%) of mothers were Dutch; 2508 (59.0%) had the first child; 2987 (76.6%) had a spontaneous vaginal delivery; and 3380 (80.2%) delivered at hospital. Supplementary Table S1 shows the differences between the study population (n=4312) and the population excluded

from analyses (n=5466). Compared with the excluded women, the study population more often had higher social economic status and better health.

Bivariate Analyses

Table 2 shows mean scores of PCS-12 and MCS-12, standard deviations, p-values and effect sizes across the subgroups regarding the categorical variables. The average PCS-12 score was significantly different across subgroups regarding maternal educational level, maternal ethnic background, marital status, household income, parity, pregnancy-induced hypertension, mode of delivery, location of delivery, loss of energy, headache, and hospital admission of the baby ($p<0.05$). The effect sizes regarding the above-mentioned determinants ranged from 0.07 to 0.49. In particular, PCS-12 of women who had elective cesarean delivery was on average lower than that of women who had a spontaneous vaginal delivery ($p<0.001$, $d=0.49$). The average MCS-12 score was significantly associated with infant gender, maternal educational level, maternal ethnical background, marital status, household income, unplanned pregnancy, location of delivery, loss of energy, headache, preterm birth and hospital admission of the baby ($p<0.05$). The effect sizes regarding the above-mentioned determinants ranged from 0.07 to 1.10. In particular, the average MCS-12 score of women with most psychopathological symptoms (i.e. the highest tertile) was lower than that of women with least psychopathological symptoms ($p<0.001$, $d=1.10$).

Regression analyses

Table 3 shows the coefficient betas and corresponding 95% confidence intervals and p values based on imputed data. Older maternal age at enrolment, shorter time after delivery, low household income, elective/emergency cesarean delivery, loss of energy, maternal psychopathology, and the hospital admission of the baby were significantly associated with lower PCS-12 scores ($p<0.05$). Older maternal age at enrolment, non-western background, low household income, unplanned pregnancy, loss of energy, headache and maternal psychopathology were significantly associated with lower MCS-12 scores ($p<0.05$). In addition, Supplementary Table S2 presents the coefficient betas and corresponding 95% confidence intervals and p values based on the non-imputed data. The patterns of significant determinants are similar in both datasets.

DISCUSSION

We have assessed an extensive set of potential determinants of maternal HRQOL at two months postpartum in a large, population-based sample of women in the Netherlands. Multiple factors were found to be significantly associated with worse postpartum physical and mental HRQOL.

Table 1. Characteristics of the study population (n=4312)

Characteristics	Values
Mother/ infant demographic characteristics	
Maternal age at enrollment, in years; mean (standard deviation)	31.0 (4.7)
Time after delivery, in months, median (interquartile range)	2.8 (2.3 – 3.5)
Range	0.4 – 6.0
missing(n)	350
Gender of infants, n (%)	
Girl	2145 (49.7)
Boy	2167 (50.3)
Maternal ethnic background, n (%)	
Dutch	2692 (63.4)
Other western	385 (9.1)
Non-western	1170 (27.5)
missing(n)	65
Maternal educational level, n (%)	
High	1307 (31.6)
Mid-high	1023 (24.7)
Mid-low	1190 (28.7)
Low	622 (15.0)
missing(n)	170
Marital status, n (%)	
Married/living together	3703 (90.2)
No partner	401 (9.8)
missing(n)	208
Household income, n (%)	
≤2200 euro/month	1280 (34.1)
>2200 euro/month	2474 (65.9)
missing(n)	558
Pregnancy-related characteristics	
Parity, n (%)	
Unplanned pregnancy, n (%)	844 (21.7)
missing	414
Gestational weight gain, n (%)	
Inadequate weight gain	578 (19.9)
Adequate weight gain[1]	1024 (35.2)
Excessive weight gain	1307 (44.9)
missing(n)	1403
Preeclampsia, n (%)	75 (2.0)
missing(n)	473
Pregnancy induced hypertension, n (%)	165 (4.2)
missing(n)	370
Gestational diabetes, n (%)	26 (0.6)
missing(n)	116
Hospitalization during pregnancy, n (%)	71 (1.9)
missing(n)	567

Table 1. Continued

Characteristics	Values
Delivery characterisitcs	
Mode of delivery, n (%)	
Spontaneous vaginal delivery	2987 (76.6)
Induced vaginal delivery	437 (11.2)
Elective cesarean delivery	199 (5.1)
Emergency cesarean delivery	276 (7.1)
missing(n)	413
Place of delivery, n (%)	
At home	771 (17.9)
At hospital	3433 (79.9)
In childbirth clinic or other places	95 (2.2)
missing(n)	13
Maternal postpartum health-related factors	
Loss of energy (yes), n (%)	2151 (51.3)
missing(n)	118
Headache (yes), n (%)	590 (14.0)
missing(n)	93
Maternal psychopathology[2]	
Lowest tertile	1517 (35.7)
Middle tertile	1322 (31.1)
Highest tertile	1414 (33.2)
missing(n)	59
Infant health-related factors	
Mecomium-stained amnoitic fluid, n (%)	624 (15.1)
missing(n)	169
Apgar score of <7 at 5 minutes, n (%)	43 (1.0)
missing(n)	177
Preterm birth, n (%)	219 (5.1)
missing(n)	1
Low birth weight[3], n (%)	183 (4.2)
Small size for gestational age, n (%)	360 (8.4)
missing(n)	4
Intrauterine growth restriction (IUGR), n (%)	60 (1.4)
missing(n)	129
Hospital admission of the baby in the first week, n (%)	706 (16.7)
missing(n)	95
Health-related quality of life (SF-12 Summary scores**)**	
Physical Component Summary score (PCS-12), mean (standard deviation)	44.8 (7.3)
Range	9.6 – 65.4
Mental Component Summary score (MCS-12), mean (standard deviation)	54.2 (10.2)
Range	8.0 – 70.8

[1]Adequate weight gain was defined depending on pre-pregnancy BMI categories. In accordance with the Institute of Medicine guideline, underweight women (BMI <18.5 kg/m2) should gain 12.5-18 kg during pregnancy, normal weight women (BMI 18.5–24.9 kg/m2) should gain 11.5-16 kg, overweight women (BMI 25.0–29.9 kg/m2) should gain 7-11.5 kg, and obese women (BMI ≥ 30 kg/m2) should gain 5-9 kg. [2] Maternal psychopathology was measured by the Brief Symptom Inventory. [3]Low birth weight was defined as the birth weight is lower than 2500 grams.

Table 2. Differences in physical and mental HRQOL scores across subgroups (n=4312)

	Physical Component Summary Score (PCS-12)			Mental Component Summary Score (MCS-12)		
	Mean (SD)	P value	Effect size	Mean (SD)	P value	Effect size
Mother/ infant demographic characteristics						
Infant gender		0.95	0.01		0.02	0.07
Girl (n=2145)	44.8 (7.2)			54.6 (9.9)		
Boy (n=2167)	44.7 (7.4)			53.9 (10.6)		
Maternal educational level		0.02	0.11		<0.001	0.24
High (n=1307)	45.1 (7.0)			55.7 (8.5)		
Mid-high (n=1023)	44.4 (7.4)			54.4 (10.0)		
Mid-low (n=1190)	44.4 (7.5)			53.7 (10.9)		
Low (n=622)	45.2 (7.0)			52.9 (11.4)		
Maternal ethnic background		0.03	0.14		<0.001	0.31
Dutch (n=2692)	44.8 (7.0)			55.4 (9.1)		
Other western (n=385)	45.5 (7.1)			54.0 (10.2)		
Non-western (n=1170)	44.4 (7.8)			51.7 (12.0)		
Marital status		0.04	0.10		<0.001	0.21
Married/living together (n=3703)	44.8 (7.2)			54.5 (10.0)		
No partner (n=401)	44.0 (8.0)			52.0 (11.7)		
Household income		0.04	0.07		<0.001	0.33
≤2200 euro/month (n=1280)	44.4 (7.5)			51.8 (11.7)		
>2200 euro/month (n=2474)	44.9 (7.1)			55.7 (8.9)		
Pregnancy-related characteristics						
Parity		0.04	0.07		0.45	0.02
Nullipara (n=2508)	44.5 (7.4)			54.3 (10.2)		
Multipara (n=1746)	45.0 (7.2)			54.1 (10.3)		
Twin birth		0.29	0.15		0.11	0.20
Yes (n=53)	45.8 (6.8)			51.9 (11.6)		
No (n=4259)	44.7 (7.3)			54.2 (10.2)		
Unplanned pregnancy		0.93	0.01		<0.001	0.25
Yes (n=844)	44.7 (7.5)			52.1 (11.5)		
No (n=3054)	44.8 (7.2)			55.0 (9.6)		
Gestational weight gain		0.49	0.06		0.24	0.08
Adequate weight gain1 (n=1024)	44.8 (7.3)			54.8 (9.7)		
Inadequate weight gain (n=578)	45.1 (7.0)			54.0 (10.5)		
Excessive weight gain (n=1307)	44.6 (7.3)			54.2 (10.4)		
Preeclampsia		0.42	0.07		0.22	0.13
Yes (n=75)	44.2 (8.5)			52.8 (10.9)		
No (n=3764)	44.8 (7.2)			54.2 (10.2)		
Pregnancy-induced hypertension		0.004	0.21		0.64	0.04
Yes (n=165)	43.2 (7.7)			54.6 (11.0)		
No (n=3764)	44.8 (7.2)			54.2 (10.2)		
Gestational diabetes		0.40	0.15		0.85	0.03
Yes (n=26)	43.5 (7.9)			54.6 (12.2)		
No (n=4170)	44.7 (7.3)			54.2 (10.3)		

Table 2. Continued

	Physical Component Summary Score (PCS-12)			Mental Component Summary Score (MCS-12)		
	Mean (SD)	P value	Effect size	Mean (SD)	P value	Effect size
Hospitalization during pregnancy		0.10	0.17		0.05	0.18
Yes (n=71)	43.4 (8.1)			52.1 (12.5)		
No (n=3674)	44.8 (7.2)			54.5 (10.0)		
Delivery characteristics						
Mode of delivery		<0.001	0.49		0.26	0.12
Spontaneous vaginal delivery (n=2987)	45.2 (7.0)			54.4 (9.9)		
Induced vaginal delivery (n=437)	44.2 (7.6)			53.6 (11.2)		
Elective cesarean delivery (n=199)	41.1 (8.4)			54.1 (10.9)		
Emergency cesarean delivery (n=276)	42.3 (8.2)			53.2 (10.2)		
Location of delivery		0.01	0.10		<0.001	0.33
At home (n=771)	45.4 (6.8)			55.5 (8.2)		
At hospital (n=3433)	44.6 (7.3)			54.0 (10.6)		
In childbirth clinics or other places (n=95)	44.6 (8.3)			51.7 (11.6)		
Maternal postpartum health-related factors						
Loss of energy		<0.001	0.26		<0.001	0.24
Yes (n=2152)	43.8 (7.7)			52.8 (10.9)		
No (n=2043)	45.8 (6.6)			56.0 (8.9)		
Headache		<0.001	0.14		<0.001	0.30
Yes (n=590)	43.8 (7.7)			51.2 (12.2)		
No (n=3629)	44.9 (7.2)			54.8 (9.7)		
Maternal psychopathology2		<0.001	0.28		<0.001	1.10
Lowest tertile	46.1 (5.8)			59.8 (4.7)		
Middle tertile	44.3 (7.2)			56.4 (6.2)		
Highest tertile	43.7 (8.5)			46.3 (12.3)		
Infant health-related factors						
Mecomium-stained amnoitic fluid		0.07	0.08		0.64	0.02
Yes (n=624)	45.2 (6.7)			54.0 (10.6)		
No (n=3519)	44.6 (7.4)			54.2 (10.2)		
Apgar score of <7 at 5 minutes, n (%)		0.35	0.14		0.19	0.16
Yes (n=43)	43.7 (7.4)			52.2 (12.0)		
No (n=4092)	44.7 (7.3)			54.2 (10.2)		
Preterm birth		0.18	0.10		0.003	0.18
Yes (n=219)	45.4 (7.3)			52.2 (11.7)		
No (n=4092)	44.7 (7.3)			54.3 (10.2)		
Low birth weight3		0.54	0.19		0.47	0.08
Yes (n=183)	45.4 (7.3)			53.6 (10.4)		
No (n=4129)	44.7 (7.3)			54.2 (10.2)		
Small size for gestational age		0.14	0.08		0.20	0.07
Yes (n=360)	45.3 (6.9)			53.5 (10.6)		
No (n=3948)	44.7 (7.3)			54.2 (10.2)		

Table 2. Continued

	Physical Component Summary Score (PCS-12)			Mental Component Summary Score (MCS-12)		
	Mean (SD)	P value	Effect size	Mean (SD)	P value	Effect size
Intrauterine growth restriction (IUGR)		0.21	0.16		0.48	0.09
Yes (n=60)	45.9 (7.2)			53.2 (11.0)		
No (n=4170)	44.7 (7.3)			54.2 (10.3)		
Hospital admission of the baby		<0.001	0.17		0.002	0.12
Yes (n=706)	43.7 (7.8)			53.1 (10.7)		
No (n=3511)	45.0 (7.2)			54.4 (10.1)		

[1]Adequate weight gain was defined depending on pre-pregnancy BMI categories. In accordance with the Institute of Medicine guideline, underweight women (BMI <18.5 kg/m2) should gain 12.5-18 kg during pregnancy, normal weight women (BMI 18.5–24.9 kg/m2) should gain 11.5-16 kg, overweight women (BMI 25.0–29.9 kg/m2) should gain 7-11.5 kg, and obese women (BMI ≥ 30 kg/m2) should gain 5-9 kg. [2] Maternal psychopathology was measured by the Brief Symptom Inventory. [3]Low birth weight was defined as the birth weight is lower than 2500 grams. Effect size (d) calculated by dividing the difference in mean scores between subgroups by the largest standard deviation and interpreted as: 0.2 ≤ d < 0.5 small difference, 0.5 ≤ d <0.8 moderate difference, and d ≥0.8 large difference.

Table 3. Multivariable associations with Physical (PCS-12) and Mental Component Summary (MCS-12) scores in the imputed dataset (n=4312)

	PCS-12		MCS-12	
	B (95% CI)	P value	B (95% CI)	P value
Maternal age at intake (in years)	**-0.10 (-0.15, -0.04)**	**<0.001**	**-0.14 (-0.20, -0.08)**	**<0.001**
Time after delivery (in months)	**0.58 (0.34, 0.82)**	**<0.001**	-0.21 (-0.52, 0.10)	0.19
Infant's gender				
Boy			Reference	
Girl			0.36 (-0.14, 0.87)	0.16
Maternal Educational level				
High education	Reference		Reference	
Mid-high education	-0.47 (-1.06, 0.12)	0.12	-0.25 (-0.95, 0.44)	0.48
Mid-low education	-0.46 (-1.09, 0.16)	0.15	-0.32 (-1.05, 0.41)	0.39
Low education	0.13 (-0.66, 0.92)	0.74	-0.78 (-1.74, 0.21)	0.12
Maternal ethnic background				
Dutch	Reference		Reference	
Other western	0.73 (-0.04, 1.49)	0.06	-0.45 (-1.35, 0.46)	0.33
Non-western	-0.33 (-0.87, 0.22)	0.24	**-1.19 (-1.84, -0.54)**	**<0.001**
Household income				
High household income	Reference		Reference	
Low household income	**-0.68 (-1.32, -0.04)**	**0.04**	**-1.28 (-2.00, -0.56)**	**0.001**
Marital status				
Married or living together	Reference		Reference	
Single	-0.33 (-1.16, 0.50)	0.44	0.88 (0.-0.14, 1.62)	0.09

Table 3. Continued

	PCS-12		MCS-12	
	B (95% CI)	**P value**	**B (95% CI)**	**P value**
Parity				
Nullipara	Reference			
Multipara	0.28 (-0.20, 0.76)	0.25		
Unplanned pregnancy				
No			Reference	
Yes			**0.87 (0.11, 1.62)**	**0.02**
Pregnancy-induced hypertension				
No	Reference			
Yes	-0.26 (-1.01, 0.50)	0.49		
Mode of delivery				
Spontaneous vaginal delivery	Reference			
Induced vaginal delivery	-0.58 (-1.32, 0.17)	0.13		
Elective cesarean delivery	**-2.76 (-5.09, -0.42)**	**0.03**		
Emergency cesarean delivery	**-1.91 (-2.97, -0.85)**	**<0.001**		
Location of delivery				
At home				
At hospital			Reference	
At childbirth clinic or other places			-0.36 (-1.03,0.32)	0.30
Loss of energy			-0.56 (-2.38, 1.26)	0.55
No	Reference		Reference	
Yes	**-1.46 (-1.90, -1.02)**	**<0.001**	**-1.60 (-2.15, -1.06)**	**<0.001**
Headache				
No	Reference		Reference	
Yes	-0.58 (-1.22, -0.07)	0.08	**-1.51 (-2.26, -0.76)**	**<0.001**
Psychopathologic symptoms[1]				
Lowest tertile	Reference		Reference	
Middle tertile	**-1.53 (-2.05, -1.00)**	**<0.001**	**-2.98 (-3.60, -2.34)**	**<0.001**
Highest tertile	**-1.87 (-2.41, -1.33)**	**<0.001**	**-12.42 (-13.07, -11.78)**	**<0.001**

Table 3 is based on the imputed dataset. Values represent betas with 95% CIs (confidence intervals) and p values derived from multiple linear regression analyses. Bold print indicates the statistical significance. The significance level is $p<0.05$. [1] Maternal psychopathology was measured by the Brief Symptom Inventory.

In interpreting our results, it is important to be aware that a statistically significant difference does not necessarily indicate clinical relevance. In the present study, we indicated the clinical relevance of findings using Cohen's effect size (d); the difference in the average level of physical and mental HRQOL is clinically relevant when $d \geq 0.5$. Based on this classification, the clinical relevance of most of the significant differences in our study can be considered small. There are a few exceptions, which we will describe in somewhat more detail. The difference in the average level of postpartum physical HRQOL between women having elective cesarean delivery and those having spontaneous vaginal delivery can be interpreted as clinically relevant (d=0.49). Cesarean delivery is a surgery operation that can cause pain, discomfort and other health symptoms. Therefore, women may perceive their physical health as worse than that of women who had a vaginal delivery. (8, 28, 29) We recommend taking and the potential downstream effects of a cesarean delivery on postpartum HRQOL into consideration when deciding about cesarean delivery.

A notable clinically relevant finding in our study is the large difference of 14 points between the average level of mental HRQOL between mothers with most psychopathological symptoms (i.e. defined as highest tertile) and those with least psychopathological symptoms (i.e. defined as lowest tertile). Though adjusted by other variables, results from the regression analyses show that the difference between the above two groups is still large in terms of clinical relevance; maternal postpartum psychopathology was profoundly associated with worse mental HRQOL. Our finding is consistent with a study in Australia by Emmanuel et al. They found that even when they controlled for other confounding variables, having psychopathological symptoms was significantly associated with almost all domains of quality of life in the period from late pregnancy towards 12 weeks after delivery.(30) In the early postpartum period, psychopathological symptoms have been shown to disturb women's ability to function, mental health status, inter-personal relationships, social engagement and overall quality of life.(31) Women with postpartum psychopathological symptoms may need support. We therefor call for awareness among health care professionals.

In the present study, longer time after delivery was associated with better physical HRQOL, indicating women's physical HRQOL improved over time. This finding is consistent with the natural course of recovery after delivery.(30)

Factors associated with maternal postpartum HRQOL reported by previous studies, such as multiparity, more gestational weight gain,(5) preeclampsia,(6) and gestational hypertension,(10) were not confirmed in the present study. This may be caused by the differences in measurements of HRQOL, the culture contexts, and the severity of health conditions (e.g. preeclampsia) between our study and other studies.

In the present study, we aimed to assess HRQOL at two months postpartum. However, the questionnaire was completed between 2 weeks and 6 months postpartum. 25% percent women filled in the postpartum questionnaire within two months after delivery; 50% during 2-3.5 months; and 25% after 3.5 months postpartum. In case of a longer interval after delivery HRQOL may have reached the pre-pregnancy level. To check this issue, we compared the average PCS-12 and MCS-12 score with the Dutch normative SF-12 data of women aged 30-39 years old.(32) We found that the average score of PCS-12 in our study was below the normative data ($p<0.001$), indicating that women still had not fully recovered physically. The average score of MCS-12 in our study was similar to the normative data ($p=0.28$).

Strengths and Limitations

The major strengths of this study are the large sample size and the availability of an extensive set of potential determinants of maternal HRQOL after delivery including socio-demographic characteristics, pregnancy- and delivery-related factors, maternal postpartum health-related factors and infant's health-related factors.

There are several limitations that need attention.

First, even though we aimed to include as many potential determinant variables as possible, still some relevant factors were not measured. This applies, for instance, to symptoms that may occur after delivery such as difficulties in breastfeeding, urinary incontinence, fecal incontinence, constipation, sleeping difficulties, and back pain. (4, 5, 30, 33) Also, sexual problems such as lack of sexual desire and painful intercourse may be important causes of unhappiness for women.(34) The relationship with the partner and the social support can also affect postpartum HRQOL, particularly mental HRQOL.(35) These factors were not included in our study.

Second, the specificity of the population in the present study should be considered when interpreting results. The women included in the Generation R Study were healthier than the general population.(36) Additionally, compared with the women who were excluded from the analyses due to missing data, the women who were included in the analyses had a relatively high socioeconomic status, and they had a better health, which may limit the generalizability of our findings.

Third, the postpartum questionnaire was completed by women around two months postpartum. Some items, such as SF-12, refer to a recall period of one month, while others, such as items about headache and loss of energy, refer to the first two weeks after delivery; and hospital admission of the baby refers to the first week after birth. This should be taken into consideration

CONCLUSIONS

The present study has assessed an extensive set of determinants of maternal postpartum HRQOL in a large general population in the Netherlands. We have identified multiple factors associated with worse physical and mental HRQOL. Particularly, maternal psychopathology is profoundly associated with postpartum mental HRQOL. These women may need support. We therefore call for awareness among health care professionals.

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REFERENCES

1. Central Intelligence Agency. (2013 est). The World Factbook in birth rate. https://www.cia.gov/library/publications/the-world-factbook/rankorder/2054rank.html
2. Golmezuglu A, Pattinson R, Hofmeyr G, Lumbiganon P. Global maternal and perinatal health issues. High Risk Pregnancy: Management Options 4th ed Philadelphia: Elsevier. 2011:1-7.
3. SchipperH,ClinchJJ,OlwenyCLM(1996). Quality of life studies:definitions and conceptual issues, InSpilkerB (ed)Quality of Life and Pharmacoeconomics in clinical trials. Lippincott-Raven Publishers:Philadelphia. PP11–23.
4. Van der Woude DAA, Pijnenborg JMA, de Vries J. Health status and quality of life in postpartum women: a systematic review of associated factors. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2015 2015/02/01/;185(Supplement C):45-52.
5. Mortazavi F, Mousavi SA, Chaman R, Khosravi A. Maternal quality of life during the transition to motherhood. Iran Red Crescent Med J. 2014 May;16(5):e8443.
6. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Steegers EA, et al. Poor health-related quality of life after severe preeclampsia. Birth. 2011 Sep;38(3):246-55.
7. Webster J, Nicholas C, Velacott C, Cridland N, Fawcett L. Quality of life and depression following childbirth: impact of social support. Midwifery. 2011 2011/10/01/;27(5):745-9.
8. Jansen AJ, Duvekot JJ, Hop WC, Essink-Bot ML, Beckers EA, Karsdorp VH, et al. New insights into fatigue and health-related quality of life after delivery. Acta Obstet Gynecol Scand. 2007;86(5):579-84.
9. Symon A, MacKay A, Ruta D. Postnatal quality of life: a pilot study using the Mother-Generated Index. J Adv Nurs. 2003 Apr;42(1):21-9.
10. Prick BW, Bijlenga D, Jansen AJG, Boers KE, Scherjon SA, Koopmans CM, et al. Determinants of health-related quality of life in the postpartum period after obstetric complications. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2015 2015/02/01/;185(Supplement C):88-95.
11. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004 Jan;18(1):61-72.
12. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
13. Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, et al. The Generation R Study: design and cohort update 2010. Eur J Epidemiol. 2010 Nov;25(11):823-41.
14. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2000 Dec 20;284(23):3043-5.
15. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical Care. 1996 Mar;34(3):220-33.
16. Ware JE, Kosinski M, Keller SD, QualityMetric I, New England Medical Center H, Health Assessment L. SF-12 : how to score the SF-12 physical and mental health summary scales. Lincoln, R.I.; Boston, Mass.: QualityMetric Inc. ; Health Assessment Lab; 2002.
17. Statistics Netherlands. The Dutch Standard Classification of Education, SOI 2006. Voorburg/Heerlen; 2008
18. Statistics Netherlands. Migrants in the Netherlands 2004 (Allochtnen in Nederland 2004). Voorburg/Heelen, the Netherlands: Centraal Bureau voor de Statistiek; 2004.
19. Institute of Medicine. Weight gain during pregnancy: Reexamining the guidelines. Washington, DC: National Academies Press. 2009
20. Blom EA, Jansen PW, Verhulst FC, Hofman A, Raat H, Jaddoe VW, et al. Perinatal complications increase the risk of postpartum depression. The Generation R Study. Bjog. 2010 Oct;117(11):1390-8.

21. de beurs E. Brief Symptom Inventory, Handleiding. The Netherlands: Leiden, 2004.
22. Desrogatis, L. R. (1993). Brief Symptom Inventory (BSI): Administration, scoring, and procedures manual (3rd ed.). Minneapolis, MN: National Computer Systems, Inc.
23. Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. European Respiratory Journal. 2013;41(4):952-9.
24. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound Obstet Gynecol. 2008 Apr;31(4):388-96.
25. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010 Jan;88(1):31-8.
26. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol. 1995 Dec 15;142(12):1255-64.
27. Cohen J. Satistical Power Analysis for the Behavioral Sciences. 2nd edn. Hilllsdale, New Jersey: L.Erlbaum; 1988.
28. Jansen AJ, Essink-Bot ML, Duvekot JJ, van Rhenen DJ. Psychometric evaluation of health-related quality of life measures in women after different types of delivery. J Psychosom Res. 2007 Sep;63(3):275-81.
29. Baghirzada L, Downey KN, Macarthur AJ. Assessment of quality of life indicators in the postpartum period. International Journal of Obstetric Anesthesia. 2013 2013/07/01/;22(3):209-16.
30. Emmanuel EN, Sun J. Health related quality of life across the perinatal period among Australian women. J Clin Nurs. 2014 Jun;23(11-12):1611-9.
31. Emmanuel E, St John W. Maternal distress: a concept analysis. J Adv Nurs. 2010 Sep;66(9):2104-15.
32. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. Qual Life Res. 2009 May;18(4):403-14.
33. Ansara D, Cohen MM, Gallop R, Kung R, Schei B. Predictors of women's physical health problems after childbirth. J Psychosom Obstet Gynaecol. 2005 Jun;26(2):115-25.
34. Saurel-Cubizolles MJ, Romito P, Lelong N, Ancel PY. Women's health after childbirth: a longitudinal study in France and Italy. BJOG. 2000 Oct;107(10):1202-9.
35. Emmanuel E, St John W, Sun J. Relationship between social support and quality of life in childbearing women during the perinatal period. J Obstet Gynecol Neonatal Nurs. 2012 Nov-Dec;41(6):E62-70.
36. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. Eur J Epidemiol. 2012 Sep;27(9):739-56.

SUPPLEMENTARY

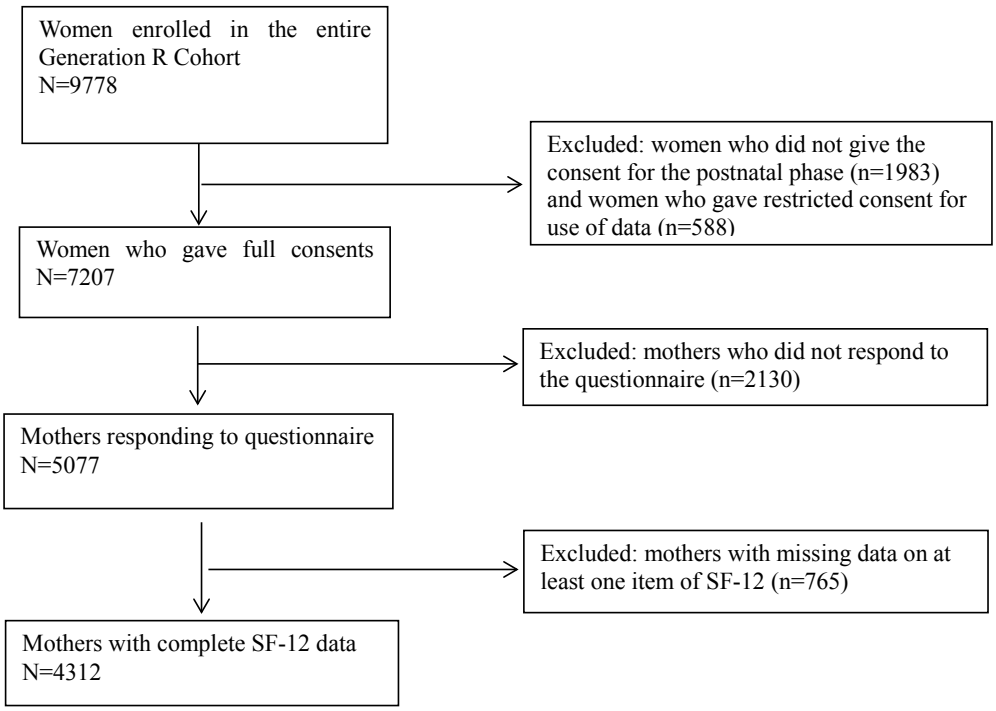

Figure S1. Flow chart of the study population

Table S1. Characteristics of the study population (n=4321) and the population excluded from analyses (n=5466)

Characteristics	Study population (n=4312)	Exclude population (n=5466)	P value
Mother/ infant demographic characteristics			
Maternal age at enrollment, in years; mean (standard deviation)	31.0 (4.7)	29.0 (5.7)	<0.001
missing	0	3	
Time after delivery, in months, median (interquartile range)	2.8 (2.3 – 3.5)	2.9 (2.3 – 3.8)	0.004
Range	0.4 – 6.0	0.8 – 6.0	
missing	350	4811	
Gender of infants, n (%)			0.49
Girl	2145 (49.7)	2604 (49.0)	
Boy	2167 (50.3)	2708 (51.0)	
missing	0	154	
Maternal ethnic background, n (%)			<0.001
Dutch	2692 (63.4)	1853 (38.3)	
Other western	385 (9.1)	391 (8.1)	
Non-western	1170 (27.5)	2592 (53.6)	
missing	65	630	
Maternal educational level, n (%)			<0.001
High	1307 (31.6)	698 (15.8)	
Mid-high	1023 (24.7)	632 (14.3)	
Mid-low	1190 (28.7)	1436 (32.5)	
Low	622 (15.0)	1648 (37.3)	
missing	170	1052	
Marital status, n (%)			<0.001
Married/living together	3703 (90.2)	3623 (81.2)	
No partner	401 (9.8)	837 (18.8)	
missing	208	1006	
Household income, n (%)			<0.001
≤2200 euro/month	1280 (34.1)	1784 (60.3)	
>2200 euro/month	2474 (65.9)	1173 (39.7)	
missing	558	2400	
Pregnancy-related characteristics			
Parity, n (%)			<0.001
Nullipara	2508 (59.0)	2669 (51.9)	
Multipara	1746 (41.0)	2476 (48.1)	
missing	58	510	
Twin birth, n (%)	53 (1.2)	70 (1.3)	0.86
missing			
Unplanned pregnancy, n (%)	844 (21.7)		
missing	414		
Gestational weight gain, n (%)			0.10
Inadequate weight gain	578 (19.9)	104 (23.9)	
Adequate weight gain[1]	1024 (35.2)	154 (35.4)	
Excessive weight gain	1307 (44.9)	177 (40.7)	
missing	1403	5031	
Preeclampsia, n (%)	75 (2.0)	112 (2.6)	0.06
missing	473	1136	
Pregnancy induced hypertension, n (%)	165 (4.2)	153 (3.5)	0.11
missing	370	1095	

Table S1. Continued

Characteristics	Study population (n=4312)	Exclude population (n=5466)	P value
Gestational diabetes, n (%)	26 (0.6)	77 (1.5)	<0.001
Gestational diabetes, n (%)			
missing	116	483	
Hospitalization during pregnancy, n (%)	71 (1.9)	90 (3.0)	0.003
missing	567	2492	
Delivery characteristics			
Mode of delivery, n (%)			0.03
Spontaneous vaginal delivery	2987 (76.6)	3360 (74.1)	
Induced vaginal delivery	437 (11.2)	575 (12.7)	
Elective cesarean delivery	199 (5.1)	227 (5.0)	
Emergency cesarean delivery	276 (7.1)	374 (8.2)	
missing	413	930	
Location of delivery, n (%)			<0.001
At home	771 (17.9)	452 (8.7)	
At hospital	3433 (79.9)	4552 (87.3)	
In childbirth clinic or other places	95 (2.2)	211 (4.0)	
missing	13	251	
Maternal postpartum health-related factors			
Loss of energy (yes), n (%)	2151 (51.3)	285 (42.2)	<0.001
Missing	118	4791	
Headache (yes), n (%)	590 (14.0)	116 (17.1)	0.04
missing	93	4786	
Maternal psychopathology			0.001
Lowest tertile	1517 (35.7)	200 (30.8)	
Middle tertile	1322 (31.1)	186 (28.6)	
Highest tertile	1414 (33.2)	264 (40.6)	
missing	59	4816	
Infant health-related factors			
Mecomium-stained amnoitic fluid, n (%)	624 (15.1)	733 (15.0)	0.95
missing	169	582	
Apgar score of <7 at 5 minutes, n (%)	43 (1.0)	57 (1.2)	0.55
missing	177	645	
Preterm birth, n (%)	219 (5.1)	404 (7.7)	<0.001
missing	1	239	
Low birth weight[3], n (%)	183 (4.2)	335 (6.4)	<0.001
Small size for gestational age, n (%)	360 (8.4)	232	
missing	4		
Intrauterine growth restriction (IUGR), n (%)	60 (1.4)	99 (2.0)	0.04
missing	129	506	
Hospital admission of the baby, n (%)	706 (16.7)	153 (17.6)	0.55
missing	95	4597	

[1]Adequate weight gain was defined depending on pre-pregnancy BMI categories. In accordance with the Institute of Medicine guideline, underweight women (BMI <18.5 kg/m2) should gain 12.5-18 kg during pregnancy, normal weight women (BMI 18.5–24.9 kg/m2) should gain 11.5-16 kg, overweight women (BMI 25.0–29.9 kg/m2) should gain 7-11.5 kg, and obese women (BMI ≥ 30 kg/m2) should gain 5-9 kg. [2] Maternal psychopathology was measured by the Brief Symptom Inventory. [3]Low birth weight was defined as the birth weight is lower than 2500 grams.

Table S2. Multivariable associations with Physical (PCS-12) and Mental Component Summary (MCS-12) scores in the non-imputed datasets

	PCS-12 (n=2727)		MCS-12 (n=2859)	
	B (95% CI)	P value	B (95% CI)	P value
Maternal age at intake (in years)	**-0.10 (-0.17, -0.04)**	**0.003**	**-0.12 (-0.19, -0.04)**	**0.002**
Time after delivery (in months)	**0.66 (0.39, 0.94)**	**<0.001**	-0.11 (-0.42, 0.20)	0.49
Infant's gender				
Boy			Reference	
Girl			0.37 (-0.22, 0.96)	0.22
Maternal Educational level				
High education	Reference		Reference	
Mid-high education	**-0.88 (-1.57, -0.18)**	**0.01**	-0.02 (-0.76, 0.80)	0.96
Mid-low education	-0.68 (-1.42, 0.06)	0.07	-0.20 (-1.02, 0.62)	0.64
Low education	0.15 (-0.85, 1.14)	0.77	-0.91 (-2.02, 0.20)	0.11
Maternal ethnic background				
Dutch	Reference		Reference	
Other western	0.39 (-0.60, 1.38)	0.44	-0.38 (-1.48, 0.72)	0.50
Non-western	-0.26 (-0.94, 0.42)	0.46	-0.74 (-1.51, 0.02)	0.06
Household income				
High household income	Reference		Reference	
Low household income	-0.37 (-1.07, 0.32)	0.29	**-0.99 (-1.77, -0.21)**	0.01
Marital status				
Married or living together	Reference		Reference	
Single	-0.24 (-1.26, 0.78)	0.65	0.31 (-0.88, 1.49)	0.61
Parity				
Nullipara	Reference			
Multipara	0.14 (-0.45, 0.73)	0.64		
Unplanned pregnancy				
No			Reference	
Yes			0.61 (-0.19, 1.40)	0.13
Pregnancy-induced hypertension				
No	Reference			
Yes	-0.95 (-2.23, 0.33)	0.15		
Mode of delivery				
Spontaneous vaginal delivery	Reference			
Induced vaginal delivery	**-1.09 (-2.01, -0.17)**	**0.02**		
Elective cesarean delivery	**-3.75 (-5.06, -2.45)**	**<0.001**		
Emergency cesarean delivery	**-2.40 (-3.48, -1.33)**	**<0.001**		
Location of delivery				
At home	Reference		Reference	
At hospital	0.04 (-0.69, 0.78)	0.91	0.20 (-0.95,0.56)	0.62
At childbirth clinic or other places	-1.52 (-3.56, 0.52)	0.14	-1.12 (-3.24, 1.01)	0.30
Loss of energy				
No	Reference		Reference	
Yes	**-1.51 (-2.06, -0.97)**	**<0.001**	**-1.54 (-2.15, -0.93)**	**<0.001**
Headache				
No	Reference		Reference	
Yes	-0.73 (-1.50, 0.04)	0.06	**-1.47 (-2.33, -0.61)**	0.001

Table S2. Continued

	PCS-12 (n=2727)		MCS-12 (n=2859)	
	B (95% CI)	**P value**	**B (95% CI)**	**P value**
Maternal psychopathology				
Lowest tertile	reference		reference	
Middle tertile	**-1.40 (-2.04, -0.76)**	**<0.001**	**-3.00 (-3.72, -2.28)**	**<0.001**
Highest tertile	**-1.73 (-2.40, -1.06)**	**<0.001**	**-11.55 (-12.30, -10.79)**	**<0.001**
Preterm birth				
No			Reference	
Yes			-0.33 (-1.86, 1.21)	0.68
Hospital admission of the baby				
No	Reference		Reference	
Yes	**-1.04 (-1.78, -0.30)**	**0.006**	-0.11 (-0.97, 0.75)	0.80

Supplementary Table S2 is based on the non-imputed data. Values represent betas with 95% CIs (confidence intervals) and p values derived from multiple linear regression analyses. The significance level is p<0.05. 1 Maternal psychopathology was measured by the Brief Symptom Inventory.

PART II

Assessing the Association between Maternal Health-related Quality of Life during Pregnancy and Birth Outcomes

CHAPTER 5

Associations between Maternal Health-Related Quality of Life during Pregnancy and Birth Outcomes: The Generation R Study

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Submitted

ABSTRACT

Aims

We aimed to assess associations between maternal HRQOL in early, mid- and late pregnancy and birth outcomes; we additionally aimed to assess the differences in birth outcomes between subgroups of mothers reporting 'the worst' and 'the best' HRQOL.

Methods

HRQOL was measured by SF-12 in early (n=6334), mid- (n=6204) and late pregnancy (n=6048) in a population-based mother- and child cohort in the Netherlands; Physical (PCS-12) and Mental Component Summary (MCS-12) scores were calculated. Birth outcomes included pregnancy duration, preterm birth, birth weight, low birth weight and small for gestational age (SGA). We defined very high PCS-12/MCS-12 scores as > 90th percentile and very low score as < 10th percentile.

Results

Ten points increase in PCS-12 score in late pregnancy was significantly associated with a higher chance of having small-for-gestational-age birth (OR=1.20, 95% CI:1.08, 1.33, p value=0.0006). The incidence of having a small-for-gestational-age birth was lower when mothers reported very low PCS-12 scores in late pregnancy than that when mothers had very high scores (7.5% vs. 12.3%, p=0.005). In early, mid- and late pregnancy, mothers with very low MCS-12 scores had infants with a lower average birth weight than those with very high scores ($p<0.05$); the effect sizes vary from 0.15 to 0.24.

Conclusions

In the total study population, our findings did not confirm the hypotheses that worse maternal physical and mental HRQOL in early, mid- and late pregnancy is associated with more preterm birth, shorter pregnancy duration, and lower birth weight. In contrast, in late pregnancy, we saw that a relatively better physical HRQOL is associated with a higher chance of having a small-for-gestational-age birth. This requires further study. Our study showed only small effects regarding a relatively low average birth weight and more frequent small-for-gestational-age birth in the subgroup with worst mental HRQOL compared with the subgroup with the best mental HRQOL. The importance of mother's mental HRQOL during pregnancy and the potential consequences for the child requires further study.

INTRODUCTION

Preterm birth, small-for-gestational-age birth and low birth weight are relevant indicators for new-born mortality and morbidity.[1-3] Health impairments due to these adverse birth outcomes may last until adulthood.[3; 4] Maternal health factors are associated with adverse birth outcomes; examples are maternal lifestyle-related factors (e.g. tobacco/alcohol use, body mass index) and medical conditions during pregnancy (e.g. preeclampsia, diabetes, depression).[5; 6] Therefore, it is plausible that indicators of the overall maternal health during pregnancy, for example, health-related quality of life (HRQOL), may be associated with birth outcomes.

HRQOL is a measure of the personal perception of the quality and value of life in the context of impairments, functional states, and opportunities, as influenced by disease, injury, treatment and policy.[7] The rating of HRQOL could be used in health care as a tool for identifying patients who are in need of additional care. For example, in the adult population, a relatively low level of HRQOL has shown to be predictive of short- and long-term hospitalization, morbidity and mortality.[8-11] However, data on the associations between maternal HRQOL during pregnancy and normal or adverse birth outcomes are scarce.

To our knowledge, only two relevant studies were conducted.[12; 13] A study in Austria among 90 women showed that those who gave birth to a preterm infant reported worse physical HRQOL during pregnancy, than those who gave birth to a term infant.[12] This study concluded that the decreased HRQOL during pregnancy was associated with the risk for preterm delivery. The other study, among 198 women in Hong Kong, China, demonstrated associations between three domains of HRQOL (i.e. physical, mental and social) during pregnancy and preterm birth and low birth weight. The authors concluded that poor quality of life in late pregnancy can predict preterm birth. [13]

Given the limited number of relevant studies, the present study aimed to assess the associations between maternal physical and mental HRQOL in early, mid- and late pregnancy and birth outcomes in a large prospective population-based mother- and child cohort, the Generation R study.[14] Our hypothesis is that low (physical/mental) HRQOL is associated with adverse birth outcomes. In addition, we aimed to evaluate the differences in birth outcomes between the subgroups of pregnant women who reported 'the worst' (<10th percentile) and 'the best' (>90th percentile) (physical/mental) HRQOL. Our hypothesis is that pregnant women reporting the worst HRQOL during pregnancy have on average worse birth outcomes than women who reported the best HRQOL during pregnancy.

METHODS

Data Sources

The present study was embedded in the Generation R Study, a prospective population-based mother and child cohort from fetal life until adulthood in the Netherlands. Briefly, the cohort includes 9,778 mothers living in the Rotterdam area and their children born between April 2002 and January 2006. The response rate was approximately 61%. Although when Generation R was being set up, the aim was to enroll women in early pregnancy (gestational age < 18 weeks), enrolment was possible until parturition. 7069 mothers were enrolled in early pregnancy, 1594 mothers in mid-pregnancy (gestational age 18-25 weeks), 216 mothers in late pregnancy (gestational age ≥25 weeks) and 899 mothers in postpartum phase. The Generation R Study has been described previously in detail.[14; 15] The study was conducted in accordance with the World Medical Association's Helsinki guidelines and was approved by the Medical Ethical Committee of the Erasmus Medical Center, University Medical Center Rotterdam.[16] Written consent was obtained from all participating women.

Study Population

Of 9,778 women who were enrolled in the cohort study, 8,879 women enrolled during the prenatal period. We excluded women with pregnancies with the following outcomes: twin birth (n=97), induced abortion (n=29), fetal deaths before 20 weeks of gestation (n=75), loss to follow-up in the prenatal period (n=45). Additionally, we excluded women with missing data on pregnancy duration, infant's birth weight and the infant being small for gestational age (n=87). Further we excluded women with missing data on one or more SF-12 items in early (n=2212), mid- (n=2342) and/or late pregnancy (n=2498). Thus, data of 6334 women in early pregnancy (Dataset 1), of 6204 women in mid-pregnancy (Dataset 2) and of 6048 women in late pregnancy (Dataset 3) were included in the analyses. (See Figure 1).

Health-related Quality of Life

HRQOL was measured using the 12-item Short Form Survey (SF-12) in early, mid- and late pregnancy. It is a reliable and well-validated instrument to measure HRQOL and is widely used in studies with large sample sizes.[17] SF-12 consists of 12 items regarding eight areas: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems and perceived mental health. The SF-12 yields two component summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores.[18] A higher score indicates better HRQOL.

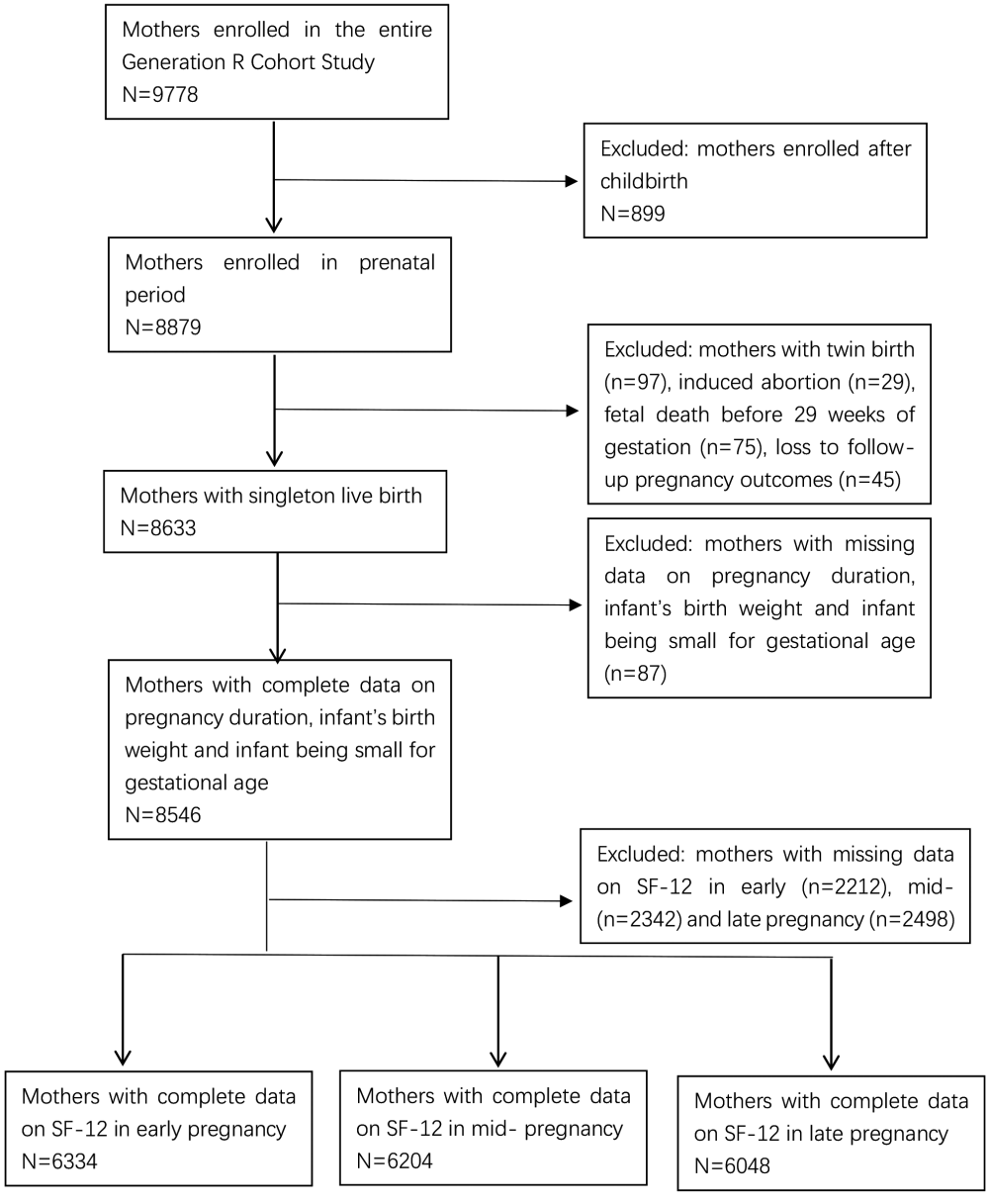

Figure 1. Flow chart for the study populations.

Birth Outcomes

Information on pregnancy duration (weeks) and birth weight (grams) was obtained from patient records as completed by community midwives and obstetricians. Preterm birth was defined as the birth of an infant before 37.0 weeks of gestation,[1] and low birth weight was defined as a birth weight < 2500 grams.[19] In this study, being small for gestational age was defined as a birth weight below the 10th percentile for gestational age and based on standard deviation curves derived from this cohort.[20]

Covariates

We included the following covariates in the regression analyses: maternal age at enrolment, gestational age at enrolment, parity, ethnic background (native Dutch, other Western immigrant and non-Western immigrant), educational level (low, mid-low, mid-high, high), Body Mass Index (BMI) at enrolment and maternal smoking measured in each gestational period. Maternal ethnic background was defined according to the classification of Statistics Netherlands.[21] Education was categorized into four subsequent levels based on the Dutch Standard Classification of Education: high (university degree), mid-high (higher vocational training, Bachelor's degree), mid-low (>3 years general secondary school, intermediate vocational training) and low (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school).[22] Maternal smoking in pregnancy was measured in early, mid- and late pregnancy by self-report questionnaires. In early pregnancy, women were asked "Have you smoked in the past three months", with three answer options; "never", "stopped when pregnancy was known" and "continued with smoking during pregnancy". In mid- and late pregnancy, women were asked "Have you smoked in the past three months" with two answer options; "yes" and "no".

Statistical Analyses

Descriptive analyses were applied to characterize women enrolled in early pregnancy (n=6334). We applied multivariate linear regression analysis (for continuous outcome variables) and logistic regression model (for categorical outcome variables) to assess the associations between PCS-12/MCS-12 in early, mid- and late pregnancy and birth outcomes. In these models, we recoded the original PCS-12/MCS-12 score, i.e. we divided by 10; so, in the regression models 1 point reflects 10 points of the original PCS-12 and MCS-12 following the approach proposed by Mapes et al.[9] The regression models were adjusted by the covariates.

Differences in birth weight and pregnancy duration were assessed between subgroups of women reporting very low (<10th percentile) and very high (>90th percentile) PCS-12/MCS-12 scores using two independent sample t-tests. Cohen's effect sizes (d) were calculated by dividing the difference in mean scores among subgroups by largest SD and

interpreted as: 0.2≤d<0.5 small difference, 0.5≤d<0.8 moderate difference, d≥0.8 large difference. Differences in the incidence of infants of low birth weight, preterm birth and being small for gestational age were assessed between subgroups of women reporting very low (<10th percentile) and very high (>90th percentile) PCS-12/MCS-12 scores using Chi Square tests.

Because we have conducted multiple analyses with the dependent variable, a Bonferroni correction was conducted. The Bonferroni corrected p value was calculated by dividing the original p value (p=0.05) by the number of analyses with the dependent variable, i.e. $p_{corrected}$ = 0.05/6=0.008. In our study, p < 0.008 indicated statistical significance. All analyses were conducted with the Statistical Package for Social Sciences (SPSS) version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

General characteristics

Table 1 presents the characteristics of women enrolled in early pregnancy. The mean maternal age is 29.9 years (SD 5.2). The mean gestational age at intake was 15 weeks (SD 4.0). 3679 (58.2%) of women had their first pregnancy. 3375 (53.5%) of women were Dutch; 1563 (25.1%) and 1234 (19.8%) had high or mid-high educational level. The mean BMI at enrolment was 24.7 (SD 4.5). In early pregnancy, 4738 (75.9%) of women had never smoked; 761 (12.2%) stopped smoking when the pregnancy became known; 746 (11.9%) continued to smoke during pregnancy. In mid-pregnancy, 935 (15.4%) of women had smoked in the previous three months (data not shown). In late pregnancy, 891 (14.9%) of women had smoked in the previous three months (data not shown). The average PCS-12 as reported in early, mid- and late pregnancy was 47.6 (SD 9.1) (see Table 1), 46.2 (SD 9.5) and 39.0 (SD 9.1), while the average MCS-12 as reported in early, mid- and late pregnancy was 48.7 (SD 10.4) (see Table 1), 51.3 (SD 9.7) and 54.1 (SD 10.4). The mean pregnancy duration was 39.9 weeks (SD 1.7); 331 (5.2%) of women had preterm infants. Mean birth weight was 3428 grams (SD 558); 290 (4.6%) of women had infants with low birth weight. 604 (9.5%) of women had infants who were small for gestational age.

Associations between HRQOL in each gestational period and birth outcomes

Table 2 presents the associations between physical and mental HRQOL score in each gestational period and birth outcomes adjusted by the covariates (maternal age at enrolment, gestational age at enrolment, maternal educational level, maternal ethnic background, BMI at enrolment, and maternal smoking in each gestational period). Applying the adjusted significance level, a ten points increase in PCS-12 score in late

pregnancy was statistically significantly associated with a higher chance of having small-for-gestational-age birth (OR=1.20, 95% CI:1.08, 1.33, p value=0.0006). No other significant associations between PCS-12/MCS-12 scores in pregnancy and birth outcomes were found.

Table 1. Personal characteristics of mothers at baseline and birth outcomes (N=6334)

Variables	Values*
Maternal age at enrolment (years), mean (SD)	29.9 (5.2)
Gestational age at enrolment (weeks), mean (SD)	15.0 (4.0)
Parity, number (%)	
Nulliparous	3679 (58.2)
Multiparous	2642 (41.8)
Missing	13
Educational level, number (%)	
High education	1563 (25.1)
Mid-high	1234 (19.8)
Mid-low	1929 (30.9)
Low	1507 (24.2)
Missing	101
Ethnic background, number (%)	
Dutch	3375 (53.5)
Non-Dutch, Western	552 (8.8)
Non-Dutch, non-Western	2378 (37.7)
Missing	29
Body Mass Index at enrolment, mean (SD)	24.7 (4.5)
Missing	29
Maternal smoking in early pregnancy, number (%)	
Never smoking	4738 (75.9)
Stopped smoking when the pregnancy was known	761 (12.2)
Continuing smoking in pregnancy	746 (11.9)
Missing	89
Health-related quality of life	
Physical Component Summary score (PCS-12), mean (SD)	47.6 (9.1)
Mental Component Summary score (MCS-12), mean (SD)	48.7 (10.4)
Birth outcomes	
Pregnancy duration (weeks), number (%)	39.9 (1.7)
Preterm birth (yes), number (%)	331 (5.2)
Birth weight (grams), mean (SD)	3428 (558)
Low birth weight (yes), number (%)	290 (4.6)
Small for gestational age (yes), number (%)	604 (9.5)

High education corresponds to university degree; mid-high level corresponds to higher vocational training, Bachelor's degree; mid-low level corresponds to more than 3 years general secondary school, intermediate vocational training; low level corresponds to no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school.

Table 2. Associations between Physical (PCS-12) and Mental Component Summary score (MCS-12) in each gestational period and birth outcomes [b]

	Pregnancy duration	Preterm birth	Birth weight	Low birth weight	Small size for gestational age
	B (95% CI)	Exp (B) (95%CI)	B (95% CI)	Exp (B) (95%CI)	Exp (B) (95%CI)
Health-related quality of life in early pregnancy					
PCS-12	0.05 (0.00, 0.10)	0.96 (0.85, 1.08)	-4.57 (-19.55, 10.42)	1.07 (0.94, 1.23)	1.05 (0.96, 1.16)
MCS-12	0.01 (-0.03, 0.06)	0.90 (0.82, 1.00)	7.90 (-5.62, 21.42)	0.96 (0.86, 1.08)	1.02 (0.94, 1.10)
Health-related quality of life in mid-pregnancy					
PCS-12	0.004 (-0.001, 0.008)	0.99 (0.98, 1.00)	-0.45 (-1.92, 1.03)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
MCS-12	-0.002 (-0.007, 0.002)	1.00 (0.99, 1.02)	0.44 (-1.92, 1.05)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)
Health-related quality of life in late pregnancy					
PCS-12	0.08 (0.03, 0.13)	0.90 (0.79, 1.03)	-18.10 (-33.43, -2.78)	1.01 (0.88, 1.17)	1.20 (1.08, 1.33)*
MCS-12	0.007 (-0.04, 0.05)	0.96 (0.85, 1.09)	14.06 (0.01, 28.10)	0.96 (0.85, 1.09)	0.93 (0.85, 1.01)

[b] Regarding PCS-12 and MCS-12, one unit change in the regression model is 10 points of the original score. Values in this table are values of coefficient B, exp (B) with 95% CI (confidence interval). Values are not present in this table of coefficient B, exp (B) with 95% CI (confidence interval) of covariates. One cell is corresponding to one full model adjusted by covariates including maternal age at enrolment, gestational age at enrolment, parity, maternal educational level, ethnic background, Body Mass Index at enrolment, and maternal smoking in each gestational period. *Asterisks indicates statistical significance based on the Bofferroni corrected *p* value ($p<0.008$).

Differences in birth outcomes between subgroups reporting very high versus very low HRQOL scores

Table 3 shows differences in birth outcomes between subgroups reporting very high (>90th percentile) and very low (<10th percentile) PCS-12/MCS-12 scores in early, mid- and late pregnancy.

According to the Bofferroni corrected p value, the average pregnancy duration, the average birth weight, the incidence of preterm birth and low birth weight did not significantly differ between subgroups of women reporting a very low PCS-12 score and the subgroup reporting a very high score in early, mid- and late pregnancy (p values >0.008). Having a small-for-gestational-age birth was less frequent in the subgroup mothers who reported a very low PCS-12 score compared to the subgroup mothers who reported a very high score in late pregnancy (7.5% vs. 12.3%, p=0.005). The average pregnancy duration, the occurrence of preterm birth and low birth weight did not differ between subgroups of women reporting a very low MCS-12 score compared to women reporting a very high score in early, mid- and late pregnancy (p values >0.008). The average birth weight of infants whose mothers reported a very low MCS-12 score was significantly lower than that of infants whose mothers reported a very high score (early pregnancy: 3351 vs. 3440 grams, p=0.005, d=0.15; mid-pregnancy: 3376 vs. 3474 grams, p=0.001, d=0.18; late pregnancy: 3344 vs. 3474 grams, p<0.001, d=0.24). The occurrence of having a small-for-gestational-age birth was significantly higher in the subgroup mothers reporting a very low MCS-12 score compared with the subgroup mothers reporting a very high score in late pregnancy (12.3% vs. 6.4%, p=0.001).

DISCUSSION

Our study explored the associations between women's physical and mental HRQOL in each gestational period and birth outcomes. We did not find significant associations between HRQOL in early, mid- and late pregnancy and birth outcomes, except for the association between better physical HRQOL in late pregnancy and higher chances of having a small-for-gestational-age birth. In addition, we found statistically significant differences in several birth outcomes between the subgroups of women reporting the best and the worst HRQOL in pregnancy, but Cohen's effect sizes were small.

Physical HRQOL during pregnancy and birth outcomes

Our study did not confirm the hypothesis that worse physical HRQOL in early, mid- and late pregnancy is associated with preterm birth, gestational duration and (lower) birth weight. In contrast with our hypothesis, in late pregnancy only, an increase in physical HRQOL was associated with more frequent small-for gestational-age births. Also, only in

Table 3. Differences of birth outcomes between subgroups with very high and very low score of Physical (PCS-12) and Mental Component Summary score (MCS-12) in each gestational period

	Pregnancy duration (week)			Preterm Birth			Birth weight (gram)			Low birth weight			Small for gestational age (<10th)		
	Mean (SD)	P value	effect size	Yes (%)	No (%)	P value	Mean (SD)	P value	effect size	Yes (%)	No (%)	P value	Yes (%)	No (%)	P value
Health-related quality of life in early pregnancy															
PCS-12															
<10th (n=634)	39.8 (1.8)	0.18	0.06	32 (5.0)	602 (95.0)	0.60	3425 (559)	0.81	0.01	24 (3.8)	610 (96.2)	0.42	56 (8.8)	578 (91.2)	0.70
>90th (n=686)	39.9 (1.8)			30 (4.4)	656 (95.6)		3418 (551)			33 (4.8)	653 (95.2)		65 (9.5)	621 (90.5)	
MCS-12															
<10th (n=633)	39.8 (1.8)	0.31	0.06	40 (6.3)	593 (93.7)	0.55	**3351 (550)**	**0.005**	**0.15**	36 (5.7)	597 (94.3)	0.81	68 (10.7)	565 (89.3)	0.46
>90th (n=640)	39.9 (1.8)			35 (5.5)	605 (94.5)		**3440 (582)**			34 (5.3)	606 (94.7)		60 (9.4)	580 (90.6)	
Health-related quality of life in mid-pregnancy															
PCS-12															
<10th (n=621)	39.8 (1.7)	0.01	0.12	38 (6.1)	583 (93.9)	0.03	3444 (555)	0.71	0.02	27 (4.3)	594 (95.7)	0.47	53 (8.5)	568 (91.5)	0.61
>90th (n=622)	40.0 (1.6)			22 (3.5)	600 (90.5)		3433 (513)			22 (3.5)	600 (96.5)		48 (7.7)	574 (92.3)	
MCS-12															
<10th (n=621)	39.8 (1.8)	0.08	0.11	40 (6.4)	581 (93.6)	0.17	**3376 (546)**	**0.001**	**0.18**	27 (4.3)	594 (95.7)	0.23	62 (10.0)	559 (90.0)	0.04
>90th (n=631)	40.0 (1.5)			29 (4.6)	602 (95.4)		**3474 (518)**			19 (3.0)	612 (97.0)		42 (6.7)	589 (93.3)	
Health-related quality of life in late pregnancy															
PCS-12															
<10th (n=604)	39.7 (1.6)	0.01	0.18	36 (6.0)	568 (94.0)	0.62	3480 (564)	0.01	0.15	27 (4.5)	577 (95.5)	0.79	**45 (7.5)**	**559 (92.5)**	**0.005**
>90th (n=608)	40.0 (1.7)			32 (5.3)	576 (94.7)		3397 (563)			30 (4.7)	578 (95.1)		**75 (12.3)**	**533 (87.7)**	
MCS-12															
<10th (n=604)	39.9 (1.7)	0.07	0.06	35 (5.8)	569 (94.2)	0.08	**3344 (542)**	**<0.001**	**0.24**	30 (5.0)	574 (95.0)	0.15	**74 (12.3)**	**530 (87.7)**	**0.001**
>90th (n=605)	40.0 (1.5)			22 (3.6)	583 (96.4)		**3474 (524)**			20 (3.3)	585 (96.7)		**39 (6.4)**	**566 (93.6)**	

The bold print indicates the statistical significance according to the Bofferroni corrected p value (i.e. p < 0.008).

late pregnancy, in the subgroup of women reporting the worst HRQOL in late pregnancy, the occurrence of having a small-for-gestational-age birth was significantly lower than in the subgroup of women reporting the best physical HRQOL. An explanation may be that women who will give birth to infants with a relatively small size may themselves gain less weight during pregnancy, which might impose less burden on their physical health[23] This issue needs further research.

Mental HRQOL during pregnancy and birth outcomes

Our study did not confirm the hypotheses that worse mental HRQOL in early, mid- and late pregnancy were associated with more preterm birth, shorter gestational duration, lower birth weight and more often small-for-gestational-age birth. The study by Wang et al. showed that women reporting better mental health in pregnancy (25-29 weeks) had a lower risk of having low-birth-weight infants; but we did not replicate that finding in the analyses in the total sample.[13]

The subgroup of women reporting the worst mental HRQOL in the present study had infants with lower average birth weight in comparison with the subgroup of women reporting the best mental HRQOL. This confirms the above-mentioned finding by Wang et al.[13] However, given the small effect sizes, we recommend further studies in other populations to confirm or reject our findings. [24]

We found a higher incidence of having a small-for-gestational-age birth in the subgroup women who reported the worst mental HRQOL in early, mid- and late pregnancy compared with the subgroup who reported the best mental HRQOL. The lower level of mental HRQOL may be related to a worse maternal mental health status. This, in turn, may be influenced by psychological symptoms and disorders, for instance, maternal depressive symptoms and depression that have been reported by approximately 20% of pregnant women. [25] Depression is known to be related to impaired fetal growth.[26-30] However, it might also be the case that the results from antenatal examinations may inform mothers that their infant might be at risk for becoming small for gestational age; this may have affected mother's mental HRQOL in a negative way.

Strengths and limitations

This is one of the few studies regarding the association between women's HRQOL during pregnancy and birth outcomes. The present study was embedded in large prospective population-based mother and cohort study, which enabled a large sample size for the analyses. Data on more than 6,000 women in early, mid- and late pregnancy was available. To prevent collinearity that was observed in an earlier study,[13] we analysed the associations of HRQOL in each gestational period separately with birth outcomes.

There are some limitations that we need to acknowledge. First, it should be noted that relatively healthy women were enrolled in the Generation R Study; participants were relatively more often high educated and were in general healthier than the general population. [24]

So, the number of infants with clinically severe outcomes, such as early/moderate preterm birth, very low birth weight, was relatively low. This limits the power to detect significant associations between worse HRQOL during pregnancy and adverse birth outcomes.

Therefore, we recommend evaluating mother's HRQOL during pregnancy and the associations with birth outcomes in other large and varied community samples, and in clinical samples. Such studies may enhance our understanding of the association between mother's HRQOL in pregnancy and birth outcomes. Second, restricted growth, or risk factors thereof, may appear already at the beginning of the pregnancy. Therefore, we propose to measure women's HRQOL before pregnancy in future cohort studies of parents who anticipate having children, such as the Generation R Next.[31]

CONCLUSIONS

In the total study population, our findings did not confirm the hypotheses that worse maternal physical and mental HRQOL in early, mid- and late pregnancy were associated with more preterm birth, shorter pregnancy duration, and lower birth weight. In contrast, in late pregnancy, we saw that a relatively better physical HRQOL is associated with a higher chance of having a small-for-gestational-age birth. This requires further study. Our study showed only small effects regarding a relatively low average birth weight and more frequent small-for-gestational-age birth in the subgroup with worst mental HRQOL compared with the subgroup with the best mental HRQOL. The importance of mother's mental HRQOL during pregnancy and the potential consequences for the child requires further study.

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REFERENCES

1. Beck, S., Wojdyla, D., Say, L., Betran, A. P., Merialdi, M., Requejo, J. H., Rubens, C., Menon, R., & Van Look, P. F. (2010). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ, 88(1), 31-38.
2. Kristensen, S., Salihu, H. M., Keith, L. G., Kirby, R. S., Fowler, K. B., & Pass, M. A. (2007). SGA subtypes and mortality risk among singleton births. Early Hum Dev, 83(2), 99-105.
3. Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A.-B., Kinney, M., & Lawn, J. (2013). Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health, 10(Suppl 1), S2-S2.
4. Oudgenoeg-Paz, O., Mulder, H., Jongmans, M. J., van der Ham, I. J. M., & Van der Stigchel, S. (2017). The link between motor and cognitive development in children born preterm and/or with low birth weight: A review of current evidence. Neuroscience & Biobehavioral Reviews, 80, 382-393.
5. Heaman, M., Kingston, D., Chalmers, B., Sauve, R., Lee, L., & Young, D. (2013). Risk Factors for Preterm Birth and Small-for-gestational-age Births among Canadian Women. Paediatric and Perinatal Epidemiology, 27(1), 54-61.
6. Frey, H. A., & Klebanoff, M. A. (2016). The epidemiology, etiology, and costs of preterm birth. Seminars in Fetal and Neonatal Medicine, 21(2), 68-73.
7. Kaplan RM. Quality of Life Measures: Measurement Strategies in Health Psychology. New York: John Wiley; 1985.
8. Tibblin, G., Svardsudd, K., Welin, L., Erikson, H., & Larsson, B. (1993). Quality of life as an outcome variable and a risk factor for total mortality and cardiovascular disease: a study of men born in 1913. J Hypertens Suppl, 11(4), S81-86.
9. Mapes, D. L., Lopes, A. A., Satayathum, S., McCullough, K. P., Goodkin, D. A., Locatelli, F., Fukuhara, S., Young, E. W., Kurokawa, K., Saito, A., Bommer, J., Wolfe, R. A., Held, P. J., & Port, F. K. (2003). Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney International, 64(1), 339-349.
10. Stamnes Koepp, U. M., Frost Andersen, L., Dahl-Joergensen, K., Stigum, H., Nass, O., & Nystad, W. (2012). Maternal pre-pregnant body mass index, maternal weight change and offspring birthweight. Acta Obstet Gynecol Scand, 91(2), 243-249.
11. Rodríguez-Artalejo, F., Guallar-Castillón, P., Pascual, C., & et al. (2005). Health-related quality of life as a predictor of hospital readmission and death among patients with heart failure. Archives of Internal Medicine, 165(11), 1274-1279.
12. Mautner, E., Greimel, E., Trutnovsky, G., Daghofer, F., Egger, J. W., & Lang, U. (2009). Quality of life outcomes in pregnancy and postpartum complicated by hypertensive disorders, gestational diabetes, and preterm birth. J Psychosom Obstet Gynaecol, 30(4), 231-237.
13. Wang, P., Liou, S.-R., & Cheng, C.-Y. (2013). Prediction of maternal quality of life on preterm birth and low birthweight: a longitudinal study. BMC Pregnancy and Childbirth, 13(1), 124.
14. Hofman, A., Jaddoe, V. W., Mackenbach, J. P., Moll, H. A., Snijders, R. F., Steegers, E. A., Verhulst, F. C., Witteman, J. C., & Buller, H. A. (2004). Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol, 18(1), 61-72.
15. Jaddoe, V. W., Mackenbach, J. P., Moll, H. A., Steegers, E. A., Tiemeier, H., Verhulst, F. C., Witteman, J. C., & Hofman, A. (2006). The Generation R Study: Design and cohort profile. Eur J Epidemiol, 21(6), 475-484.
16. General Assembly of the World Medical, A. (2014). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent, 81(3), 14-18.
17. Ware, J., Jr., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care, 34(3), 220-233.

18. Ware JE, Kosinski M, Keller SD, QualityMetric I, New England Medical Center H, Health Assessment L. SF-12: how to score the SF-12 physical and mental health summary scales. Lincoln, R.I.; Boston, Mass.: QualityMetric Inc.; Health Assessment Lab; 2002
19. Wardlaw TM. Low birthweight: country, regional and global estimates: UNICEF; 2004.
20. Verburg, B. O., Steegers, E. A., De Ridder, M., Snijders, R. J., Smith, E., Hofman, A., Moll, H. A., Jaddoe, V. W., & Witteman, J. C. (2008). New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound Obstet Gynecol, 31(4), 388-396.
21. Statistics Netherlands. Migrants in the Netherlands 2004 (Allochtnen in Nederland 2004). Voorburg/Heelen, the Netherlands: Centraal Bureau voor de Statistiek; 2004.
22. Statistics Netherlands. The Dutch Standard Classification of Education, SOI 2006. Voorburg/ Heerlen; 2008
23. Ludwig, D. S., & Currie, J. (2010). The Relationship Between Pregnancy Weight Gain and Birth Weight: A Within Family Comparison. Lancet, 376(9745), 984-990.
24. Jaddoe, V. W., van Duijn, C. M., Franco, O. H., van der Heijden, A. J., van Iizendoorn, M. H., de Jongste, J. C., van der Lugt, A., Mackenbach, J. P., Moll, H. A., Raat, H., Rivadeneira, F., Steegers, E. A., Tiemeier, H., Uitterlinden, A. G., Verhulst, F. C., & Hofman, A. (2012). The Generation R Study: design and cohort update 2012. Eur J Epidemiol, 27(9), 739-756.
25. Lee, A. M., Lam, S. K., Sze Mun Lau, S. M., Chong, C. S., Chui, H. W., & Fong, D. Y. (2007). Prevalence, course, and risk factors for antenatal anxiety and depression. Obstet Gynecol, 110(5), 1102-1112.
26. Bowen, A., Bowen, R., Butt, P., Rahman, K., & Muhajarine, N. (2012). Patterns of depression and treatment in pregnant and postpartum women. Can J Psychiatry, 57(3), 161-167.
27. Alder, J., Fink, N., Bitzer, J., Hosli, I., & Holzgreve, W. (2007). Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med, 20(3), 189-209.
28. Feldman, P. J., Dunkel-Schetter, C., Sandman, C. A., & Wadhwa, P. D. (2000). Maternal Social Support Predicts Birth Weight and Fetal Growth in Human Pregnancy. Psychosomatic Medicine, 62(5), 715-725.
29. Hedegaard, M., Henriksen, T. B., Sabroe, S., & Secher, N. J. (1993). Psychological distress in pregnancy and preterm delivery. Bmj, 307(6898), 234-239.
30. Glynn, L. M., Schetter, C. D., Hobel, C. J., & Sandman, C. A. (2008). Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. Health Psychol, 27(1), 43-51.
31. Generation R Next.https://www.generationr.nl/next/

PART III

Assessing Determinants of Childhood Health-Related Quality of Life

CHAPTER 6

Determinants of Health-Related Quality of Life in School-Aged Children: A General Population Study in the Netherlands

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ABSTRACT

Background

Health related quality of life is the functional effect of a medical condition and/or its therapy upon a patient, and as such is particularly suitable for describing the general health of children. The objective of this study was to identify and confirm potential determinants of health-related quality of life in children aged 4-11 years in the general population in the Netherlands. Understanding such determinants may provide insights into more targeted public health policy.

Methods

As part of a population based cross sectional study, the Child Health Questionnaire (CHQ) Parental Form 28 was used to measure health-related quality of life in school-aged children in a general population sample. Parents of 10,651 children aged 4-11 years were interviewed from January 2001 to December 2009.

Results

Multivariate and regression analyses demonstrated a declined CHQ Physical Summary score for children who had >1 conditions, disorders or acute health complaints and who were greater consumers of healthcare; children with a non-western immigrant background; and children whose parents did not work. Lower CHQ Psychosocial Summary score was reported for children who had >1 conditions, disorders or acute health complaints, boys, children of single parents and obese children.

Conclusion

The best predictors of health-related quality of life are variables that describe use of health care and the number of disorders and health complaints. Nonetheless, a number of demographic, socio-economic and family/environmental determinants contribute to a child's health-related quality of life as well.

INTRODUCTION

Good health is something all parents want for their children as it contributes to their happiness and well-being [1]. Health-related quality of life (HRQOL) is the functional effect of a medical condition and/or its therapy upon a patient [2,3]. It is thus subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation [3]. It is therefore, particularly suitable for describing the health of children in a general representative sample that may also include specific condition groups [4–7].

Previous studies have shown that many factors are associated with HRQOL in children. Logically, variables correlating with bad health, e.g., the number of conditions or health problems [8] or more indirectly the number of health care visits [9], are negatively associated with HRQOL. Additional studies have examined the potential demographic and/or socioeconomic determinants of diminished HRQOL. Girls tend to have lower HRQOL than boys [9–12].

HRQOL declines with age [10–12], although sometimes this was found to be more distinctive for girls [11]. Also, a low socioeconomic position of the child or the child's family, as measured by income [12], parental education level or family wealth [13], negatively influences parental reports of child HRQOL. In addition, children living in neighbourhoods scoring high on satisfaction to live there and on good access to services like recreational programmes and stores with fresh fruit and vegetables reported higher HRQOL [14].

Most studies mentioned examined different and limited numbers of potential determinants. Thus, findings from each of these separate studies need to be combined to generate an overall understanding of potential determinants of HRQOL. Such efforts are hampered because of differences in key study components such as overall design, data collection methodology child age and use of differing HRQOL survey instruments. The current study avails the opportunity to further assess identified determinants in a more robust and potential diverse population—i.e., not a community or clinical sample, but a very large randomly selected sample drawn from national data, and therefore generalizable. It includes not only known variables such as gender, age, socioeconomic position, and health but also variables that, to our knowledge, have not been addressed before such as cultural/ethnic differences and family composition. To assess HRQOL, the Child Health Questionnaire short-form (CHQ-PF28) was used.

The CHQ-PF28 focusses on the health-related part of quality of life, so we expect that the strongest determinants are factors that directly or indirectly describe the child's health.

That is, the number of chronic conditions or health complaints, or the use of health care, which may be considered as manifestation of acute health problems or limitations. We expect only minor effects for determinants like demographic, socio-economic or family/ environmental variables.

METHODS

Data source

The study data source was the national Dutch Health Interview Survey (DHIS), conducted by Statistics Netherlands, using trained in-house interviewers. The DHIS is a cross-sectional survey, conducted yearly, amongst the Dutch population living in non-institutionalised households. Each month, a stratified two-step-sample of persons is taken from the Dutch Municipal Personal Records. The yearly response rate of the age group 4–11 years is approximately 75%. For this study, a 9 year set of surveys was used. For respondents aged 0–11 years, one parent participates in the interview. Between January 2001 and December 2009, the parents of 10,651 children aged 4–11 years were interviewed. The mean age was 7.47 years (SD = 2.29), 49.1% were girls. Data was weighted to take into account the person's probability of selection and to compensate for (selective) nonresponse. By so doing, responses are adjusted to the actual distribution of persons in the target population, allowing generalization at the national level. The weighting model included sex, age, marital status, regional information (province, part of the country, urbanization), household size, ethnicity and interview month.

Parents received written study information and participation was elective. According to Dutch law (Wet medisch wetenschappelijk onderzoek met mensen), formal consent (e.g., from a medical ethics committee) was not required as this study relied on secondary anonymised data collection in the context of performing statutory tasks. Data collection and processing was in strict accordance with the national standard. At no time did the datasets contain direct identifiers.

Questionnaire

The Dutch version of the parent-completed CHQ-PF28 was administered via structured interview as part of the larger DHIS interview. This CHQ measure was selected because it has been rigorously translated into 78 languages (http://www.healthactchq.com/chq-t.php) and specifically evaluated for use in the Netherlands in very young children [15,16] and is easy to administer in large population studies [4]. The CHQ-PF28 includes multi-item Likert-type scales and global items that assess 14 unique physical and psychosocial concepts. Per published instructions [4], a mean scale score is derived and items are then standardized on a 0–100 continuum with a higher score representing

better HRQOL. Scores can also be combined to derive a two component summary—the CHQ Physical (PhS) and Psychosocial Summary (PsS) Scales. The CHQ Summaries are based on factor weights from a US representative sample of children ages 5–18 years of age [4]. A score of 50 represents the mean of the US reference population sample and the standard deviation is ten points above/below the mean [4]. The weighted US values to derive 2 component summary scales (PhS and PsS) have been used with success in both the aforementioned Dutch and other international studies [17,18]. See Table 1 for a description/interpretation of scales.

Description of determinants

The potential determinants are listed in Table 2 and were selected a priori based on literature study and their availability in the current DHIS dataset. Ethnicity (western immigrant, non- western immigrant and native Dutch people) and household level of income were identified from separate databases (Dutch Municipal Personal Records and Dutch Tax Authorities, respectively). Children whose parents were born outside the Netherlands were identified as immigrants (even if the child was of Dutch nationality). Western immigrants originated from Europe (excluding Turkey), North America, Oceania, Indonesia or Japan. Non-western immigrants originated from Africa, South America, Asia (excluding Indonesia and Japan) or Turkey. Low income households had an income below the Dutch low income threshold using the Dutch supplementary benefit level. "Urbanization" of the child's primary place of residence was defined as the average number of addresses per square kilometre within a one kilometre radius. For exact boundaries see http://www.cbs.nl/en-GB/menu/methoden/toelichtingen/ alfabet/u/ urbanisation-rate.htm.

Parents were asked to indicate if their child ever had cancer, or experienced health or behavioural issues during the previous 12 months: congenital defects, diabetes, migraine/ severe headache, asthma, psoriasis, eczema, arthritis/rheumatism, severe/ protracted disorders of the intestines, back, neck/shoulder, arm or hand; dyslexia, intellectual disability, and presence of at least three core ADHD symptoms (DSM-criteria: restless behaviour/not being able to sit still, fidgeting/squirming, short attention span). An open-ended question about any other chronic conditions and behavioural issues not mentioned was also included. The occurrence of headache, tiredness, back, muscle and joint pains during the last 14 days were used to determine "number of health complaints". Body-Mass Index (BMI) was calculated using child's height/ weight as reported by the parent. International age- and sex specific boundaries [19] were used to define weight categories (normal weight, overweight, obese).

Statistical Analyses

Analyses were performed using SPSS 14.0. Outliers (values above/below 3xSD +/- mean) were deleted. Non-response was compensated using weights [20]. Bivariate analyses were performed to assess differences in the two CHQ Summaries between (independent) groups of children. Distributions of the summary scores were somewhat negatively skewed (PhS: Skewness = -1.85, se =. 027. PsS: Skewness = -.65, se =. 027). Because of the large number of respondents, however, parametric tests are preferred to nonparametric alternatives [21]. Oneway ANOVA's were used; a p-value <0.05 was considered to be statistically significant. In case of a significant effect, post-hoc Tukey HSD analyses were performed. Clinical significance was assessed using effect size which was estimated by dividing the difference in mean scores between subgroups by the largest SD and interpreted by using Cohen's effect sizes (d): 0.2≤ d <0.5 small difference, 0.5 ≤ d < 0.8 moderate, and d ≥ 0.8 large [22]. In order to interpret the effect size in real-world terms, the minimum important difference (MID) was used [23–25]. In most circumstances, the threshold of discrimination for changes in HRQOL for chronic diseases appears to be approximately half a standard deviation (SD) [26,27].

Stepwise multivariate linear regression was performed to identify determinants that could best explain the two CHQ-PF28 Summary Scale means. Variables were entered independently, commencing with the highest F-value as determined by the bivariate analyses. The procedure was repeated until the addition of another independent variable did not increase the explained variation (adjusted R-square) or until the variable included was not statistically significant.

Thus, the final models included only those variables that were statistically significant and enhanced the degree of explanation. Multicollinearity was checked.

RESULTS

General characteristics of the study population (N = 10,651, mean age of 7.47 years, 49.1% were girls), can be found in Table 2. Mean scores for several age and gender groups are presented exclusively for illustration purposes in S1 Table.

Bivariate Analyses

Table 3 provides CHQ mean scores, standard deviations, F-values, p-values and effect sizes of the tested determinants of the CHQ Summary Scores. Summary Scores were not calculated for 3.1% of the cases (327 of 10,651) because one or more items were missing or answered 'don't know'.

Table 1. CHQ-PF28 scales, number of items per scale, and score interpretation. [a]

Scale	Nr of items	Description low score	Description high score
Physical functioning (PF)	3	Child is limited a lot in performing all physical activities, including self-care, because of health	Child performs all types of physical activities, including the most vigorous, without limitations attributable to health
Role functioning: emotional/behaviour (REB)	1	Child is limited a lot in school work or activities with friends as a result of emotional or behavioural problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behavioural problems
Role functioning: physical (RP)	1	Child is limited a lot in school work or activities with friends as a result of physical health	Child has no limitations in school work or activities with friends as a result of physical health
Bodily pain (BP)	1	Child has extremely severe, frequent, and limiting bodily pain	Child has no pain or limitations because of pain
General behaviour (BE)	4	Child very often exhibits aggressive, immature, delinquent behaviour	Child never exhibits aggressive, immature, delinquent behaviour
Mental health (MH)	3	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy, and calm all of the time
Self-esteem (SE)	3	Child is very dissatisfied with abilities, looks, family/peer relationships, and life overall	Child is very satisfied with abilities, looks, family/peer relationships, and life overall
General health perceptions (GH)	4	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact: emotional (PE)	2	Parent experiences a great deal of emotional worry/ concern as a result of child's physical and/or psychosocial health	Parent doesn't experience feelings of emotional worry/ concern as a result of child's physical and/or psychosocial health
Parental impact: time (PT)	2	Parent experiences a lot of limitations in time available for personal needs because of child's physical and/or psychosocial health	Parent doesn't experience limitations in time available for personal needs because of child's physical and/or psychosocial health
Family activities (FA)	2	The child's health very often limits or interrupts family activities or is a source of family tension	The child's health never limits and interrupts family activities or is a source of family tension
Family cohesion (FC)	1	Family's ability to get along is rated 'poor'	Family's ability to get along is rated 'excellent'
Change in health (CH)	1	Child's health is much worse now than one year ago	Child's health is much better now than one year ago

[a]. From the CHQ manual [2]. Reproduced with permission from JM Landgraf.

Table 2. General characteristics of the study population

Variable	Levels	PhS		PsS	
		N	%	N	%
Gender	Male	4227	51.2%	4258	50.9%
	Female	4033	48.8%	4108	49.1%
Age	4	1024	12.4%	1054	12.6%
	5	1048	12.7%	1078	12.9%
	6	1038	12.6%	1055	12.6%
	7	1038	12.6%	1046	12.5%
	8	1041	12.6%	1039	12.4%
	9	1043	12.6%	1046	12.5%
	10	1000	12.1%	1011	12.1%
	11	1028	12.4%	1037	12.4%
Ethnicity	Native Dutch people	5924	79.8%	5985	79.7%
	Immigrants, Western	431	5.8%	440	5.9%
	Immigrants, Non-west.	1066	14.4%	1080	14.4%
Urbanisation rate	Very high	1395	16.9%	1415	16.9%
	High	2213	26.8%	2232	26.7%
	Moderately high	1675	20.3%	1698	20.3%
	Low	1853	22.4%	1873	22.4%
	Very low	1124	13.6%	1147	13.7%
Single parent family	Two parent family	7402	89.7%	7501	89.8%
	Single parent family	849	10.3%	856	10.2%
Siblings in household	Only child	865	10.5%	870	10.4%
	1 brother or sister	4245	51.5%	4297	51.4%
	More brothers/sisters	3140	38.1%	3187	38.1%
Working situation parents[a]	Both parents work	5173	69.3%	5230	69.2%
	One parent works	1829	24.5%	1858	24.6%
	Parents do not work	466	6.2%	473	6.3%
Highest parental educational level[b]	Low	437	7.5%	434	7.4%
	Medium	2883	49.6%	2909	49.5%
	High	2495	42.9%	2532	43.1%
Low household income	No	7068	88.7%	7154	88.7%
	Yes	900	11.3%	913	11.3%
Parents' smoking behaviour[c]	Both parents smoke	939	13.1%	945	13.0%
	One parent smokes	2072	28.8%	2090	28.8%
	Parents don't smoke	4173	58.1%	4234	58.2%
BMI child	Normal weight	4885	83.1%	4934	83.0%
	Overweight	751	12.8%	760	12.8%
	Obese	242	4.1%	250	4.2%
Nr of chronic conditions	None	6475	78.4%	6496	77.6%
	1	1461	17.7%	1506	18.0%
	2 or more	324	3.9%	364	4.4%
Nr of behavioural/ learning disorders	None	7528	91.2%	7663	91.6%
	1	651	7.9%	632	7.6%
	2 or more	78	0.9%	68	0.8%
Nr of acute health complaints	None	5001	60.6%	4997	59.8%

Table 2. Continued

Variable	Levels	PhS		PsS	
		N	%	N	%
(Nr of acute health complaints)	1	2010	24.4%	2037	24.4%
	2	941	11.4%	983	11.8%
	3 or more	294	3.6%	335	4.0%
Visited GP last 14 days	No	7675	92.9%	7725	92.3%
	Yes	585	7.1%	641	7.7%
Visited a medical specialist last 14 days	No	7984	96.6%	8063	96.4%
	Yes	277	3.4%	303	3.6%
Used prescription medicines last 14 days	No	7092	85.9%	7133	85.3%
	Yes	1168	14.1%	1232	14.7%
Used non-prescription medicines last 14 days	No	5960	72.2%	5996	71.7%
	Yes	2299	27.8%	2369	28.3%
Hospitalisation last year	No	8121	98.3%	8211	98.1%
	Yes	140	1.7%	155	1.9%

a. If a parent in a single family works, he/she is included in the category 'Both parents work'.
b. Parental education is missing for some years.
c. If a parent in a single family smokes, he/she is included in the category 'One parent smokes'

The number of chronic conditions or number of acute health complaints (i.e, health problems), were associated with lower observed scores for both the CHQ PhS and PsS Summary Scales ($p<.001$). Large effect sizes (d) were found for: the PhS score in children who had ≥3 health complaints (e.g., headache /tiredness)($d = 0.90$, $p<.001$); the PsS score in children with ≥2 chronic conditions ($d = 0.92$, $p<.001$); and the PsS score in children with ≥2 reported behavioural or learning disorders ($d = 1.26$, $p<.001$), all compared to children without such disorders (Table 3). The variables with moderate or large effect sizes ($d\geq 0.5$) also met the criterion of the minimal important difference, i.e. a difference of half a SD.

Regression Analyses

For the PhS, the final multivariate regression model included: ethnicity, parent work status, number of chronic conditions, behavioural/learning disorders, health complaints, general practitioner and/or medical specialist consultations, medication status and hospitalization. The adjusted R-square for the final model was. 24. For the PsS, the final regression model included: gender, single parent family, obesity, number of chronic conditions, behavioural/learning disorders, and health complaints. The adjusted R-square for the final model was 0.08. See Table 4 for the coefficients and corresponding confidence intervals.

Table 3. Bivariate associations with CHQ-score and effect sizes based on interview administration methods#

Variable	Levels	PhS		PsS	
		mean (F-value, p-value)	sd effect size	mean (F-value, p-value)	sd effect size
Gender	Male	57.04	6.22	52.68	6.66
	Female	56.95	6.04	53.36	6.29
		(<1, .51)	*0.01*	(22.93, <.001)*	*0.10*
Age	4	56.63	6.47	53.30	6.12
	5	56.86	6.33	53.75	6.17
	6	57.42	5.90	53.06	6.28
	7	57.03	6.09	53.21	6.54
	8	57.09	5.92	52.49	6.64
	9	57.20	5.96	52.65	6.73
	10	56.73	6.33	52.70	6.78
	11	57.02	6.01	52.88	6.58
		(<2, .09)	*0.12*	(4.26, <.001)*	*0.19*
Ethnicity	Native Dutch people	57.15	6.11	53.10	6.42
	Immigrants, Western	56.50	6.52	52.68	6.72
	Immigrants, Non-western	56.35	6.31	52.68	6.60
		(9.13, <.001)*	*0.12*	(<2.5, .08)	*0.06*
Urbanisation rate	Very high	56.58	6.17	52.89	6.45
	High	56.96	6.09	53.04	6.55
	Moderately high	56.98	6.29	52.89	6.46
	Low	57.18	6.09	52.99	6.48
	Very low	57.32	5.98	53.32	6.49
		(2.82, .02)*	*0.12*	(<1, .44)	*0.07*
Single parent family	Two parent family	57.05	6.09	53.24	6.38
	Single parent family	56.60	6.47	50.95	7.07
		(4.01, .04)*	*0.07*	(96.81, <.001)*	*0.32*[a]
Siblings in household	Only child	56.65	6.34	52.53	6.80
	Has 1 brother or sister	56.93	6.18	53.00	6.42
	Has more brothers/ sisters	57.19	6.02	53.15	6.49
		(3.06, .05)*	*0.07*	(3.11, .04)*	*0.09*
Working situation Parents	Both parents work	57.17	6.01	53.13	6.35
	One parent works	56.90	6.32	53.09	6.48
	Parents do not work	55.53	6.98	51.63	7.25
		(15.62, <.001)*	*0.24*[a]	(11.78, <.001)*	0.21[a]
Highest parental educational level	Low	56.63	6.20	52.20	6.87
	Medium	57.19	6.16	52.96	6.52
	High	57.02	5.95	53.52	6.22
		(<2, .17)	*0.09*	(10.30, <.001)*	*0.19*
Low household income	No	57.04	6.10	53.17	6.39
	Yes	56.80	6.20	52.37	6.82
		(<1.5, .27)	*0.04*	(12.71, <.001)*	0.12

Table 3. Continued

Variable	Levels	PhS		PsS	
		mean (F-value, p-value)	sd effect size	mean (F-value, p-value)	sd effect size
Parents' smoking behaviour	Both parents smoke	57.05	6.16	52.82	6.49
	One parent smokes	56.75	6.36	52.71	6.59
	Parents do not smoke	57.12	6.08	53.22	6.38
		(<2.5, .08)	0.06	(4.84, .01)*	0.08
BMI child	Normal weight	57.06	6.08	53.12	6.46
	Overweight	56.68	6.33	52.90	6.57
	Obese	55.86	6.31	51.49	7.02
		(5.37, .005)*	0.19	(7.65, <.001)*	0.23[a]
Nr of chronic conditions	None	57.77	5.47	53.27	6.25
	1	55.04	6.96	52.41	6.98
	2 or more	50.36	8.27	50.80	7.92
		(341.50, <.001)*	0.90[c]	(33.19, <.001)*	0.31[a]
Nr of behavioural / learning disorders	None	57.05	6.02	53.45	6.21
	1	56.68	6.93	48.58	7.41
	2 or more	54.33	8.94	44.42	7.17
		(8.63, <.001)*	0.30[a]	(237.35, <.001)*	1.26[c]
Number of acute health complaints	None	58.44	4.79	53.86	6.07
	1	55.93	6.45	52.48	6.63
	2	53.70	7.59	51.53	7.25
	3 or more	50.51	8.67	50.94	7.58
		(353.60, <.001)*	0.92[c]	(52.07, <.001)*	0.36[a]
Visited a GP last 14 days	No	57.35	5.77	53.02	6.43
	Yes	52.41	8.49	52.84	7.20
		(367.28, <.001)*	0.58[b]	(<1, .49)	0.03
Used prescription medicines last 14 days	No	57.60	5.60	53.16	6.31
	Yes	53.32	7.74	52.14	7.42
		(519.34, <.001)*	0.55[b]	(26.03, <.001)*	0.14
Used non pre-scription medicines last 14 days	No	57.86	5.39	53.24	6.34
	Yes	54.77	7.27	52.41	6.83
		(441.49, <.001)*	0.42[a]	(27.85, <.001)*	0.12
Hospitalization last year	No	57.07	6.07	53.02	6.47
	Yes	52.88	8.03	52.45	7.62
		(64.39, <.001)*	0.52[b]	(<1.5, .28)	0.07

Effect sizes are highest vs. lowest mean CHQ-score. a = small difference, b = moderate difference, c = large difference. # Data were calculated using US based weights and are provided for illustrative purposes. Not for general use. * Statistically significant

Table 4. Multivariate analysis of CHQ-PF28 scores.

Variable	Physical Summary scale			Psychosocial Summary scale		
	Coefficient (N = 7171)	95% confidence interval		coefficient (N = 8340)	95% confidence interval	
		lower bound	upper bound		lower bound	upper bound
Gender (male = Ref)				0.51*	0.22	0.80
Ethnicity (native Dutch = Ref)	-0.63+	-1.00	-0.25			
Single parent family (Two parent = Ref)				-0.96*	-1.20	-0.71
Number of working parents	0.32+	0.10	0.53			
Obesity (no obesity = Ref)				-1.53*	-2.31	-0.74
Number of chronic conditions	-2.00*	-2.25	-1.76	-0.50*	-0.75	-0.24
Number of behavioural/learning disorders	0.44+	0.06	0.82	-4.29*	-4.74	-3.84
Number of acute health complaints	-1.85*	-2.00	-1.69	-0.92*	-1.09	-0.75
Visited a general practitioner last 14 days	-2.89*	-3.39	-2.39			
Visited a medical specialist last 14 days	-3.33*	-4.01	-2.65			
Used prescription medicines last 14 days	-2.01*	-2.40	-1.61			
Used non-prescription medicines last 14 days	-1.71*	-2.01	-1.42			
Hospitalization last year	-2.86*	-3.82	-1.90			

Ref indicates a category used as a standard reference. If there is no reference, the variable is treated as a continuous variable in the model. * $p < .001$ + $p < .005$

DISCUSSION

For policy makers, understanding the variables that determine children's HRQOL can provide insight into developing more targeted public health policies. In this study, we examined a large range of determinants of HRQOL, i.e., demographic, socio-economic, health and family/environmental, in a national school-aged Dutch sample using the CHQ-PF28. The bivariate analyses have mapped the different determinants. The multivariate regression analyses allowed for an independent comparison of the determinants to identify the most defining ones.

As expected, and as was reported previously by others [8], conducting bivariate analyses, large clinically significant differences for both CHQ-PF28 PhS and PsS Summaries were observed for the number of parent-reported health conditions/disorders/complaints. Moderate differences were found for "use of health care" (consulting a GP or medical specialist, use of prescribed medication, hospitalization). Hence, the best predictors in the multivariate regression analysis are variables that describe the use of health care and the number of chronic conditions and health complaints for PhS and the number of behavioural/learning disorders for PsS. This difference is understandable given that the "psychosocial CHQ scales" (e.g., mental health, behaviour, self-esteem) load more substantially on the PsS. For PsS, health care determinants do not contribute to the scale variance. The moderate and large effect sizes we found can be regarded as clinically important differences, i.e. they met the criterion of the minimum important difference (half a SD).

A number of demographic, social-economic and family/environmental determinants were found with small or even no clinical significance using bivariate analysis. However, some contributed significantly, although only slightly, in the regression analyses. This finding suggests that gender, ethnicity, parent work status, single parent family and obesity affected HRQOL independent of the number of chronic conditions or health issues.

For PhS, one important significant contributor was the non-western immigrant status. Several surveys conducted at the national and local level showed inequalities in health in non-western immigrant children compared to non-migrant children in the Netherlands [28]. Children of non-working parents had a lower mean score, which had been reported in a previous study using the PedsQL [9]. The positive effect of working parents may be explained by the better family socio-economic position which theoretically can provide a more stimulating and healthier environment. A recent Dutch study showed that children from low socio-economic families experience more asthma symptoms, poorer general health, more frequent respiratory infections, and are more often overweight or obese

[29]. Conversely, the child's poor health— as perceived by the parent—may be the reason for the parent to stay at home, or reduce working hours. An effect in an unexpected direction was found for the number of behavioural/learning disorders. While bivariate analyses showed that parents reported lower PhS for children with at least one learning/ behaviour disorder, multivariate regression analysis showed the op- posite, to a small extent. We examined whether this is a consequence of the fact that our multivariate analyses included suppressive factors for low PhS. In the models, no multicollinearity was found and we could not identify a suppressor effect (data not shown). The relatively high PhS for children with a learning or behavioural disorder may be considered a chance finding.

For PsS, the best predictor among the non-health-related determinants was obesity. Several studies have shown that obese children have lower HRQOL than normal weight children [30– 33]. In addition, parents of girls reported slightly higher scores. However, lower HRQOL has been reported for girls using the KIDSCREEN [34–37] and PedsQL [9]. This difference may be explained by the item content for the General Behaviour subscale which is weighted highly in the calculation of the PsS and which asks about frequency of aggressive/immature/delinquent behaviour (arguing, inability to concentrate, lying/ cheating). Boys tend to employ direct means of aggression, whereas girls more often employ indirect, often less visible, means of aggression [35]. Also, most respondents (81%) were mothers and parental gender has been shown to be a mediating factor in the reporting of a child's health [37]. Finally, living in single parent families was a significant contributor to PsS score variance: a lower mean score was observed for children living in a single parent family. This has been reported by others as well [37].
Collectively, these data suggest that a child's HRQOL—as reported by the parent—is mainly dependent on the child's health, and to a smaller extent on demographic, socioeconomic and family/environmental factors.

Strengths and Limitations

Overall, this effort to explore the determinants of HRQOL in children extended the current literature by measuring a wider array of variables than previous studies and did so in a large, representative sample. Even still, the independent variables were limited to those found in the dataset DHIS (demographic, social-economic factors and parents' reports of children's medical care use and medical conditions), and explained only a small part of the variance of the CHQ-PF28 PhS and especially PsS. Although the result does not change how we might think about the factors that contribute to children's HRQOL, they do confirm the role of various factors in a large, representative sample. Other important determinants were not captured and thus further study is needed. For example, early life experiences and maternal factors (gestation, health symptoms in pregnancy, anxiety and depression) were found to impact HRQOL[38] and Mansour

et al. found that children's perceived closeness to school personnel and the school environment are positively associated with HRQOL [9].

Other methodological considerations are warranted. First, although the CHQ-PF28 was developed for parents of children aged 5 years and older, the focus was on school-aged children, which in the Netherlands includes 4-year-olds. Previous work has demonstrated that the Dutch CHQ-PF28 can be successfully applied and validated among children aged 4–13 [15]. Further, data used in these analyses were gathered at home using face to face interviews. US factor weights to calculate the CHQ summaries were derived using paper-and-pencil methods. However, publications using the same data source (but from earlier years) and a school based sample demonstrated that the CHQ-PF28 is a feasible instrument in the Netherlands irrespective of administration [15,39]. Thirdly, both Cohen's d and difference of half a SD were used for the interpretation of relevant differences in HRQOL. Although this is an accepted method[40] and helpful to interpret findings in real-world terms, there are still insufficient data to understand the relative impact of the observed score differences. Empirically defined cut-off points for minimal important differences for HRQOL measures such as the CHQ-PF28 are important in future research [41]. Finally, a cross-sectional design was applied with data that were collected during nine consecutive years; it is therefore possible that a time trend in the data could potentially confound findings. To determine if such was the case, additional bivariate analyses were performed to evaluate the impact of the variable 'Year of data collection' on the CHQ Physical and Psychosocial Summary Scale Scores (statistical significance and effect sizes were evaluated). Bivariate analyses showed that survey year did not significantly effect PhS (d = 0.07, p =. 888) or PsS (d = 0.10, p =. 390). Thus, the trend was not considered a serious threat to the overall findings.

REFERENCES

1. Gerdtham UG, Johannesson M. The relationship between happiness, health, and socio-economic factors: results based on Swedish microdata. J Socio Econ. 2001; 30: 553–7.
2. Cella D. Measuring quality of life in palliative care. Seminars in Oncology. 1995; 22:73–81. PMID: 7537908
3. Schipper H, Clinch JJ, Olweny CLM. Quality of life studies: definitions and conceptual issues. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. Philadelphia: Lippincott-Raven Publishers;1996. PMID: 17615046
4. Landgraf JM, Abetz L, Ware JE. The Child Health Questionnaire (CHQ): A user's manual (2nd printing). Boston: HealthAct; 1999.
5. Landgraf JM. Practical considerations in the measurement of health-related quality of life in child/adolescent clinical trial. In: Fayers P, Hays RD, 2nd edition editors. Assessing the Quality of life in Clinical Trials. Oxford: Oxford Press; 2004. PMID: 15266485
6. Landgraf JM. Health-related quality of life assessment in pediatric clinical trials: a brief introduction. In: Helms P, Stonier P, editors. Paediatric Clinical Research Manual. Euromed Communications; 2005.
7. Bullinger M. Assessing health related quality of life in medicine: an overview over concepts, methods and applications in international research. Restor Neurol Neurosci. 2002; 20:93–101. PMID: 12454358
8. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev. 2008; 34:418–29. doi: 10.1111/j.1365- 2214.2008.00825.x PMID: 19154551
9. Mansour ME, Kotagal U, Rose B, Ho M, Brewer D, Roy-Chaudhury A, et al. Health-Related Quality of Life in Urban Elementary Schoolchildren. Pediatrics. 2003; 111:1372–81. PMID: 12777555
10. Michel G, Bisegger C, Fuhr DC, Abel T, The KIDSCREEN group. Age and gender differences in health- related quality of life of children and adolescents in Europe: a multilevel analysis. Qual Life Res. 2009; 18:1147–57. doi: 10.1007/s11136-009-9538-3 PMID: 19774493
11. Ravens-Sieberer U, Gosch A, Rajmil L, Erhart M, Bruil J, Duer W, et al. The KIDSCREEN-52 quality of Life Measure for Children and Adolescents: Psychometric results from a cross-cultural survey in 13 European countries. Value Health. 2007; 11:645–58. doi: 10.1111/j.1524-4733.2007.00291.x PMID: 18179669
12. Simon AE, Chan KS, Forrest CB. Assessment of children's health-related quality of life in the United States with a multidimensional index. Pediatrics. 2008; 121:118–26.
13. Von Rueden A, Gosch LR, Bisegger C, Ravens-Sieberer U. Socioeconomic determinants of health related quality of life in childhood and adolescence: results from a European study. J Epidemiol Community Health. 2006; 60:130–5. PMID: 16415261
14. Wu XY, Ohinmaa A, Veugelers PJ. Sociodemographic and neighbourhood determinants of health-related quality of life among grade-five students in Canada. Qual Life Res. 2010; 19:969–76. doi: 10. 1007/s11136-010-9663-z PMID: 20446044
15. Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. Epidemiol Community Health.2005; 59:75–82. PMID: 15598731
16. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population Qual Life Res. 2002; 11:575– 81. PMID: 12206578
17. Beckung E, White-Koning M, Marcelli M, McManus V, Michelsen S, Parkes J, et al. Health status of children with cerebral palsy living in Europe: a multi-centre study. Child Care Health. 2008; 34:806–14. doi: 10.1111/j.1365-2214.2008.00877.x PMID: 18959578

18. Spurrier NJ, Sawyer MG, Clark JJ, Baghurst P. Socio-economic differentials in the health-related quality of life of Australian children: results of a national study. Aust N Z J Public Health. 2003; 27:27–33. PMID: 14705264
19. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. BMJ. 2007; 335:194. PMID: 17591624
20. Banning R, Camstra A, Knottnerus P. Sampling theory: Sampling design and estimation methods. The Hague/Heerlen: Statistics Netherlands; 2012.
21. Fagerland MW. T-tests, non-parametric tests, and large studies—a paradox of statistical practice? BMC Med Res Methodol. 2012; 12:78. PMID: 22697476
22. Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press; 1977.
23. Nichol MB, Epstein JD. Separating gains and losses in health when calculating the minimum important difference for mapped utility measures. Qual Life Res. 2008; 17(6):955–61. doi: 10.1007/s11136-008- 9369-7 PMID: 18615271
24. Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. Cephalalgia. 2009; 29(11):1180–7. PMID: 19830883
25. Jaeschke R, Singer J, Guyatt GH. Measurement of health status.Ascertaining the minimal clinically important difference. Control Clin Trials. 1989; 10(4):407–15. PMID: 2691207
26. Masood M, Masood Y, Saub R, Newton JT. Need of minimal important difference for oral health-related quality of life measures. J Public Health Dent. 2014; 74(1):13–20. doi: 10.1111/j.1752-7325.2012. 00374.x PMID: 22994869
27. Norman GR 1, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003; 41(5):582–92. PMID: 12719681
28. Schulpen TW. Migration and child health: the Dutch experience. Eur J Pediatr. 1996; 155:351–6. PMID: 8741029
29. Ruijsbroek A, Wijga AH, Kerkhof M, Koppelman GH, Smit HA, Droomers M. The development of socioeconomic health differences in childhood: results of the Dutch longitudinal PIAMA birth cohort. BMC Public Health. 2011; 11:225. doi: 10.1186/1471-2458-11-225 PMID: 21486447
30. Grieken van A, Veldhuis L, Renders CM, Landgraf JM, Hirasing RA, Raat H. Impaired parent-reported health-related quality of life of underweight and obese children at elementary school entry. Qual Life Res. 2013; 22:917–28. doi: 10.1007/s11136-012-0211-x PMID: 22695828
31. Wake M, Salmon L, Waters E, Wright M, Hesketh K. Parent-reported health status of overweight and obese Australian primary school children: a cross-sectional population survey. Int J Obes Relat Metab Disord. 2002; 26:717–24. PMID: 12032758
32. Ottova V, Erhart M, Rajmil L, Dettenborn-Betz L, Ravens-Sieberer U. Overweight and its impact on the health-related quality of life in children and adolescents: results from the European KIDSCREEN survey. Qual Life Res. 2012; 21:59–69. doi: 10.1007/s11136-011-9922-7 PMID: 21557001
33. Williams J, Wake M, Hesketh K, Maher E, Waters E. Health-related quality of life of overweight and obese children. JAMA. 2005; 293:70–6. PMID: 15632338
34. Bisegger C, Cloetta B, von Rueden U, Abel T, Ravens- Sieberer U. Health-related quality of life: Gender differences in childhood and adolescence. Soz Praventivmed. 2005; 50:281–91. PMID: 16300172
35. Björkqvist K, Lagerspetz KMJ, Kaukiainen A. Do girls manipulate and boys fight? Developmental trends in regard to direct and indirect aggression. Aggress Behav. 1992; 18:117–27.
36. Waters E, Doyle J, Wolfe R, Wright M, Wake M, Salmon L. Influence of parental gender and self-reported health and illness on parent-reported child health. Pediatrics. 2000; 106:1422–8. PMID: 11099598

37. Landgraf JM, Abetz L. Influences of sociodemographic characteristics on parental reports of children's physical and psychosocial well-being: Early experiences with the Child Health Questionnaire. In: Drotar D, editor. Measuring Health-Related Quality of Life in Children and Adolescents: Implications for Research and Practice. Mahwah: Lawrence Erlbaum Associates; 1998.
38. Wilkins AJ, O'Callaghan MJ, Najman JM, Bor W, Williams GM, Shuttlewood G. Early childhood factors influencing health-related quality of life in adolescents at 13 years. J. Paediatr Child Health. 2004; 40:102–9. PMID: 15009573
39. Botterweck A, Frenken F, Janssen S, Rozendaal L, de Vree M, Otten Fl. Feasibility, reliability and validity of the new measurements in the Dutch Health Interview Survey 2001 [Plausibiliteit nieuwe metingen algemene gezondheid en leefstijlen 2001]. Voorburg/Heerlen: Statistics Netherlands; 2003.
40. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care. 2003; 41(5):582–92. PMID: 12719681
41. Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. Eur Respir J. 2013; 41 (4):952–9. doi: 10.1183/09031936.00015712 PMID: 22790911

S1 Table. Illustration of age-gender groupings using interview administration.[a]

Parameters		Age-gender group										
		4-5 years		6-7 years		8-9 years		10-11 years		Total		
		Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Total
PF	Mean	94.3	93.9	94.7	95.3	95.3	95.2	94.4	93.9	94.7	94.6	94.6
	95% CI	93.4 - 95.2	92.9 - 95.0	93.8 - 95.6	94.4 - 96.1	94.5 - 96.0	94.3 - 96.0	93.5 - 95.3	92.9 - 94.8	94.2 - 95.1	94.1 - 95.0	94.3 - 94.9
	Sample N	1420	1300	1355	1328	1334	1291	1314	1303	5423	5222	10645
REB	Mean	97.0	97.1	95.4	96.5	94.2	96.8	94.2	96.7	95.3	96.7	96.0
	95% CI	96.4 - 97.7	96.3 - 97.9	94.5 - 96.4	95.7 - 97.3	93.2 - 95.2	95.9 - 97.6	93.2 - 95.3	95.9 - 97.4	94.8 - 95.7	96.4 - 97.1	95.7 - 96.3
	Sample N	1418	1299	1352	1329	1335	1289	1313	1301	5418	5218	10636
RF	Mean	95.0	94.7	95.2	95.4	95.9	96.3	95.4	95.2	95.4	95.4	95.4
	95% CI	94.1 - 95.5	93.7 - 95.7	94.2 - 96.1	94.4 - 96.4	95.1 - 96.8	95.4 - 97.1	94.5 - 96.4	94.2 - 96.2	94.9 - 95.8	94.9 - 95.9	95.1 - 95.7
	Sample N	1419	1299	1352	1330	1336	1290	1314	1301	5421	5220	10641
BP	Mean	85.7	85.5	87.0	84.7	85.7	85.7	84.7	83.7	85.8	84.9	85.3
	95% CI	84.6 - 86.7	84.4 - 86.5	86.0 - 88.1	83.6 - 58.9	84.6 - 86.8	84.7 - 86.7	83.5 - 85.8	82.6 - 84.8	85.2 - 86.3	84.4 - 85.4	85.0 - 85.7
	Sample N	1420	1300	1354	1330	1336	1290	1312	1303	5422	5223	10645
BE	Mean	69.3	71.3	69.0	73.1	69.3	72.7	69.5	73.6	69.3	72.7	71.0
	95% CI	68.4 - 70.1	70.5 - 72.2	68.1 - 70.0	72.2 - 74.0	68.4 - 70.3	71.7 - 73.6	68.5 - 70.5	72.7 - 74.5	68.8 - 69.8	72.2 - 73.1	70.6 - 71.3
	Sample N	1400	1287	1339	1319	1324	1279	1299	1292	5362	5177	10539
MH	Mean	83.9	83.0	82.0	82.4	80.3	80.5	81.3	80.9	81.9	81.7	81.8
	95% CI	83.1 - 84.7	82.2 - 83.8	81.1 - 82.9	81.5 - 83.3	79.4 - 81.2	79.6 - 81.5	80.3 - 82.2	80.0 - 81.8	81.4 - 82.3	81.3 - 82.1	81.5 - 82.1
	Sample N	1401	1283	1345	1316	1323	1282	1300	1293	5369	5174	10543
SE	Mean	83.2	84.1	81.0	82.7	79.4	80.0	78.1	79.7	80.5	81.6	81.0
	95% CI	82.5 - 83.9	83.4 - 84.9	80.2 - 81.7	81.9 - 83.4	78.6 - 80.2	79.2 - 80.8	77.3 - 79.0	78.9 - 80.4	80.1 - 80.9	81.2 - 82.0	80.8 - 81.3
	Sample N	1385	1273	1338	1321	1324	1287	1306	1299	5353	5180	10533
GH	Mean	84.9	86.5	85.6	87.5	84.9	86.1	84.5	86.5	85.0	86.6	85.8
	95% CI	83.8 - 85.9	85.6 - 87.5	84.6 - 86.7	86.5 - 88.4	83.8 - 85.9	85.0 - 87.2	83.4 - 85.6	85.5 - 87.5	84.4 - 85.5	86.1 - 87.1	85.4 - 86.1
	Sample N	1420	1299	1355	1329	1334	1291	1314	1301	5423	5220	10643
PE	Mean	89.4	90.5	88.4	89.6	87.6	89.2	88.2	89.5	88.4	89.7	89.0
	95% CI	88.5 - 90.3	89.6 - 91.4	87.5 - 89.3	88.7 - 90.5	86.7 - 88.5	88.3 - 90.2	87.3 - 89.2	88.3 - 90.5	88.0 - 88.9	89.3 - 90.2	88.7 - 89.4
	Sample N	1417	1299	1352	1330	1335	1290	1313	1301	5417	5220	10637

S1 Table. Continued

Parameters		Age-gender group										
		4-5 years		6-7 years		8-9 years		10-11 years		Total		
		Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Total
PT	Mean	92.0	91.7	91.9	92.6	92.5	92.7	91.7	93.5	92.1	92.6	92.3
	95% CI	91.0 - 93.1	90.5 - 92.8	90.7 - 93.1	91.4 - 93.8	91.5 - 93.6	91.5 - 93.9	90.6 - 92.8	92.4 - 94.5	91.5 - 92.6	92.0 - 93.2	91.9 - 92.7
	Sample N	1416	1300	1351	1328	1335	1289	1314	1302	5416	5219	10635
FA	Mean	88.2	88.8	88.8	91.0	89.9	91.6	90.6	92.6	89.4	91.0	90.2
	95% CI	87.3 - 89.2	87.8 - 89.9	87.7 - 89.8	90.0 - 92.0	88.9 - 90.9	90.6 - 92.6	89.6 - 91.5	91.8 - 93.4	88.9 - 89.9	90.5 - 91.5	89.8 - 90.5
	Sample N	1417	1297	1352	1328	1333	1289	1314	1301	5416	5215	10631
FC	Mean	77.8	77.5	75.6	77.5	74.3	74.8	73.1	75.1	75.2	76.2	75.7
	95% CI	76.8 - 78.7	76.5 - 78.6	74.6 - 76.6	76.5 - 78.5	73.3 - 75.4	73.8 - 75.8	72.1 - 74.2	74.1 - 76.1	74.7 - 75.8	75.7 - 76.7	75.4 - 76.1
	Sample N	1419	1300	1355	1329	1335	1291	1313	1302	5422	5222	10644
CH	Mean	59.0	57.6	58.4	56.8	57.0	56.4	56.8	54.7	57.8	56.4	57.1
	95% CI	58.0 - 60.0	56.6 - 58.6	57.4 - 59.5	55.9 - 57.7	56.0 - 58.1	55.5 - 57.3	55.7 - 57.8	53.8 - 55.5	57.3 - 58.4	55.9 - 56.8	56.8 - 57.5
	Sample N	1421	1299	1355	1330	1335	1290	1313	1303	5424	5222	10646
PhS	Mean	55.5	55.4	56.2	56.1	56.4	56.3	55.9	55.6	56.0	55.9	55.9
	95% CI	55.0 - 56.1	54.9 - 56.0	55.7 - 56.7	55.6 - 56.6	55.9 - 56.8	55.8 - 56.7	55.4 - 56.4	55.1 - 56.1	55.8 - 56.3	55.6 - 56.1	55.8 - 56.1
	Sample N	1355	1249	1313	1295	1300	1261	1276	1275	5244	5080	10324
PsS	Mean	53.2	53.5	52.1	53.3	51.5	52.5	51.6	52.9	52.1	53.1	52.6
	95% CI	52.8 - 53.6	53.1 - 53.9	51.7 - 52.5	52.9 - 53.7	51.0 - 52.0	52.1 - 52.9	51.1 - 52.1	52.5 - 53.3	51.9 - 52.3	52.9 - 53.3	52.4 - 52.7
	Sample N	1355	1249	1313	1295	1300	1261	1276	1275	5244	5080	10324

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CHAPTER 7

Childhood Chronic Conditions and Health-Related Quality of Life: Findings from a Large Population-based Study

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ABSTRACT

The objective of this study was to assess the impact of health-related quality of life (HRQOL) across prevalent chronic conditions, individually and comorbid, in school-aged children in the Netherlands. 5301 children aged 4–11 years from the Dutch Health Interview Survey were included. Parents completed questionnaires regarding child and parental characteristics. HRQOL of children was measured using the Child Health Questionnaire Parent Form 28 (CHQ-PF28). Independent-t tests were used to assess differences in the mean scores of the CHQ-PF28 summary scales and profile scales between children with a prevalent chronic condition (excluding or including children with multiple chronic conditions) and children without a chronic condition. Cohen's effect sizes (d) were calculated to assess the clinical significance of difference. The mean age of children was 7.55 (SD 2.30) years; 50.0% were boys. In children without any chronic condition, the mean score of physical summary scale (PhS) was 58.53 (SD 4.28) and mean score of the psychosocial summary scale (PsS) was 53.86 (SD 5.87). Generally, PhS and/or PsS scores in children with only one condition were lower ($p<0.05$) than for children without chronic conditions. When children with multiple conditions were included, mean scores of CHQ-PF28 summary and profile scales were generally lower than when they were excluded. The present study shows important information regarding the impact of prevalent chronic conditions on HRQOL in a representative population-based sample of school-aged children in the Netherlands. The information could be used for developing a more holistic approach to patient care and a surveillance framework for health promotion.

INTRODUCTION

Over the past decades, the prevalence of chronic conditions of children has increased over time [1, 2]. Particularly, asthma and behavioral problems (e.g. attention deficit/hyperactivity disorder) show a greater increase in prevalence [3–5]. Clinical studies have suggested that children with particular chronic conditions may experience impairments of health-related quality of life (HRQOL) [6–15]. HRQOL is a multidimensional concept that focuses on the individuals' perceptions of their physical, psychological, and social functioning [16]. However, the generalization of findings is often restricted by the small sample size in the above studies. In recognition of this need, recently the associations of childhood chronic conditions with HRQOL have been assessed in representative population samples [17–23]. The chronic conditions evaluated in most of the above studies were selected based on experts' opinions [20] or on clinical importance rather than prevalence in the population [19, 21, 22]. The association between prevalent chronic conditions of children and HRQOL is not clear. A relevant issue is comorbidity, which is also common in the child population. Only three studies evaluated the impact of comorbidity on children's HRQOL [19–21] in population-based studies. Little is known about the profiles of child's HRQOL across prevalent childhood chronic conditions in a representative population sample.

The present investigation used data embedded in the Dutch Health Interview Survey (DHIS) conducted from 2010 to 2013. The five most prevalent child chronic conditions were identified (asthma; eczema; dyslexia; ADHD; migraine/severe headache). The goal of the current investigation was to assess difference in HRQOL for children with only one of the five prevalent conditions (without co-morbidity) in comparison to children without any chronic condition. Difference in HRQOL for children with one of the five prevalent conditions including the presence of co-morbidity was also compared.

METHODS

Participants and procedures

Data used for the current investigation was extrapolated from the Dutch Health Interview Survey (DHIS), conducted by Statistics Netherlands. DHIS is a cross-sectional survey amongst the Dutch population living in non-institutionalized households. Each month, a stratified two- step-sample of persons is taken from the Dutch Municipal Personal Records [23]. For this investigation, a four-year set of survey responses for children ages 4–11 years were used. Only one parent participated in the interview. Between January 2010 and December 2013, parents of 6499 children aged 4–11 years were interviewed. The yearly response rate for children ages 4–11 years is approximately 73%.

Parents received written study information from Statistic Netherlands and participation was elective. According to Dutch law (Wet medisch wetenschappelijk onderzoek met mensen), formal approval (e.g., from a medical ethics committee) was not required as this study relied on secondary anonymized data collection in the context of performing statutory tasks. Data collection and processing was in strict accordance with the national standard. At no time did the datasets contain direct identifiers [23].

Measures

Chronic conditions

Parents were asked to indicate if their child had ever had cancer, or experienced other health or behavioral issues during the previous 12 months: congenital heart defect, diabetes, migraine/ severe headache, asthma, psoriasis, eczema, arthritis/rheumatism, severe/protracted disorders of the intestines, back, neck/shoulder, arm or hand; dyslexia, autism or conditions related to autism like Asperger's, intellectual disability, and presence of at least three core ADHD symptoms (DSM-criteria: restless behavior/ not being able to sit still, fidgeting/squirming, short attention span). An open-ended question about any other chronic conditions and behavioral issues not mentioned was also included. For each condition, possible responses were "no" (i.e. does not have the condition), "yes" (i.e. has the condition). For all chronic conditions except for ADHD, if the parent answered "yes", a following question should be answered: "Has your child been seen by the family physician or medical specialist in the previous 12 months".

Health-related quality of life

CHQ-PF28 is a 28-item, parent-reported measurement of children's HRQOL. CHQ-PF 28 was selected because it has been rigorously translated into 78 languages (http://www.healthactchq.com/chq-t.php) and specifically evaluated for use in the Netherlands and it is easy to administer in large population studies [28–30]. Based on 13 scales, CHQ-PF28 measures the HRQOL of children and their families. The child's HRQOL is measured by the following ten scales: Physical Functioning (PF)); Role/Social-Physical (RP); General Health Perception (GP); Bodily Pain (BP); Role/Social Emotional/Behavioral (REB); Self- Esteem (SE); Mental Health (MH); Behavior (BE); Parental Impact-Time (PT); and Parental Impact-Emotional (PE). These ten scales are involved into scoring the Physical Summary Component Scale (PhS) and the Psychosocial Summary Component Scale (PsS). Furthermore, there are Family Activities (FA), Family Cohesion (FC) and Change in Health (CH) scales. In the present study, data on the 'Change in Health Scale' was not reported. Items are responded on four-, five-, or six- Likert-type scales and then standardized on a 0–100 continuum. Higher scores represent better HRQOL. PhS and PsS are based on factor weights from a US representative sample of children aged 5–18 years of age [31]. A score of 50 represents the mean of the US reference population sample and the standard deviation is ten points above/below the mean. The weighted

US values to derive two component summary scales have been used with success in both Dutch and other international studies [19, 20, 23, 28, 29]. In our study, the Dutch version of the parent-completed CHQ-PF28 was administered via the internet, or via a structured telephone or face-to-face interview as part of the larger DHIS interview [32].

Covariates

Data regarding children's age, sex, ethnic background, body mass index, single parent family, number of acute health complaints and education level of the parent who completed the interview, which were considered as potential confounders, were collected by questionnaire during the interview. Acute health complaints in the present study are defined as the occurrence of headache, tiredness, back pains, muscle or joint pains during the last 14 days.

Parental education level (low, medium, high) and ethnic background of the child were defined according to the Dutch standards classifications [33][34]. Low education level includes pre-primary, primary and lower secondary education; medium education level is similar to upper secondary education; high education level includes bachelor and master degrees and doctorate. If there are two parents with a different education level, then the highest level is chosen. Children for whom at least one parent was born outside the Netherlands were identified as (second generation) immigrants (even if the child was born in the Netherlands). Western immigrants were classified as those originating from Europe (excluding Turkey), North America, Oceania, Indonesia or Japan; Non-western immigrants were classified as those originating from Africa, South America, Asia (excluding Indonesia and Japan) or Turkey.

Statistical analyses

6499 parents of the same number of children were interviewed at enrollment. Children with 'outliers' (values above/below 3xSD +/- mean) regarding one of the two summary CHQ-PF28 scales were deleted (n = 252). Additionally, 122 children were excluded due to missing more than one item on the CHQ-PF28. Also excluded were children with a reported condition that was not asthma, eczema, ADHD, dyslexia and severe headache (n = 430) or for whom >2 chronic conditions were reported (n = 394). Thus a final sample of 5301 children was used for data analyses. (see S1 Fig).

Mean and standard deviations of the CHQ-PF28 scale and summary scores were calculated for children without reported chronic conditions (n = 4539), and for children with one of the five prespecified chronic conditions (asthma, n = 235; eczema, n = 192; dyslexia, n = 207; ADHD, n = 51; and migraine/severe headache, n = 77). Independent sample t-tests were used to assess differences in the mean scores of the scales and summary scales between children with and without a chronic condition. The relevance of the difference was assessed using Cohen's effect size. The difference in mean scores was divided by the largest SD and interpreted as (d): $0.2 \leq d < 0.5$ small difference,

$0.5 \leq d < 0.8$ moderate, and $d \geq 0.8$ large [35]. Additionally, taking into account the covariates, general linear models were applied to assess differences in the mean scores of scales and summary scales between the subgroups.

Independent sample t-tests were also applied to assess differences in the mean scores of CHQ-PF28 scales and summaries between children with and without a chronic condition when children with multiple conditions were included. Cohen's effect size was used to assess the clinical relevance of the difference. Additionally, we assessed the differences in the CHQ-PF28 mean scores of the scales and summaries between children who were seen by the family physician or medical specialist in the previous 12 months and children who were not. A p-value <0.05 was considered to be statistically significant. Analyses were performed using SPSS 22.0.

RESULTS

Table 1 presents the general characteristics of the population for analysis. There were 5301 children (2651 girls and 2650 boys) aged 4–11 years (mean: 7.55, standard deviation: 2.30). 19.4% of the children were non-Dutch; 11.1% from a single parent family; 32.2% children had one or more acute health complaints. Compared to children without any chronic condition, children with dyslexia were more often male, older, Dutch and had more acute health complaints; children with asthma and children with eczema more often lived in the single parent family; parents of children with migraine/severe headache more often reported low/medium education.

Mean scores of CHQ-PF28 scales and summaries in children with a specific condition (asthma, eczema, dyslexia, ADHD, migraine/severe headache) were lower than children without any chronic condition (see Table 2). Regarding the summary scales, children with only asthma were reported with a relatively lower mean score of the physical summary scale than children without any chronic condition (54.49 vs. 58.53, $p<0.05$, $d = 0.67$), and children with only ADHD were reported to have a relatively lower mean score in the psychosocial summary scale than children without any chronic condition (46.57 vs. 53.86, $p<0.05$, $d = 1.17$). As noted in Table 2, in the subgroup children with migraine/severe headache all 12 scale scores were lower ($p<0.05$) compared to the subgroup children without any chronic condition, particularly regarding bodily pain (75.84 vs. 88.85, $p<0.05$, $d = 0.62$). The lowest mean score for children with asthma was observed for the general health scale (77.30 vs. 90.47, $p<0.05$, $d = 0.77$); and the lowest mean score for children with ADHD was observed for the behavior scale (53.90 vs. 73.44, $p<0.05$, $d = 1.21$). Across all the five conditions, and in particular for children with ADHD and children with migraine/severe headache, lower mean scale scores were observed for

Table 1. General characteristics of study population (n=5301)

Variables	Total (N=5301)	No chronic condition (n=4539)	Asthma (n=235)	Eczema (n=192)	ADHD (n=51)	Dyslexia (n=207)	Migraine/ severe headache (n=77)
Children							
Sex							
Male	2650 (50.0)	2242 (49.4)	**141 (60.0)**	87 (45.3)	29 (56.9)	**118 (57.0)**	33 (42.9)
Female	2651 (50.0)	2297 (50.6)	**94 (40.0)**	105 (54.7)	22 (43.1)	**89 (43.0)**	44 (57.1)
Age (years), mean (SD)	7.55±2.30						
4	634 (12.0)	570 (12.6)	25 (10.6)	28 (14.6)	7 (13.7)	**1 (0.5)**	3 (3.9)
5	654 (12.3)	579 (12.8)	33 (14.0)	27 (14.1)	8 (15.7)	**3 (1.4)**	4 (5.2)
6	654 (12.3)	582 (12.8)	27 (11.5)	25 (13.0)	4 (7.8)	**7 (3.4)**	9 (11.7)
7	680 (12.8)	579 (12.8)	38 (16.2)	24 (12.5)	10 (19.6)	**18 (8.7)**	11 (14.3)
8	645 (12.2)	549 (12.1)	24 (10.2)	23 (12.0)	10 (19.6)	**26 (12.6)**	13 (16.9)
9	663 (12.5)	557 (12.3)	23 (9.8)	22 (11.5)	5 (9.8)	**46 (22.2)**	10 (13.0)
10	667 (12.6)	551 (12.1)	35 (14.9)	20 (10.4)	3 (5.9)	**46 (22.2)**	12 (15.6)
11	704 (13.3)	572 (12.6)	30 (12.8)	23 (12.0)	4 (7.8)	**60 (29.0)**	15 (19.5)
Ethnic background							
Native Dutch	4273 (80.6)	3655 (80.5)	177 (75.3)	142 (74.0)	46 (90.2)	**188 (90.8)**	65 (84.4)
Immigrant, Western	324 (6.1)	275 (6.1)	18 (7.7)	14 (7.3)	0 (0.0)	**14 (6.8)**	3 (3.9)
Immigrant, Non-western	704 (13.3)	609 (13.4)	40 (17.0)	36 (18.8)	5 (9.8)	**5 (2.4)**	9 (11.7)
Body mass index							
Normal weight	3755 (70.8)	3221 (71.0)	161 (68.5)	142 (74.0)	33 (64.7)	135 (65.2)	63 (81.8)
Overweight	397 (7.5)	323 (7.1)	28 (11.9)	18 (9.4)	3 (5.9)	20 (9.7)	5 (6.5)
Obese	113 (2.1)	93 (2.0)	5 (2.1)	6 (3.1)	4 (7.8)	4 (1.9)	1 (1.3)
Unknown	1036 (19.5)	902 (19.9)	41 (17.4)	26 (13.5)	11 (21.6)	48 (23.2)	8 (10.4)
Family structure							
Two parent family	4683 (88.3)	4049 (89.2)	**193 (82.1)**	**157 (81.8)**	43 (84.3)	181 (87.4)	**60 (77.9)**
Single parent family	590 (11.1)	466 (10.3)	**41 (17.4)**	**35 (18.2)**	7 (13.7)	25 (12.1)	**16 (20.8)**
Other/Unknown	28 (0.5)	24 (0.5)	**1 (0.4)**	**0 (0.0)**	1 (2.0)	1 (0.5)	**1 (1.3)**

Table 1. Continued

Variables	Total (N=5301)	No chronic condition (n=4539)	Asthma (n=235)	Eczema (n=192)	ADHD (n=51)	Dyslexia (n=207)	Migraine/ severe headache (n=77)
Number of acute health complaints							
None	3596 (67.8)	3180 (70.1)	**140 (59.6)**	**104 (54.2)**	**25 (49.0)**	**133 (64.3)**	**14 (18.2)**
1	1139 (21.5)	927 (20.4)	**55 (23.4)**	**59 (30.7)**	**18 (35.3)**	**48 (23.2)**	**32 (41.6)**
2	450 (8.5)	356 (7.9)	**26 (11.1)**	**23 (12.0)**	**7 (13.7)**	**16 (7.7)**	**22 (28.6)**
3 or more	116 (2.2)	76 (1.7)	**14 (6.0)**	**6 (3.1)**	**1 (2.0)**	**10 (4.8)**	**9 (11.7)**
Parental education level							
Low	713 (13.4)	603 (13.3)	34 (14.5)	31 (16.1)	9 (17.6)	24 (11.6)	**12 (15.6)**
Medium	1689 (31.9)	1423 (31.4)	76 (32.3)	62 (32.3)	21 (41.2)	73 (35.3)	**34 (44.2)**
High	2230 (42.1)	1936 (42.7)	91 (38.7)	78 (40.6)	14 (27.5)	94 (45.4)	**17 (22.1)**
Unknown	669 (12.6)	577 (12.7)	34 (14.5)	21 (10.9)	7 (13.7)	16 (7.7)	**14 (18.2)**

Values are numbers and percentages. Bold print indicates significant difference ($p<0.05$) of children with only one condition (asthma, eczema, dyslexia, ADHD, or migraine/severe headache) compared with children without chronic conditions.

the parent-family specific scales (parental impact-emotional, family activities and family cohesion). S2 Figure shows that the pattern of impairments on HRQOL varies across the five pre- specified chronic conditions.
Adjusting for potential confounders, the same pattern of significant differences was observed using General Linear Models (see Table 3).

Percentages of children with multiple chronic conditions are presented in S1 Table. When children with multiple chronic conditions were taken into account, the mean scores of CHQ-PF28 summary and profile scales were generally lower (see Supplementary S2 Table) compared to children with only one of the five prevalent chronic conditions. But patterns of differences between children with and without specific chronic conditions are similar.

Gender-specific differences in CHQ-PF28 scales between children with only one chronic condition and children with no chronic condition are presented in S3 Table. Compared to girls with no chronic condition, girls with asthma had significantly lower scores in Mental Health Scale, while the difference between boys with asthma and boys with no chronic condi tion was not significant. Girls with eczema had significantly lower scores in Psychosocial Component Summary Scale, Behavior, Self Esteem, Family Activities and Family Cohesion scales than girls with no chronic condition, while these differences between boys with eczema and boys with no chronic condition were not significant. The patterns were almost the same in girls and boys with dyslexia. Girls with ADHD were reported with significantly higher score in the Physical Component Summary Scale, Physical Functioning and Bodily Pain scales than girls with no chronic condition, while impacts of ADHD on boys in psychology/behavior- related scales (i.e. Psychosocial Component Summary Scale, Behavior, Mental Health, Self Esteem scales) were stronger than on girls. Patterns were found to vary across boys and girls with migraine/severe headache.

Regarding children with asthma, mean scores of the physical summary scale, physical functioning scale, role functioning-physical scale and general health perception scale were significantly lower in children who were seen by the family physician or medical specialist compared to children who were not (see S4 Table). Children with dyslexia who were seen by the family physicians or medical specialists were presented with somewhat higher scores of the parental impact-emotional scale than children did not.

Regarding children with asthma, mean scores of the physical summary scale, physical functioning scale, role functioning-physical scale and general health perception scale were significantly lower in children who were seen by the family physician or medical specialist compared to children who were not (see S4 Table). Children with dyslexia who

Table 2. CHQ-PF28 scores of children with one condition and of children without any reported chronic conditions (n=5301)

	No chronic condition	Asthma		Eczema		Dyslexia		ADHD		Migraine/severe headache	
	(n = 4539)	(n=235)		(n=192)		(n=207)		(n=51)		(n=77)	
	mean score (SD)	mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size
CHQ-PF28 Summary scales											
Physical Component Summary Component Scale	58.53 (4.28)	54.49* (6.01)	0.67[b]*	56.75* (5.40)	0.33[a]*	58.53 (4.90)	0,00	59.93 * (5.13)	-0.27[a]*	54.89* (6.68)	0.55[b]*
Psychosocial Component Summary Component Scale	53.86 (5.87)	53.72 (5.89)	0.02	52.66* (6.37)	0.19 *	51.51* (6.23)	0.38[a]*	46.57 * (6.21)	1.17[c]*	49.72* (8.69)	0.48[a]*
CHQ-PF28 Child scales											
Physical Functioning	98.44 (6.51)	93.14* (11.97)	0.44[a]*	96.70* (8.20)	0.21[a]*	96.99* (9.63)	0.15 *	98.69 (5.73)	-0.04	94.81 * (9.97)	0.36[a]*
Role/Social Emotional Behavioral	98.80 (6.58)	97.59 (12.28)	0.10	97.05* (11.69)	0.15 *	95.17* (12.65)	0.29[a]*	96.73* (10.01)	0.21[a]*	92.21* (18.65)	0.35[a]*
Role/Social-Physical	98.84 (6.65)	97.31* (11.42)	0.13 *	97.57 (9.94)	0.13	97.91 (8.11)	0.12	97.39 (14.67)	0.10	95.24* (12.93)	0.28[a]*
Bodily Pain	88.85 (15.99)	84.51* (17.98)	0.24[a]*	82.19* (17.41)	0.38[a]*	87.73 (15.46)	0.07	89.41 (14.06)	-0.04	75.84* (20.86)	0.62[b]*
Behavior	73.44 (14.04)	72.91 (13.84)	0.04	70.66 (14.76)	0.19 *	69.43 (13.50)	0.29[a]*	53.90 (16.15)	1.21[c]*	67.94 (16.99)	0.32[a]*
Mental Health	83.19 (13.54)	82.62 (13.87)	0.04	82.03 (12.64)	0.09	81.04 (13.33)	0.16 *	73.37 (13.64)	0.72[b]*	73.92 (17.75)	0.52[b]*
Self-Esteem	82.38 (12.64)	80.60 (11.86)	0.14 *	79.45 (12.03)	0.23[a]*	77.54 (12.65)	0.38[a]*	75.90 (11.94)	0.51[b]*	77.65 (12.52)	0.38[a]*
General Health Perception	90.47 (12.17)	77.30 (17.05)	0.77[b]*	86.69 (14.19)	0.27[a]*	90.92 (11.72)	-0.04	88.16 (14.36)	0.16	82.19 (16.01)	0.52[b]*
CHQ-PF28 Parent and Family Impact scales											
Parental Impact-Emotional	92.96 (11.22)	89.10 (13.63)	0.28[a]*	89.52 (13.42)	0.26[a]*	89.55 (12.33)	0.26[a]*	85.29 (13.39)	0.57[b]*	85.23 (17.88)	0.43[a]*
Parental Impact-Time	97.39 (10.38)	96.60 (12.14)	0.07	96.79 (10.36)	0.06	96.78 (10.14)	0.06	90.85 (22.44)	0.29[a]*	93.07 (16.96)	0.25[a]*
Family Activities	93.47 (12.26)	92.71 (14.37)	0.05	90.30 (15.33)	0.21[a]*	94.38 (10.71)	-0.07	79.17 (23.67)	0.60[b]*	86.69 (18.06)	0.38[a]*
Family Cohesion	80.84 (17.01)	82.47 (16.87)	-0.10	76.82 (17.50)	0.23[a]*	80.39 (17.04)	0.03	71.76 (16.52)	0.53[b]*	75.84 (16.94)	0.29[a]*

SD: standard deviation. *P <0.05; [a] means small difference when 0.2≤d<0.5 small difference; [b] means moderate difference when 0.5≤d<0.8; c means large difference when d≥0.8; for others that d was less than 0.2, we didn't mark them in our table.

were seen by the family physicians or medical specialists were presented with somewhat higher scores of the parental impact-emotional scale than children did not.

DISCUSSION

The present study demonstrates lower HRQOL scores of children with a prevalent chronic condition (asthma, eczema, dyslexia, ADHD, or migraine/severe headache) compared with children without any chronic condition. The pattern of impaired HRQOL is specific across the prespecified conditions, which is consistent with clinical benchmarks reported in the CHQ Manual [31]. When comorbidity is taken into account, the HRQOL of children is generally lower than when children with comorbidity were excluded from the analysis.

Asthma

Current analyses revealed that children with asthma more often lived in the single parent family compared to children without chronic conditions, which is consistent with an early study regarding association of family structure and the prevalence of asthma [36]. As reported by parents, the greatest impact of asthma is observed for 'physical' aspects of HRQOL such as physical summary scale, physical functioning, and bodily pain. This observation is consistent with previously reported findings [9, 37]. Parents of children with asthma perceived their child's health as relatively poor and likely to get worse. As noted by others, in our study, significant difference regarding self-esteem and mental health were not observed [38], for which we have no explanation.

Eczema

An association in the present investigation was shown between the presence of eczema and the family structure, which consists with a previous study [39]. 'Physical' and 'psychosocial' aspects of HRQOL were affected by the presence of eczema, which is consistent with prior research [7]. Significantly lower scale scores were observed for physical functioning and bodily pain relative to children without any chronic condition. This observation could be explained in part by the most prevalent symptoms of eczema: itching and soreness [7, 40], which may limit children in their activities and in playing sports. Impaired self-esteem was observed in the present study. It has been suggested that children with eczema may experience comments regarding their appearance, teasing, bullying or even peer rejection, leading to embarrassments and lack of confidence[10, 40]. A gender-specific difference was observed. Girls were disturbed more than boys regarding overall psychosocial HRQOL, behavior and self-esteem. Perhaps the visible redness, inflamed and scaly rashes may causes more stress in girls than in boys, because in general, socially constructed notions require girls to be attractive in appearance.

Table 3. Difference in scale scores and summary scale scores between children with one of five common childhood conditions/disorders and children without reported chronic condition by General Linear Models when multiple conditions were excluded (n=5301).

		PF	REB	RF	BP	BE	MH
Asthma vs. No chronic condition	B	-5.34*	-0.19	-1.30*	-2.31	1.07	0.35
	[95%CI]	[-6.41, -4.26]	[-1.41, 1.03]	[-2.46, -0.14]	[-4.65, 0.02]	[-1.11, 3.26]	[-1.73, 2.44]
Eczema vs. No chronic condition	B	-1.52*	-1.85*	-1.12	-4.34*	-2.42*	-0.65
	[95%CI]	[-2.64, -0.39]	[-3.13, -0.58]	[-2.34, 0.10]	[-6.79, -1.90]	[-4.70, -0.12]	[-2.84, 1.53]
Dyslexia vs. No chronic condition	B	-1.22*	-3.09*	-0.71	-0.71	-4.41*	-2.09
	[95%CI]	[-2.38, -0.07]	[-4.41, -1.78]	[-3.22, 1.80]	[-3.22, 1.80]	[-6.76, -2.06]	[-4.33, 0.15]
ADHD vs. No chronic condition	B	1.02	-2.15	1.78	2.41	-19.51*	-8.34*
	[95%CI]	[-1.24, 3.27]	[-4.70, 0.40]	[-0.65, 4.21]	[-2.47, 7.30]	[-24.11, -14.97]	[-12.70, -3.99]
Migraine/ severe headache vs. No chronic condition	B	-2.31*	-7.83*	-2.44*	-8.15*	-4.69*	-5.94*
	[95%CI]	[-4.18, -0.44]	[-9.95, -5.71]	[-4.46, -0.42]	[-12.20, -4.09]	[-8.48, -0.90]	[-9.56, -2.33]

Children's age, gender, ethnic background, body mass index, single parent family, number of acute health complaints and paternal educational level were considered as potential confounders in General Linear Models. * P<0.05. PhS Physical Summary Component Scale ; PsS Psychosocial Summary Component Scale; PF physical functioning; REB role functioning: emotional/behavior; RF role functioning: physical; BP bodily pain and discomfort; BE general behavior; MH mental health; SE self-esteem; GH general health perceptions; PE parental impact: emotional; PT parental impact: time; FA family activities; FC family cohesion.

Dyslexia

Children with dyslexia in the present study were more often Dutch in the investigation. It is consistent with findings from DHIS 2009–2015 that showed fewer cases dyslexia in children with a western background (Dutch vs. western: 9% vs. 7%) and with a non-western background (Dutch vs. non-western: 9% vs. 2%) [41]. A possible explanation is that for children with a migration background in the Netherlands, the Dutch language may not be their primary language. Their multilingual upbringing may hamper the timely diagnosis of dyslexia, as reading problems could be mistaken for an overall struggle in learning the Dutch language. The most notable observations for children with dyslexia were on the 'psychosocial' aspects of HRQOL, including the CHQ Psychosocial Summary Component, the role functioning- behavior/emotional scale, general behavior and self-esteem. This may be due in part to the manifestations of dyslexia, which are characterized by difficulties in reading, and/or spelling, listening, writing. Children with dyslexia may be struggling with schoolwork and may feel inferior to their peers [42]. Data on HRQOL of dyslexia children is rare in both clinical and population studies.

Table 3. Continued

SE	GH	PE	PT	FA	FC	PhS	PsS
-0.76	-12.19*	-1.31	-0.18	0.68	1.67	-3.72*	0.74
[-2.72, 1.19]	[-14.10, -10.28]	[-0.36, 0.44]	[-1.79, 1.43]	[-1.24, 2.60]	[-0.96, 4.30]	[-4.39, -3.05]	[-0.18, 1.66]
-3.35*	-2.82*	-2.32*	-0.09	-2.13*	-4.17*	-1.22*	-1.08*
[-5.40, -1.30]	[-4.83, -0.82]	[-4.16, -0.48]	[-1.78, 1.60]	[-4.14, -0.12]	[-6.62, -1.41]	[-1.93, -0.52]	[-2.04, -0.12]
-3.72*	0.42	-4.43*	-1.11	-0.57	-0.96	0.07	-2.36*
[-5.82, -1.62]	[-1.64, 2.47]	[-6.32, -2.54]	[-2.85, 0.62]	[-2.63, 1.50]	[-1.88, 3.79]	[-0.66, 0.79]	[-3.35, -1.37]
-6.26*	-0.36	-7.56*	-5.18*	-11.96*	-8.24*	2.67*	-7.14*
[-10.34, -2.17]	[-4.35, 3.64]	[-11.23, -3.89]	[-8.55, -1.80]	[-15.97, -7.94]	[-13.75, -2.73]	[1.27, 4.08]	[-9.06, -5.21]
-2.24	-6.38*	-5.08*	-5.09*	-4.41*	-4.83*	-2.54*	-3.30*
[-5.63, 1.15]	[-9.70, -3.06]	[-8.13, -2.03]	[-7.89, -2.29]	[-7.75, -1.08]	[-9.40, -0.26]	[-3.70, -1.37]	[-4.90, -1.70]

ADHD

A higher score on the Physical Summary Component scale (PhS) was observed for children with ADHD compared to children without any chronic condition. It is possible that children with restless behavior and other aspects of ADHD excel in the 'physical' aspects of health given the very 'physical' nature of their condition and in direct response to the pronounced deficits on the more 'psychosocial' component. Thus, not surprising, lower scores were observed for general behavior, mental health and self-esteem for children with ADHD. Additionally, the HRQOL of parents and families were significantly impacted. These findings are inconsistent with others' previous work [31, 43, 44]. Particularly, these impacts were stronger in boys than in girls. Current analyses revealed that parents reported higher scores in physical component summary, physical functioning and bodily pain than children with no chronic condition. It should be taken cautiously considering the very small sample size of girls and boys with ADHD in the present analyses.

Migraine/Severe headache

Current analyses revealed that parents of children with migraine/severe headache had lower education level than parents of children without chronic condition, which is consistent with Bugdayci et al. who showed that low education of mothers was significantly associated with the presence of headache in children [45]. Some studies indicated that low economic status of family (income) may be a risk factor of presence of migraine/headache [45–47]. Education is often correlated with income status. Parents of children with migraine/severe headache reported lower scores for almost all CHQ-PF28 scales than children without any chronic condition. Their impaired 'physical' HRQOL might be explained by the physically painful nature of this condition. But low scores on mental health and family aspects of HRQOL suggest that the burden of this condition is also psychosocial in nature as well. Recurrent migraine/severe headaches may impact on the school performances and may limit social activities with peers, and may decreased home/family activities[48].

In reality, it is not uncommon for children to have more than one chronic condition. The present study shows that children, who had additional chronic conditions except for one of the five most prevalent conditions, generally had lower HRQOL compared to children with only one specific condition. These results are consistent with findings in two population-based studies, which reported poorer HRQOL of children with more than one chronic condition but did not explore the specific burden of chronic conditions on children's HRQOL [19, 20].

Regarding the mean score of the parental impact-emotional scale in children with dyslexia, those who were seen by the family physicians or medical specialists presented a higher score than children who did not. It might be explained by a positive treatment effect and consequently, relief with regard to the negative impact of dyslexia on parental emotions.

Linking HRQOL data in children with chronic conditions to appropriate interventions to improve HRQOL outcomes has not yet been empirically demonstrated in pediatrics [49]. However, adult studies and some pediatric trials have indicated the potential value of application of the standard HRQOL measurement in practice and research [49–52]. In addition to being of benefit to clinicians and patients, HRQOL may also be an important markers for health policy makers and payment systems to identify those "at risk" for greater need of health care services and subsequently, interventions targeted to more specific domains of impairment [50].

Strengths and limitations

There are several strengths to this study. Namely, the large population-based sample allowed us to compare HRQOL of children with regard to prevalent chronic condition(s). There have been studies assessing the impact of individual chronic conditions of children on HRQOL [6, 9, 12, 43, 53], however studies comparing HRQOL profiles across different prevalent chronic conditions compared with HRQOL of children without any conditions are scarce [20]. Second, HRQOL was evaluated using the CHQ-PF28, a widely regarded and comprehensive general measure that allowed for the assessment of both the 'psychosocial' as well as the 'physical' burden of these conditions on the child and his/her parent and family. Third, the present analyses adjusted for potential confounders on the associations between the presence of a chronic condition and HRQOL.

There are several limitations that should be noted. First, 'causation' could not be evaluated due to the cross-sectional methodology employed for this study. Second, the CHQ-PF28 is a parent proxy measure. Limitations in study design precluded use of the child self-report version (CHQ-CF87) in concert with the parent version. Thus, data presented herein are from the parents' perspective and 'burden profiles' may differ from children's point of view and may also differ by age and gender. The discordance between parent-report and child self-report has been noted in previous research [54–57]. It is known, for example, that particularly for mental disorders, parents may underestimate the impact on child's school experience and social functioning whereas children tend to estimate their HRQOL similar to their peers [13, 43, 58].

Thus, further work to better understand the unique 'burden' on HRQOL across common childhood conditions from the child perspective is warranted.

CONCLUSION

Prevalent chronic conditions during childhood may place a burden on HRQOL of schoolaged children, parents and family, however, little is known regarding the exact profiles of burden of the most prevalent chronic conditions on HRQOL in school-aged children, especially at a large-population level. The present study contributes to fill in the gap by illustrating the specific HRQOL profiles impacted by prevalent chronic conditions in a representative, national sample of school-aged children. These specific HRQOL profiles will help paediatricians and children public health professionals to understand the multidimensional impact of these specific chronic conditions on the HRQOL of children, parents and families. What´s more, the present study has provided the national reference values of HRQOL of school-aged children, which could be used for comparison of HRQOL between studies.

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REFERENCES

1. Van Cleave J, Gortmaker SL, Perrin JM. DYnamics of obesity and chronic health conditions among children and youth. JAMA. 2010; 303(7):623–30. https://doi.org/10.1001/jama.2010.104 PMID: 20159870
2. Perrin JM, Bloom SR, Gortmaker SL. The increase of childhood chronic conditions in the United States. Jama. 2007; 297(24):2755–9. https://doi.org/10.1001/jama.297.24.2755 PMID: 17595277
3. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980–2007. Pediatrics. 2009; 123 Suppl 3:S131–45.
4. Robison LM, Sclar DA, Skaer TL, Galin RS. National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990–1995. Clin Pediatr (Phila). 1999; 38(4):209–17.
5. Pastor PN, Reuben CA. Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004–2006. Vital Health Stat 10. 2008;(237):1–14.
6. Clarke SA, Eiser C. The measurement of health-related quality of life (QOL) in paediatric clinical trials: a systematic review. Health Qual Life Outcomes. 2004; 2:66. https://doi.org/10.1186/1477-7525-2-66 PMID: 15555077
7. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006; 155(1):145–51. https://doi.org/10.1111/j.1365-2133.2006.07185.x PMID: 16792766
8. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res. 1996; 5(1):35–46. PMID: 8901365
9. Merikallio VJ, Mustalahti K, Remes ST, Valovirta EJ, Kaila M. Comparison of quality of life between asthmatic and healthy school children. Pediatric Allergy and Immunology. 2005; 16(4):332–40. https:// doi.org/10.1111/j.1399-3038.2005.00286.x PMID: 15943597
10. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract. 2006; 60(8):984–92. https://doi.org/10.1111/j.1742-1241.2006.01047.x PMID: 16893440
11. Hafkamp-de Groen E, Raat H. Asthma and Health Related Quality of Life in Childhood and Adolescence: INTECH Open Access Publisher; 2012.
12. Klassen AF, Miller A, Fine S. Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder. Pediatrics. 2004; 114(5):e541–7. https://doi.org/10. 1542/peds.2004-0844 PMID: 15520087
13. Pongwilairat K, Louthrenoo O, Charnsil C, Witoonchart C. Quality of life of children with attention-deficit/ hyper activity disorder. J Med Assoc Thai. 2005; 88(8):1062–6. PMID: 16404833
14. Froisland DH, Graue M, Markestad T, Skrivarhaug T, Wentzel-Larsen T, Dahl-Jorgensen K. Health- related quality of life among Norwegian children and adolescents with type 1 diabetes on intensive insulin treatment: a population-based study. Acta Paediatr. 2013; 102(9):889–95. https://doi.org/10.1111/ apa.12312 PMID: 23738648
15. Petersen S, Hagglof BL, Bergstrom EI. Impaired health-related quality of life in children with recurrent pain. Pediatrics. 2009; 124(4):e759–67. https://doi.org/10.1542/peds.2008-1546 PMID: 19736269
16. Schipper H, Clinch J, Olweny C. (1996) Quality of Life Studies: Definitions and Conceptual Issues. New York: Lippincott-Raven
17. Hofman A, Jaddoe VWV, Mackenbach JP, Moll HA, Snijders RFM, Steegers EAP, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatric and perinatal epidemiology. 2004; 18(1):61–72. PMID: 14738548
18. Ravens-Sieberer U, Wille N, Erhart M, Bettge S, Wittchen H-U, Rothenberger A, et al. Prevalence of mental health problems among children and adolescents in Germany: results

of the BELLA study within the National Health Interview and Examination Survey. Eur Child Adolesc Psychiatry. 2008; 17(1):22– 33.
19. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev. 2008; 34(4):418–29. https://doi.org/10. 1111/j.1365-2214.2008.00825.x PMID: 19154551
20. Lee SL, Cheung YF, Wong HS, Leung TH, Lam TH, Lau YL. Chronic health problems and health- related quality of life in Chinese children and adolescents: a population-based study in Hong Kong. BMJ Open. 2013; 3(1).
21. Sawyer MG, Whaites L, Rey JM, Hazell PL, Graetz BW, Baghurst P. Health-related quality of life of children and adolescents with mental disorders. J Am Acad Child Adolesc Psychiatry. 2002; 41(5):530–7. https://doi.org/10.1097/00004583-200205000-00010 PMID: 12014785
22. Sawyer MG, Reynolds KE, Couper JJ, French DJ, Kennedy D, Martin J, et al. Health-related quality of life of children and adolescents with chronic illness—a two year prospective study. Qual Life Res. 2004; 13(7):1309–19. https://doi.org/10.1023/B:QURE.0000037489.41344.b2 PMID: 15473509
23. Houben-van Herten M, Bai G, Hafkamp E, Landgraf JM, Raat H. Determinants of health-related quality of life in school-aged children: a general population study in the Netherlands. PLoS One. 2015; 10(5): e0125083. https://doi.org/10.1371/journal.pone.0125083 PMID: 25933361
24. Banning R, Camstra A, Knottnerus P. Sampling theory: Sampling design and estimation methods. The Hague/Heerlen: Statistics Netherlands. 2012.
25. Statistics Netherlands, CBS (internet). Gezondheidsmetingen kinderen: 2001–2013. http://statline.cbs.nl/Statweb/ publication/?DM=SLNL&PA=81174NED&D1=7,9,18&D2=0&D3=2&D4=0&D5=a&VW=T
26. Statistics Netherlands, CBS (internet). Gezondheid, aandoeningen, beperkingen; leeftijd en geslacht, 2010–2013. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=81174NED&D1=7,9,18&D2= 0&D3=2&D4=0&D5=a&VW=T
27. Statistics Netherlands, CBS (internet). Health, disorders, limitations; sex and age, 2010–2013. http:// statline.cbs.nl/Statweb/publication/?VW=T&DM=SLEN&PA=81174ENG&D1=2-7,9-11,17-18,20- 21,23,26&D2=0&D3=2&D4=a&D5=a&HD=160616-1613&LA=EN&HDR=T&STB=G1,G2,G3,G4.
28. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. J Clin Epidemiol. 2002; 55(1):67–76. PMID: 11781124
29. Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. J Epidemiol Community Health. 2005; 59(1):75–82. https://doi.org/10. 1136/jech.2003.012914 PMID: 15598731
30. Raat H, Landgraf JM, Bonsel GJ, Gemke R, Essink-Bot M-L. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res. 2002; 11 (6):575–81. PMID: 12206578
31. Landgraf JM, Abetz L, Ware JE. Child Health Questionnaire (CHQ): A User's Manual. 1999. Boston, MA: HealthAct.
32. QuestionnairesHealthSurveyfrom2010to2013.StastisticsNetherlands,CBS(internet).https://www.cbs.nl/nl-nl/onze-diensten/methoden/onderzoeksomschrijvingen/aanvullende%20onderzoeksbeschrijvingen/vragenlijsten-gezondheidsenquete-2010-t-m-2013
33. Schaart R, Mies Moens B, Westerman S. The Dutch Standard Classification of Education,SOI 2006. Published in 2008. Statistics Netherlands. Voorburg/Heerlen.
34. Alders M. Classification of the population with a foreign background in the Netherlands.
35. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, New Jersey: L. Erlbaum; 1988.

36. Matthews A, Haas DM, O'Mathuna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2015;(9):CD007575. https://doi.org/10.1002/14651858. CD007575.pub4 PMID: 26348534
37. Sawyer MG, Spurrier N, Whaites L, Kennedy D, Martin AJ, Baghurst P. The relationship between asthma severity, family functioning and the health-related quality of life of children with asthma. Qual Life Res. 2000; 9(10):1105–15. PMID: 11401043
38. Mohangoo AD, de Koning HJ, Mangunkusumo RT, Raat H. Health-Related Quality of Life in Adolescents with Wheezing Attacks. Journal of Adolescent Health. 2007; 41(5):464–71. https://doi.org/10. 1016/j.jadohealth.2007.06.002 PMID: 17950166
39. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. Journal of Investigative Dermatology. 2011; 131(1):67– 73. https://doi.org/10.1038/jid.2010.251 PMID: 20739951
40. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995; 132(6):942–9. PMID: 7662573
41. tatistics Netherlands, CBS (internet). Slightly more children diagnosed with dyslexia, 2016. https:// www.cbs.nl/en-gb/news/2016/40/slightly-more-children-diagnosed-with-dyslexia
42. McNulty MA. Dyslexia and the life course. J Learn Disabil. 2003; 36(4):363–81. https://doi.org/10.1177/ 00222194030360040701 PMID: 15490908
43. Danckaerts M, Sonuga-Barke EJ, Banaschewski T, Buitelaar J, Dopfner M, Hollis C, et al. The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. Eur Child Adolesc Psychiatry. 2010; 19(2):83–105. https://doi.org/10.1007/s00787-009-0046-3 PMID: 19633992
44. Marques JC, Oliveira JA, Goulardins JB, Nascimento RO, Lima AM, Casella EB. Comparison of child self-reports and parent proxy-reports on quality of life of children with attention deficit hyperactivity disorder. Health Qual Life Outcomes. 2013; 11:186. https://doi.org/10.1186/1477-7525-11-186 PMID: 24180423
45. Bugdayci R, Ozge A, Sasmaz T, Kurt AO, Kaleagasi H, Karakelle A, et al. Prevalence and factors affecting headache in Turkish schoolchildren. Pediatr Int. 2005; 47(3):316–22. https://doi.org/10.1111/j.1442- 200x.2005.02051.x PMID: 15910458
46. Sillanpää M, Piekkala P, Kero P. Prevalence of Headache at Preschool Age in An Unselected Child Population. Cephalalgia. 1991; 11(5):239–42. https://doi.org/10.1046/j.1468-2982.1991.1105239.x PMID: 1773439
47. Padilla-Moledo C, Ruiz JR, Castro-Pinero J. Parental educational level and psychological positive health and health complaints in Spanish children and adolescents. Child Care Health Dev. 2016; 42 (4):534–43. https://doi.org/10.1111/cch.12342 PMID: 27097753
48. Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses. Pediatrics. 2003; 112(1 Pt 1):e1–5.
49. Varni JW, Limbers CA. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin North Am. 2009; 56(4):843–63. https://doi.org/10.1016/j.pcl.2009.05.016 PMID: 19660631
50. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: An appraisal and precept for future research and application. Health and Quality of Life Outcomes. 2005; 3:34–. https://doi.org/10.1186/1477-7525-3-34 PMID: 15904527
51. Mangione-Smith R, Schonlau M, Chan KS, Keesey J, Rosen M, Louis TA, et al. Measuring the effectiveness of a collaborative for quality improvement in pediatric asthma care: does implementing the chronic care model improve processes and outcomes of care? Ambul Pediatr. 2005; 5(2):75–82. https://doi.org/10.1367/A04-106R.1 PMID: 15780018
52. Vickers AJ. Statistical considerations for use of composite health-related quality-of-life scores in randomized trials. Qual Life Res. 2004; 13(4):717–23. https://doi.org/10.1023/B:QURE.0000021686. 47079.0d PMID: 15129882

53. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Arch Dis Child. 2001; 84(3):205–11. https://doi.org/10.1136/adc.84.3.205 PMID: 11207164
54. Burks ML, Brooks EG, Hill VL, Peters JI, Wood PR. Assessing proxy reports: agreement between children with asthma and their caregivers on quality of life. Ann Allergy Asthma Immunol. 2013; 111(1):14– 9. https://doi.org/10.1016/j.anai.2013.05.008 PMID: 23806454
55. Bastiaansen D, Koot HM, Ferdinand RF, Verhulst FC. Quality of life in children with psychiatric disorders: self-, parent, and clinician report. J Am Acad Child Adolesc Psychiatry. 2004; 43(2):221–30. https://doi.org/10.1097/00004583-200402000-00019 PMID: 14726730
56. Davis E, Nicolas C, Waters E, Cook K, Gibbs L, Gosch A, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. Qual Life Res. 2007; 16(5):863–71. https://doi.org/10.1007/s11136-007-9187-3 PMID: 17351822
57. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007; 5:2. https://doi.org/10.1186/1477-7525-5-2 PMID: 17201923
58. Klassen AF, Miller A, Fine S. Agreement between parent and child report of quality of life in children with attention-deficit/hyperactivity disorder. Child Care Health Dev. 2006; 32(4):397–406. https://doi.org/10. 1111/j.1365-2214.2006.00609.x PMID: 16784495

SUPPLEMENTARY

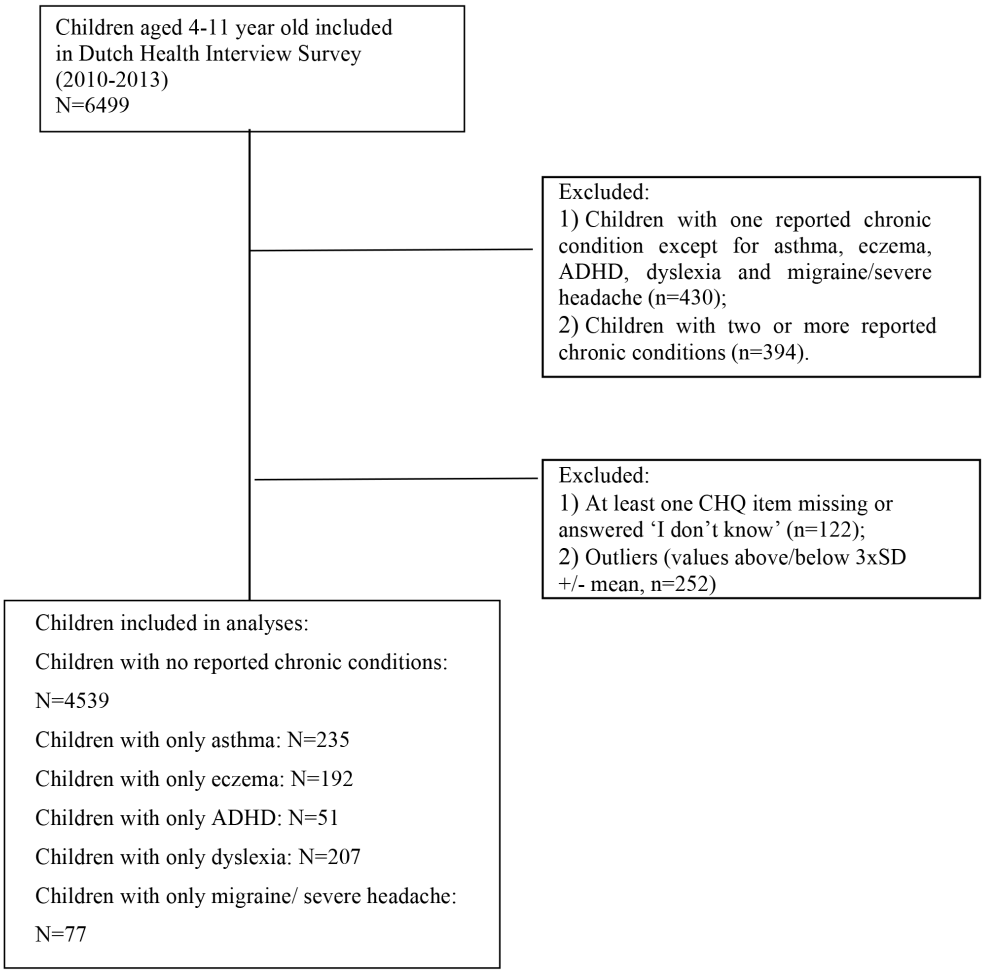

Figure S1. Flow chart of the population for analysis (N=5301)

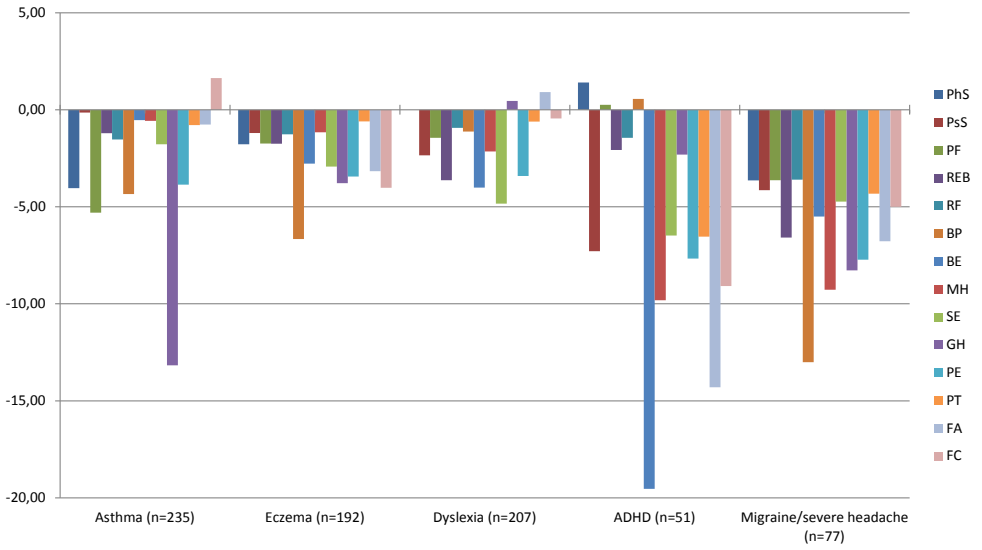

Figure S2. Differences in the mean scores on the CHQ-PF28 scales between subgroups of children with a condition (asthma, eczema, ADHD, dyslexia, migraine/severe headache) and children with no reported chronic conditions (N=5301)

PhS Physical Summary Component Scale; PsS Psychosocial Summary Component Scale; PF physical functioning; REB role functioning-emotional/behavior; RF role functioning-physical; BP bodily pain; BE general behavior; MH mental health; SE self-esteem; GH general health perceptions; PE parental impact: emotional; PT parental impact-time; FA family activities; FC family cohesion; CH change in health

Table S1. Comorbidity of children with asthma, eczema, ADHD, dyslexia and migraine[¶]

	Asthma (N = 368)		Eczema (N = 344)		Dyslexia (N=318)		ADHD (N = 140)		Migraine/severe headache (N = 143)	
	Valid N	%	Valid N	%	Valid N	%	%		Valid N	%
No comorbidity	235	63.8	192	55.8	207	65.1	51	36.4	77	53.8
Cancer (ever)	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0
Congenital heart disease	1	0.3	6	1.7	3	0.9	1	0.7	1	0.7
Diabetes	0	0.0	1	0.3	0	0.0	0	0.0	0	0.0
Migraine/severe headache	18	4.9	16	4.7	18	5.7	8	5.7	.	.
Asthma	.	.	69	20.1	31	9.7	15	10.7	18	12.6
Psoriasis	1	0.3	3	0.9	5	1.6	0	0.0	0	0.0
Eczema	69	18.8	.	.	29	9.1	15	10.7	16	11.2
Disorders of the intestines	8	2.2	13	3.8	6	1.9	7	5.0	8	5.6
Back disorders	0	0.0	2	0.6	1	0.3	0	0.0	1	0.7
Arthritis/rheumatism	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Neck shoulder disorders	1	0.3	1	0.3	0	0.0	0	0.0	2	1.4
Elbow/hand/wrist	1	0.3	1	0.3	2	0.6	0	0.0	1	0.7
Dyslexia	31	8.4	29	8.4	.	.	16	11.4	18	12.6
Intellectual disability	3	0.8	2	0.6	3	0.9	3	2.1	0	0.0
ADHD	15	4.1	15	4.4	16	5.0	.	.	8	5.6
Other chronic disease not mentioned	42	11.4	53	15.1	44	13.8	66	47.1	25	17.5

[¶] because there are overlaps between subgroups of children with asthma, eczema, ADHD, dyslexia, migraine/severe headache, it is not possible to calculate total population for supplementary analyses.

Table S2. CHQ-PF28 scores of children with one or more condition and of children without any reported chronic condition[¶]

	No chronic condition (n = 4539)	Asthma (n=368)		Eczema (n=344)		Dyslexia (n=318)		ADHD (n=140)		Migraine/severe headache (n=143)	
	mean score (SD)	mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size
CHQ-PF28 Summary scales											
Physical Component Summary Component Scale	58.53 (4.28)	53.27 (7.07)	0.74[b]*	55.28 (6.71)	0.49[a]*	57.66 (6.01)	0.15*	57.62 (6.61)	0.14	53.49 (7.19)	0.70[b]*
Psychosocial Component Summary Component Scale	53.86 (5.87)	52.09 (7.12)	0.25[a]*	51.04 (7.52)	0.37[a]*	50.14 (7.28)	0.51[b]*	44.50 (7.08)	1.32[c]*	49.45 (8.05)	0.55[b]*
CHQ-PF28 Child scales											
Physical Functioning	98.44 (6.51)	92.15 (12.25)	0.51[b]*	95.48 (9.62)	0.31[a]*	96.54 (9.39)	0.20[a]*	95.71 (10.71)	0.25[a]*	93.40 (11.13)	0.45[a]*
Role/Social Emotional Behavioral	98.80 (6.58)	94.93 (16.46)	0.24[a]*	94.19 (16.05)	0.29[a]*	92.14 (17.89)	0.37[a]*	87.62 (24.10)	0.46[a]*	92.37 (16.85)	0.36[a]*
Role/Social-Physical	98.84 (6.65)	95.74 (13.36)	0.23[a]*	96.22 (12.28)	0.21[a]	96.75 (10.91)	0.19	96.43 (13.67)	0.18	94.64 (12.91)	0.33[a]*
Bodily Pain	88.85 (15.99)	81.36 (20.65)	0.36[a]*	80.64 (20.34)	0.40[a]*	86.10 (17.60)	0.16*	85.57 (20.65)	0.16	73.29 (21.88)	0.71[b]*
Behavior	73.44 (14.04)	69.42 (15.92)	0.25[a]*	68.38 (16.15)	0.31[a]*	67.21 (14.97)	0.42[a]*	50.70 (15.06)	1.51[c]*	66.28 (16.79)	0.43[a]*
Mental Health	83.19 (13.54)	80.12 (15.48)	0.20[a]*	78.59 (15.03)	0.31[a]*	78.93 (14.74)	0.29[a]*	72.32 (16.06)	0.68[b]*	73.08 (16.77)	0.60[b]*
Self-Esteem	82.38 (12.64)	79.06 (12.67)	0.26[a]*	78.56 (13.13)	0.29[a]*	75.73 (13.55)	0.49[a]*	73.60 (13.12)	0.67[b]*	76.84 (11.73)	0.44[a]*
General Health Perception	90.47 (12.17)	73.16 (19.78)	0.88[c]*	80.22 (20.23)	0.51[b]*	86.69 (15.69)	0.24[a]*	80.36 (19.04)	0.53[b]	76.80 (17.56)	0.78[b]*
CHQ-PF28 Parent and Family Impact scales											
Parental Impact-Emotional	92.96 (11.22)	86.51 (14.60)	0.44[a]*	85.79 (15.25)	0.47[a]*	87.66 (13.13)	0.40[a]*	81.79 (15.68)	0.71[b]	83.04 (18.19)	0.54[b]*
Parental Impact-Time	97.39 (10.38)	94.61 (15.08)	0.18*	94.72 (13.84)	0.19*	95.65 (11.29)	0.15*	87.86 (22.87)	0.42[a]	94.06 (14.59)	0.23[a]*
Family Activities	93.47 (12.26)	89.33 (17.19)	0.24[a]*	87.83 (17.66)	0.32[a]*	91.82 (14.18)	0.12*	74.82 (24.50)	0.76[b]	85.58 (18.96)	0.42[a]*
Family Cohesion	80.84 (17.01)	79.13 (17.86)	0.10	76.53 (18.32)	0.24[a]*	77.42 (18.28)	0.19*	69.50 (17.27)	0.66[b]	73.78 (18.54)	0.38[a]*

SD: standard deviation. *P <0.05. Effect size (d): a means small difference when 0.2≤d<0.5 small difference; b means moderate difference when 0.5≤d<0.8; c means large difference when d≥0.8; for others that d was less than 0.2, we didn't mark them in our table. [¶]because there are overlaps between subgroups of children with asthma, eczema, ADHD, dyslexia, migraine/severe headache, it is not possible to calculate total population for supplementary analyses.

Table S3. Gender-specific difference in CHQ-PF28scores between children with one condition and children without any chronic conditions (n=5301)

	No chronic condition	Asthma		Eczema	
	(Boys n=2242 Girls n=2297)	(Boys n=141 Girls n=94)		(Boys n=87 Girls n=105)	
	mean score (SD)	mean score (SD)	effect size	mean score (SD)	effect size
CHQ-PF28 Summary					
Scales					
Physical Summary Component Scale					
Boys	58.61 (4.40)	53.95 (6.39)	0.73[b]*	56.86 (5.39)	0.32[a]*
Girls	58.46 (4.15)	55.31 (5.31)	0.59[b]*	56.66 (5.42)	0.33[a]*
Psychosocial Summary Component Scale					
Boys	53.56 (5.81)	54.16 (6.08)	-0.10	52.62 (6.86)	0.14
Girls	54.16 (5.91)	53.06 (5.57)	0.20	52.70 (5.97)	0.25[a]*
CHQ-PF28 Child Scales					
Physical Functioning					
Boys	98.22 (6.87)	92.44 (12.41)	0.47[a]*	95.91 (9.30)	0.25[a]*
Girls	98.66 (6.13)	94.21 (11.26)	0.40[a]*	97.35 (7.15)	0.18
Role/Social Emotional Behavioral					
Boys	98.81 (6.65)	97.40 (13.26)	0.11	96.93 (12.06)	0.16*
Girls	98.80 (6.53)	97.87 (10.72)	0.09	97.14 (11.43)	0.14
Role/Social-Physical					
Boys	98.72 (7.07)	96.22 (13.85)	0.18	98.08 (9.31)	0.07
Girls	98.96 (6.21)	98.94 (5.89)	0.00	97.14 (10.45)	0.17
Bodily Pain					
Boys	89.48 (15.69)	85.53 (16.41)	0.24[a]*	83.68 (16.00)	0.36[a]*
Girls	88.24 (16.25)	82.98 (20.10)	0.26[a]*	80.95 (18.48)	0.39[a]*
Behavior					
Boys	72.03 (14.12)	72.90 (14.82)	-0.06	70.03 (14.54)	0.14
Girls	74.82 (13.81)	72.94 (12.30)	0.14	71.19 (14.99)	0.24[a]*
Mental Health					
Boys	83.31 (13.35)	84.75 (13.47)	-0.11	83.05 (13.54)	0.02
Girls	83.08 (13.73)	79.43 (13.92)	0.26[a]*	81.19 (11.84)	0.14
Self-Esteem					
Boys	81.91 (12.26)	81.44 (12.01)	0.04	79.31 (11.90)	0.21[a]
Girls	82.84 (12.98)	79.34 (11.59)	0.27[a]*	79.56 (12.20)	0.25[a]*
General Health Perception					
Boys	90.20 (12.42)	76.58 (17.40)	0.78[b]*	87.01 (14.47)	0.22[a]*
Girls	90.74 (11.92)	78.38 (16.56)	0.75[b]*		86.43 (14.02)
CHQ-PF28 Parent and Family Impact scales					
Parental Impact-Emotional					
Boys	92.58 (11.27)	88.12 (14.66)	0.30[a]*	89.80 (12.14)	0.23[a]*
Girls	93.32 (11.15)	90.56 (11.84)	0.23[a]*	89.29 (14.44)	0.28[a]*
Parental Impact-Time					
Boys	97.30 (10.29)	96.22 (12.01)	0.09	95.59 (12.82)	0.13
Girls	97.48 (10.47)	97.16 (12.38)	0.03	97.78 (7.69)	-0.03
Family Activities					
Boys	93.07 (12.57)	93.00 (13.96)	0.01	90.95 (14.60)	0.15
Girls	93.87 (11.94)	92.29 (15.02)	0.11	89.76 (15.96)	0.26[a]*
Family Cohesion					
Boys	80.26 (16.97)	83.76 (16.23)	-0.21[a]*	76.72 (19.42)	0.18
Girls	81.40 (17.04)	80.53 (17.71)	0.05	76.90 (15.83)	0.26[a]*

Effect sizes: a = small difference, b = moderate difference, c =large difference. * Statistically significant difference compared to children with no chronic condition.

Table S3. Continued

Dyslexia (Boys n=118 Girls n=89)		ADHD (Boys n=29 Girls n=22)		Migraine/severe headache (Boys n=33 Girls n=44)	
mean score (SD)	effect size	mean score (SD)	effect size	mean score (SD)	effect size
58.86 (4.90)	-0.12	59.36 (6.25)	-0.12	55.17 (6.63)	0.52[b*]
58.10 (4.88)	0.07	60.68 (3.09)	-0.54[b*]	54.67 (6.78)	0.56[b*]
51.18 (6.44)	0.37[a*]	45.36 (6.81)	1.20[c*]	50.21 (8.09)	0.41[a*]
51.95 (5.95)	0.37[a*]	48.17 (5.03)	1.01[c*]	49.36 (9.19)	0.52[b*]
97.18 (9.09)	0.11	97.70 (7.50)	0.07	90.91 (12.25)	0.60[b*]
96.75 (10.35)	0.18	100.00 (0.00)	-0.22[a*]	97.73 (6.60)	0.14
94.63 (13.05)	0.32[a*]	97.70 (8.60)	0.13	93.94 (17.59)	0.28[a*]
95.88 (12.12)	0.24 [a*]	95.45 (11.71)	0.29[a*]	90.91 (19.51)	0.40[a*]
98.31 (7.35)	0.06	95.40 (19.36)	0.17	95.96 (11.05)	0.25[a*]
97.38 (9.02)	0.17	100.00 (0.00)	-0.17	94.70 (14.28)	0.30[a*]
88.31 (16.61)	0.07	87.59 (14.55)	0.12	78.18 (16.86)	0.67[b*]
86.97 (13.85)	0.08	91.82 (13.32)	-0.22 [a*]	74.09 (23.46)	0.60[b*]
68.39 (13.15)	0.26[a*]	50.00 (14.22)	1.55[c*]	65.76 (17.06)	0.37[a*]
70.80 (13.92)	0.29[a*]	59.03 (17.40)	0.91[c*]	69.57 (16.96)	0.31[a*]
80.79 (13.93)	0.18	72.13 (13.04)	0.84[c*]	72.98 (16.67)	0.62[b*]
81.37 (12.56)	0.12	75.00 (14.55)	0.56[b*]	74.62 (18.67)	0.45[a*]
76.94 (12.06)	0.41[a*]	74.57 (12.42)	0.59[b*]	78.41 (12.56)	0.28[a*]
78.32 (13.42)	0.34 [a*]	77.65 (11.32)	0.40[a*]	77.08 (12.60)	0.44[a*]
90.89 (11.77)	-0.06	88.32 (16.16)	0.12	84.05 (15.74)	0.39[a*]
0.31[a*]	90.96 (11.72)	0.02	87.95 (11.93)	0.23 [a*]	80.80 (16.24)
90.36 (11.60)	0.19*	83.19 (13.48)	0.70[b*]	88.64 (11.84)	0.33[a*]
88.48 (13.22)	0.37 [a*]	88.07 (13.07)	0.40[a*]	82.67 (21.09)	0.51[b*]
96.61 (11.44)	0.06	87.93 (23.10)	0.41[a*]	96.97 (9.73)	0.03
97.00 (8.17)	0.05	94.70 (21.45)	-0.13	90.15 (20.43)	0.36[a*]
93.86 (11.41)	-0.07	75.43 (23.74)	0.74[b*]	83.71 (18.08)	0.52[b*]
95.08 (9.72)	-0.10	84.09 (23.20)	0.42[a*]	88.92 (17.93)	0.28 [a]
79.66 (17.96)	0.03	70.17 (17.80)	0.57[b*]	78.33 (16.04)	0.11
81.35 (15.79)	0.00	73.86 (14.79)	0.44[a*]	73.98 (17.54)	0.42[a*]

Table S4. Differences in the mean scores of CHQ-PF28 scales and summaries between children who were seen by the family physicians or medical specialist and who were not&

	Asthma		Eczema		Dyslexia		Migraine/severe headache	
	Seen by the family physician or medical specialist (n=143)	Not Seen by the family physician or medical specialist (n=92)	Seen by the family physician or medical specialist (n=86)	Not seen by the family physician or medical specialist (n=106)	Seen by the family physician or medical specialist (n=86)	Not seen by the family physician or medical specialist (n=121)	Seen by the family physician or medical specialist (n=28)	Not seen by the family physician or medical specialist (n=49)
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
PhS	**53.40 (6.52)**	**56.20 (4.65)**	56.78 (5.65)	56.73 (5.21)	59.07 (4.15)	58.15 (5.34)	53.20 (8.48)	55.85 (5.25)
PsS	53.77 (5.54)	53.64 (6.43)	52.03 (6.88)	53.17 (5.91)	51.82 (5.95)	51.29 (6.44)	49.00 (7.72)	50.14 (9.25)
PF	**91.67 (12.68)**	**95.41 (10.44)**	96.64 (9.96)	96.75 (7.96)	97.67 (8.88)	96.51 (10.15)	92.86 (12.18)	95.92 (8.39)
REB	97.90 (12.64)	97.10 (11.75)	97.67 (9.95)	96.54 (12.95)	94.19 (13.71)	95.87 (11.84)	91.67 (19.51)	92.51 (18.34)
RF	96.04 (13.98)	99.28 (4.89)	98.45 (7.06)	96.85 (11.75)	98.06 (7.84)	97.80 (8.31)	91.67 (17.27)	97.28 (9.22)
BP	83.78 (19.57)	85.65 (15.21)	81.86 (17.52)	82.45 (17.39)	90.23 (13.28)	85.95 (16.66)	72.86 (21.92)	77.55 (20.26)
BE	73.16 (14.52)	72.53 (12.77)	69.36 (15.36)	71.72 (14.24)	69.81 (13.44)	69.15 (13.60)	66.61 (18.53)	68.70 (16.20)
MH	81.70 (13.68)	84.06 (14.12)	81.01 (13.44)	82.86 (11.94)	81.20 (13.90)	80.92 (12.97)	72.32 (15.56)	74.83 (18.98)
SE	80.59 (11.40)	80.62 (12.62)	79.12 (12.60)	79.72 (11.60)	79.31 (10.66)	76.27 (13.79)	76.34 (9.15)	78.40 (14.12)
GH	**74.43 (17.08)**	**81.75 (16.11)**	85.77 (14.85)	87.44 (13.65)	91.51 (10.08)	90.50 (12.78)	80.27 (15.30)	83.29 (16.45)
PE	88.72 (13.04)	89.67 (14.54)	88.23 (15.14)	90.56 (11.80)	**92.00 (9.95)**	**87.81 (13.55)**	**84.38 (20.30)**	85.71 (16.54)
PT	96.04 (12.34)	97.46 (11.83)	95.15 (12.49)	98.11 (8.07)	96.51 (13.06)	96.97 (7.45)	89.88 (23.72)	94.90 (23.72)
FA	91.96 (14.03)	93.89 (14.88)	88.23 (16.86)	91.98 (13.82)	95.35 (8.79)	93.70 (11.87)	84.37 (18.52)	88.01 (17.85)
FC	83.53 (16.73)	80.82 (17.05)	75.87 (19.43)	77.59 (15.81)	80.70 (16.70)	80.16 (17.34)	79.11 (17.80)	73.98 (16.33)

[&]data shown in this table is from children with one of the five prevalent chronic conditions (asthma, eczema, dyslexia or migraine/severe headache). The information on ADHD was not collected by the interview. Bold print indicates statistical significance ($p<0.05$).

PhS Physical Summary Component Scale ; PsS Psychosocial Summary Component Scale; PF physical functioning; REB role functioning: emotional/behavior; RF role functioning: physical; BP bodily pain and discomfort; BE general behavior; MH mental health; SE self-esteem; GH general health perceptions; PE parental impact: emotional; PT parental impact: time; FA family activities; FC family cohesion.

PART IV

Measuring Health-related Quality of life in Early Childhood

CHAPTER 8

Feasibility and Validity of the Health Status Classification System Preschool (HSCS-PS) in a Large Community Sample: The Generation R Study

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ABSTRACT

Objectives

To evaluate the feasibility, discriminant validity and concurrent validity of the Health Status Classification System-Preschool (HSCS-PS) in children aged three years in a large community sample in the Netherlands.

Design/Setting

A prospective population-based cohort in Rotterdam, the Netherlands

Participants

A questionnaire was administrated to a sample of parents of 4,546 children (36.7 ±1.5 months).

Outcome measures

Health-related quality of life of children was measured by Health Status Classification System-Preschool (HSCS-PS). The HSCS-PS consists of ten original domains. Two single-item measures of "General health" and "Behavior" were added. A disability score was calculated by summing up all ten original domains to describe the overall health status. Feasibility was assessed by the response rate, percentages of missing answers, score distributions and the presence of floor/ceiling effects. Discriminant validity was analyzed between subgroups with predefined conditions: low birth weight, preterm birth, wheezing, Ear-Nose-Throat surgical procedures, and behavior problems. In the absence of another HRQOL measure, this study uses the single-items 'General health' and 'Behavior' as a first step to evaluate concurrent validity of the HSCS-PS.

Results

Feasibility: response rate was 69%. Ceiling effects were observed in all domains. Discriminant validity: the disability score discriminated clearly between subgroups of children born with a "very low birth weight", "very preterm birth", with "four or more than four times wheezing", "at least one Ear-Nose-Throat surgical procedures", "behavior problems present", and the "reference" group. Concurrent validity: HSCS-PS domains correlated better with hypothesized parallel additional domains than with other non-hypothesized original domains.

Conclusions

This study supports the feasibility and validity of the HSCS-PS among preschoolers in community settings. We recommend developing a utility-based scoring algorithm for the HSCS-PS. Further empirical studies and repeated evaluations in varied populations are recommended.

INTRODUCTION

Patient-reported health status and health-related quality of life (HRQOL) are essential outcome measures in addition to clinical outcomes in both general medicine and pediatrics.[1, 2] HRQOL refers to quality of life as modified by the functional states, impairments, perceptions, and social opportunities as influenced by chronic conditions, injury, treatment or policy.[3],[4] Studies on HRQOL of preschool children are scarce due to the early stage of development and the need for proxy reporting.[5] In addition to 'health profile measures', e.g. the Infant and Toddler Quality of Life Questionnaire (ITQOL), for economic analyses and guiding value-based health care, we need preference-based measures where the 'health status description' is 'valued' (i.e. 'weighted') by a relevant panel in society.[6-9] The most widely used preference-based measure is the Health Utilities Index (HUI; i.e. HUI2 and HUI3) for children/people aged four years and above.[1, 10] There is a need for a similar, preference-based instrument for preschool children.

The Health Status Classification System-Preschool (HSCS-PS), developed by Saigal et al.(2005), is a multi-dimensional system to describe the HRQOL of preschool children aged 2.5-5 years.[11] It is a parental (or clinician) proxy measurement of the health status of the child with a structure similar to the HUI.[12] The instrument includes ten mutually exclusive domains, i.e. 'Vision', 'Hearing', 'Speech', 'Mobility', 'Dexterity', 'Self-care', 'Emotion', 'Learning and remembering', 'Thinking and problem solving', 'Pain and discomfort'. Saigal et al.(2005) proposed two additional parent-reported single-item measures: 'General health' and 'Behavior'.[11]

So far, the HSCS-PS has been validated in clinical cohorts of children with a very low birth weight and children with cerebral palsy.[11] The HSCS-PS was applied in studies regarding the development of health of young children after extremely preterm birth.[13, 14] The reliability and validity of the HSCS-PS were supported in previous studies that applied HSCS-PS in patients who were diagnosed with neuroblastoma at two-to-five-years of age.[15, 16] Little is known about the feasibility and validity among children in generally healthy populations.

The present study uses a large general population sample to describe and evaluate the parent-completed HSCS-PS by using information regarding birth outcomes (e.g. low birth weight and preterm birth), wheezing and Ear-Nose-Throat (ENT) surgical procedures, and behavior problem in preschool children identified by the Child Behavior Checklist (CBCL 1.5-5). Previous studies have shown that children with the above-mentioned health condition were reported by their parents or caregivers with relatively low HRQOL.[17-25] For example, the parent-reported HRQOL of preschool children born preterm

or born with a very low birth weight was lower than HRQOL of those who were not born preterm or with a low birth weight.[17-20]

In the absence of another HRQOL measure, this study uses the above-mentioned parent-reported single-items regarding 'General health'[26] and 'Behavior' [27] as a first step to evaluate concurrent validity of the HSCS-PS.

The aims of this study are to assess: (1) The feasibility of the HSCS-PS considering the response rate, missing answers, score distributions, and presence of floor/ceiling effects;(2) The discriminant validity by comparing HSCS-PS scores between subgroups in the general population with presence/absence of low birth weight, premature delivery, wheezing, Ear-Nose-Throat (ENT) surgical procedures and CBCL behavior problems; and (3) as a first step regarding the concurrent validity by evaluation of the correlations between the original HSCS-PS scores and the 'General health' and 'Behavior' single-item measures.

METHODS

Study Design

This study was embedded in the Generation R Study, a population-based prospective child cohort study from fetal life onwards in Rotterdam, the Netherlands.[28] All children were born between April 2002 and January 2006. The Study is conducted in accordance with the guidelines proposed in the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam (MEC-2007-413). Written informed consent was obtained from the parents.[29]

7893 children were included in the postnatal follow-up studies.[28] In the survey after 36 months of birth, parental consent was available for 7294 children. Children whose caregivers did not fill out the questionnaire at age three years (n=2280) were excluded. Additionally, we excluded children with missing data on one or more domains of the HSCS-PS (n=468), leaving 4546 children for the analyses (see S1 Fig).

Public Involvement

Generation R discusses the strategy of the cohort study and the outcomes of the studies with the Municipality of Rotterdam on a regular basis; as the Municipality represents parents (and youth) in general. Moreover, participating parents and youth are regularly informed by newsletters regarding general outcomes of Generation R studies, and by a personal "passport" with findings from the measurements for the participating family. Parents and youth are invited to comment on the outcomes at the website. At the

individual level, the "passport" and the individual results are discussed with the parents (and youth) by a physician, after the measurements on a certain day are finished.

Health Status Classification System-Preschool (HSCS-PS)

The HSCS-PS is a parent reported health status questionnaire applicable to 2.5-5 year-olds which consists of 10 mutually exclusive domains, based on the Health Utility Index (HUI).[11] In addition, Saigal et al. proposed two additional parent-reported single-item questions regarding 'General Health' and 'Behavior', given the relatively high prevalence of general health and behavior problems among the very-low-birth-weight (VLBW) infants.[30, 31] The HSCS-PS was initially applied to approximately 80 children across Canada by pediatricians and neonatologists regarding the structured and qualitative feedback. After several rounds of refinements, the final version contains 10 domains each with 3-5 levels, and the two additional items. (see S1 Table). The overall health status is described as a ten-element vector consisting of one level for each of the domains. In this study, to facilitate comparisons between groups, a total 'disability score' for the overall health state of a child was calculated as the sum of the level codes for the original domains. Therefore, the range of the disability score varied from 10 (no disability on any domain) to 41 (maximum disability on all 10 domains).[16]

Birth Outcomes

In the present study, birth weight and gestational age at birth was obtained from medical records. Low birth weight (LBW) was defined as a birth weight less than 2500 grams. To construct extreme groups, we further divided LBW into very low birth weight (<1500 grams) and moderate low birth weight (1500-2500 grams).[32] Children were defined as preterm when they were born alive before 37 weeks of gestation. Preterm birth was further subdivided into very preterm (<32 weeks) and moderate to late preterm (32-37 weeks). [33]

Wheezing

Parent-reported frequency of wheezing in the past 12 months at age 3 years was assessed using core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) and classified as 'no wheezing', '1-3 episodes' and '≥ 4 episodes'.[34]

Ear-Nose-Throat Surgical Procedures

At age 3 years the parents were asked whether the child had undergone an Ear-Nose-Throat surgical procedure, i.e. removal of the adenoids, removal of the tonsils, and inserting tubes to aerate the middle ear.[35] If at least one of these procedures was reported, the child was classified as 'with ENT surgical procedure(s)'.

Behavior Problems

The presence of child behavior problems was assessed at age 3 years by the Child Behavior Checklist parent questionnaire.[36] A borderline cut-off score (83rd percentile of a Dutch norm group) of the CBCL total problem score was used to differentiate between

children with and without behavior problems in the borderline/clinical range.[37]

Other Data

Socio-demographic characteristics were assessed by parent questionnaires, including marital status, educational level and ethnic background of the main caregiver, household income and child's age when the questionnaire was completed. Child's gender was obtained from medical records.

Statistical analyses

The scores of the HSCS-PS domains and the HSCS-PS disability score were treated as continuous variables. Statistical analyses were conducted in SPSS, version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Feasibility

Feasibility of the HSCS-PS was evaluated by assessing the response rate, percentage of missing answers, score distributions and the presence of floor/ceiling effects (i.e. >50% of the respondents in the best/worst option).

Discriminant Validity

We evaluated the ability of the HSCS-PS to discriminate between subgroups with and without low birth weight, preterm birth, wheezing, ENT surgical procedures and behavior problems. Additionally, we calculated how many of these five conditions a child had (i.e. whether a child had a low birth weight, was born preterm, is reported to have wheezing, to have had ENT surgical procedures, to have behavior problems). This cumulative number of conditions was recoded into four categories: no condition, 1 condition, 2 conditions and ≥ 3 conditions. The ability of the HSCS-PS to discriminate between subgroups differing in the number of conditions was assessed.

Because of the non-normal distribution of HSCS-PS scores, Mann-Whitney nonparametric tests were used to assess differences in HSCS-PS scores between subgroups. Additionally, Cohen's effect sizes (d) were calculated by dividing the difference in mean scores between subgroups by the largest standard deviation, and interpreted as: $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate difference, $d \geq 0.8$ large difference.[38] Significant differences were indicated at the level of $p<0.05$.We expected that the disability score would be higher in the subgroups in which the children were reported to have a 'condition' (see above) compared to the reference group without this condition. Additionally, we hypothesized that the disability score would be higher in the subgroups with a higher number of conditions, compared to the reference subgroup in which the children were reported to have none of the conditions.

Concurrent Validity

In the absence of a 'gold standard' measure of HRQOL, as a first step to evaluate the concurrent validity of the 10-domains HSCS-PS, it was assessed whether specific HSCS-PS

domains correlated better with their assumed 'parallel' single-item measures of 'General health' and/or 'Behavior' than with a 'non-parallel' measure. Considering the non-normal distribution of the data, Spearman rank correlation was applied. We calculated bootstrapped 95% confidence intervals for Spearman correlation coefficients. When (a) the 95% confidence interval is not 'across 0'; and (b)the p value < 0.05, the correlation coefficient was regarded as statistically significant. We hypothesized relatively high correlation coefficients between the following 'parallel' pairs of a HSCS-PS- domain/ single-item parent-rated measure (in italics): 'Pain and discomfort'/'General health'; 'Self-care'/'Behavior'; 'Emotion'/'Behavior'; 'Learning and remembering'/'Behavior'; 'Thinking and problem solving'/'Behavior'; and we hypothesized the correlation coefficients for all other pairs to be lower.

Non-response Analysis
Children with missing data on the HSCS-PS at age 3 years, including children whose parents did not complete the entire questionnaire (n=2748) were compared with children who did not have missing data on any HSCS-PS domain and thus were included in the analyses (n=4546).

RESULTS

Of the respondents, 94.3% were mothers. Children's mean age at the HSCS-PS questionnaire was 36.7 months (SD 1.5); 49.6% were boys; 5.2% of the children had a low birth weight (<2500 grams); 6% of the children were born preterm (gestational age at birth <37 weeks); 12.7% had wheezing in the previous year; 11.5% had any previous ENT surgical procedure and 5.7% had parent-reported behavior problems (see S2 Table).

Non-response Analysis
Significant differences were present in all characteristics, except for children's age, gender, and presence of ENT surgical procedures and wheezing. Excluded children relatively more often had single parents (p<0.001); parents with a low educational level (p<0.001); and more often a non-Dutch parent (p<0.001) (see Table S3).

Feasibility
The response rate of the questionnaire at 36 month after birth was 69%.[28] Considering all questionnaires that were received at age 3 years (n=5014), there were on average 1.7% missing answers regarding the HSCS-PS items in the questionnaire; this was highest for 'Vision' (4.19%) and 'Hearing' (3.19%). Score distributions of the HSCS-PS domains and the total 'disability score' are presented in Table 1. Floor effects were absent. Near to perfect scores (level 1= normal health/no impairment) were reported by >90.0% in 7 out of 10 domains; exceptions were 'Speech' (66.8%), 'Self-care' (89.4%), and 'Pain and discomfort' (88.5%). All HSCS-PS domains and the total 'disability score' showed a ceiling effect.

Table 1. Score distributions of the HSCS-PS domains in the population sample (n=4546)

HSCS-PS domains	Mean (SD)	Range	% of Min[a]	% of Max[b]	25th %tile	50th %tile[c]	75th %tile
Original domains							
Vision	1.02 (0.18)	1-4	98.9	0	1	1	1
Hearing	1.02 (0.14)	1-3	98.3	0	1	1	1
Speech	1.35 (0.51)	1-4	66.8	0.2	1	1	2
Mobility	1.02 (0.17)	1-4	98.1	0.1	1	1	1
Dexterity	1.01 (0.11)	1-3	99.5	0	1	1	1
Self-care	1.12 (0.36)	1-4	89.4	0.2	1	1	1
Emotion	1.01 (0.08)	1-3	99.5	0*	1	1	1
Learning and remembering	1.02 (0.14)	1-3	98.5	0	1	1	1
Thinking and problem solving	1.02 (0.19)	1-4	98.0	0.1	1	1	1
Pain and discomfort	1.12 (0.33)	1-3	88.5	0	1	1	1
Disability score[d]	10.69 (1.11)	10-26	54.7	0	10	10	11
Two items additional to the orginal 10-domain HUI system							
General health	1.05 (0.24)	1-4	95.8	0.1	1	1	1
Behavior	1.05 (0.23)	1-4	95.1	0*	1	1	1

[a] Percentage of respondents with the best possible score (ceiling). [b] Percentage of respondents with the worst possible score (floor). [c] Median. [d] Sum of the ten original domains. *<0.1% were observed at the maximum (floor).

Discriminant Validity

Table 2 shows the ability of the total 'disability score' to discriminate between the subgroup of children born with a 'very low birth weight' (effect size 0.39; $p<0.05$) and 'very preterm birth' (0.42; $p<0.01$), and the 'reference' subgroup; the differences between the subgroups with 'moderate low birth weight'(effect size 0.17; $p\geq0.05$) and 'moderate to late preterm' (0.20; $p<0.001$) compared to the 'reference' subgroup were lower, as hypothesized. The domains 'Learning and remembering', 'Self-care' showed the largest discriminant validity regarding 'very low birth weight' (effect size 0.44; $p<0.001$) and 'very preterm birth' (0.42; $p<0.001$).

Table 3 shows the ability of the total 'disability score' to discriminate between the subgroup of children with '≥4 times wheezing in the previous year' (effect size 0.27; $p<0.01$) and 'at least 1 ENT surgical procedure' (0.33; $p<0.001$) and CBCL 'behavior problems present' (0.52; $p<0.001$), and the 'reference' subgroup, as hypothesized. In these three comparisons (Table 4) the single 'original domains' that showed the largest discriminant validity were respectively 'Pain and discomfort' (effect size 0.31; $p<0.001$), 'Pain and discomfort' (0.35; $p<0.001$), 'Self-care' (0.40; $p<0.001$).

Table 2. Discriminative ability of the HSCS-PS between subgroups differing in birth outcomes: birth weight (n=4541) and gestational age at birth (n=4526)

	Birth weight					Gestational age				
HSCS-PS domains	**≥2500 grams (n=4307)**	**1500-2500 grams (n=206)**		**<1500 grams (n=28)**		**≥37 weeks (n=4256)**	**32-37 weeks (n=239)**		**<32 weeks (n=31)**	
	Mean (SD)[a]	**Mean (SD)[a]**	**Effect size[b1]**	**Mean (SD)[a]**	**Effect size[b2]**	**Mean (SD)[a]**	**Mean (SD)[a]**	**Effect size[b3]**	**Mean (SD)[a]**	**Effect size[b4]**
Original domains										
Vision	1.01 (0.16)	1.06 (0.37)**	0.14	1.07 (0.38)	0.16	1.01 (0.16)	1.06 (0.35)**	0.14	1.06 (0.36)	0.14
Hearing	1.02 (0.14)	1.02 (0.15)	0.00	1.04 (0.19)	0.11	1.02 (0.14)	1.02 (0.14)	0.00	1.03 (0.18)	0.06
Speech	1.34 (0.51)	1.35 (0.54)	0.02	1.43 (0.57)	0.16	1.34 (0.50)	1.42 (0.58)	0.14	1.48 (0.57)	0.25
Mobility	1.02 (0.17)	1.04 (0.22)	0.09	1.11 (0.42)*	0.21	1.02 (0.15)	1.06 (0.34)**	0.12	1.10 (0.40)*	0.20
Dexterity	1.01 (0.10)	1.03 (0.23)***	0.09	1.00 (0.00)	0.10	1.01 (0.09)	1.04 (0.25)***	0.12	1.00 (0.00)	0.11
Self-care	1.11 (0.34)	1.19 (0.50)*	0.16	1.46 (0.84)**	0.42	1.11 (0.34)	1.18 (0.50)*	0.14	1.45 (0.81)***	0.42
Emotion	1.01 (0.08)	1.00 (0.07)	0.13	1.00 (0.00)	0.13	1.01 (0.08)	1.01 (0.09)	0.00	1.00 (0.00)	0.13
Learning and remembering	1.01 (0.13)	1.05 (0.28)**	0.14	1.18 (0.39)***	0.44	1.01 (0.13)	1.05 (0.27)**	0.15	1.16 (0.37)***	0.41
Thinking and problem solving	1.02 (0.17)	1.07 (0.32)**	0.16	1.14 (0.59)*	0.20	1.02 (0.17)	1.06 (0.34)*	0.12	1.16 (0.58)**	0.24
Pain and discomfort	1.12 (0.33)	1.15 (0.35)	0.09	1.14 (0.36)	0.06	1.12 (0.33)	1.15 (0.36)	0.08	1.13 (0.34)	0.03
Disability score	10.67 (1.05)	10.98 (1.78)	0.17	11.57 (2.28)*	0.39	10.66 (1.03)	11.05 (1.92)***	0.20	11.58 (2.17)**	0.42
Two items additional to the orginal 10-domain HUI system										
General health	1.05 (0.23)	1.07 (0.29)	0.07	1.32 (0.82)***	0.33	1.04 (0.23)	1.10 (0.35)**	0.17	1.29 (0.78)***	0.32
Behavior	1.05 (0.23)	1.07 (0.25)	0.08	1.11 (0.32)	0.19	1.05 (0.23)	1.06 (0.24)	0.04	1.10 (0.30)	0.17

Data are presented as mean or standard deviation. aTwo-sided Mann-Whitney U-test given a non-normal distribution of the data. b1Difference of the means divided by the largest standard deviation between children born with a moderately low birth weight and children born with a normal birth weight. [b2]Difference of the means divided by the largest standard deviation between children born with a very low birth weight and children born with a normal birth weight. [b3]Difference of the means divided by the largest standard deviation between moderate to late preterm children and term children. [b4]Difference of the means divided by the largest standard deviation between very preterm children and term children. Cohen's effect size (d): 0.2≤d<0.5 indicates a small difference, 0.5≤d<0.8 indicates a moderate difference, d≥0.8 indicates a large difference. [c]Sum of the ten original domains. *p <0.05. **p<0.01. ***p<0.001. HSCS-PS = Health Status Classification System-Preschool.

Table 3. Discriminative ability of the HSCS-PS between subgroups differing in: wheezing chest in the previous year (n=4407), Ear-Nose-Throat (ENT) surgical procedures ever (n=4346), Child Behavior Checklist behavior problem present in the last two months (n=4490)

	Wheezing in the previous year					ENT surgical procedures			Behavior problems present in the last two months		
HSCS-PS domains	**No wheezing (n=3849)**	**1-3 times (n=454)**		**≥4 times (n=104)**		**No ENT surgical procedures (n=3956)**	**At least 1 ENT surgical procedures (n=390)**		**No behavior problems present (n=4235)**	**Behavior problems present (n=255)**	
	Mean (SD)[a]	**Mean (SD)[a]**	**Effect size[b1]**	**Mean (SD)[a]**	**Effect size[b2]**	**Mean (SD)[a]**	**Mean (SD)[a]**	**Effect size[b3]**	**Mean (SD)[a]**	**Mean (SD)[a]**	**Effect size[b4]**
Original domains											
Vision	1.02 (0.18)	1.02 (0.16)	0.00	1.05 (0.32)	0.09	1.02 (0.18)	1.01 (0.10)	0.06	1.02 (0.17)	1.04 (0.27)	0.07
Hearing	1.02 (0.14)	1.03 (0.17)	0.06	1.05 (0.22)*	0.14	1.01 (0.12)	1.07 (0.28)***	0.21	1.02 (0.13)	1.05 (0.25)**	0.12
Speech	1.34 (0.50)	1.37 (0.54)	0.06	1.37 (0.58)	0.05	1.33 (0.49)	1.48 (0.60)***	0.25	1.33 (0.50)	1.57 (0.63)***	0.38
Mobility	1.02 (0.15)	1.05 (0.27)***	0.11	1.05 (0.32)	0.09	1.02 (0.14)	1.08 (0.36)***	0.17	1.02 (0.15)	1.09 (0.36) ***	0.19
Dexterity	1.00 (0.08)	1.02 (0.19)*	0.11	1.02 (0.20)	0.10	1.01 (0.09)	1.02 (0.18)	0.06	1.00 (0.08)	1.06 (0.31) ***	0.19
Self-care	1.11 (0.34)	1.17 (0.47)*	0.13	1.21 (0.57)	0.18	1.11 (0.34)	1.16 (0.46)	0.11	1.10 (0.33)	1.35 (0.62) ***	0.40
Emotion	1.00 (0.07)	1.01 (0.12)	0.08	1.00 (0.00)	0.00	1.00 (0.07)	1.02 (0.12)**	0.17	1.00 (0.05)	1.05 (0.23) ***	0.22
Learning and remembering	1.01 (0.13)	1.02 (0.19)	0.05	1.06 (0.27)**	0.19	1.01 (0.12)	1.07 (0.28)***	0.21	1.01 (0.11)	1.13 (0.39) ***	0.31
Thinking and problem solving	1.02 (0.17)	1.04 (0.27)	0.07	1.03 (0.17)	0.06	1.02 (0.17)	1.05 (0.27)**	0.11	1.02 (0.14)	1.15 (0.45) ***	0.29
Pain and discomfort	1.11 (0.31)	1.18 (0.41)***	0.17	1.26 (0.48)***	0.31	1.10 (0.31)	1.27 (0.48)***	0.35	1.11 (0.32)	1.25 (0.45) ***	0.31
Disability score[c]	10.65 (1.01)	10.90 (1.64)***	0.15	11.09 (1.64)**	0.27	10.62 (0.98)	11.22 (1.84)***	0.33	10.62 (0.97)	11.75 (2.17) ***	0.52
Two items additional to the orginal 10-domain HUI system											
General health	1.03 (0.18)	1.13 (0.40)***	0.25	1.45 (0.65)***	0.65	1.03 (0.19)	1.20 (0.50)***	0.34	1.04 (0.22)	1.15 (0.44) ***	0.25
Behavior	1.05 (0.23)	1.06 (0.23)	0.04	1.12 (0.35)**	0.20	1.05 (0.22)	1.08 (0.30)*	0.10	1.03 (0.18)	1.35 (0.57)***	0.56

Data are presented as mean or standard deviation. aTwo-sided Mann-Whitney U-test given a non-normal distribution of the data. b1Difference of the means divided by the largest standard deviation between children with 1-3 times of wheezing in the past one year and children with no wheezing. [b2]Difference of the means divided by the largest standard deviation between children with at least four times of wheezing in the past one year and children with no wheezing. [b3]Difference of the means divided by the largest standard deviation between children had at least one ENT surgical procedures and children had no ENT surgical procedures. [b4]Difference of the means divided by the largest standard deviation between children had behavior problems and children had no behavior problems. Cohen's effect size (d): 0.2≤d<0.5 indicates a small difference, 0.5≤d<0.8 indicates a moderate difference, d≥0.8 indicates a large difference. [c]Sum of the ten original domains. *p <0.05. **p<0.01. ***p<0.001. HSCS-PS = Health Status Classification System-Preschool CBCL = Child Behavior Checklist

The total 'disability score' discriminated clearly between the subgroup with a total of '≥3 conditions present' (0.47; p<0.001), and the 'reference' subgroup, as hypothesized. The domain 'Pain and discomfort' (0.56; p<0.001) showed the largest discriminant validity (S4 Table).

Concurrent Validity

All 5 hypothesized correlation coefficients between the 'parallel' HSCS-PS-domains and 'General health'/'Behavior' were positive (0.21, 0.17, 0.16, 0.16, 0.18 respectively; p<0.01). All 15 'non-hypothesized correlations' were lower than the hypothesized correlations (see Table 4).

Table 4. Concurrent validity of the HSCS-PS assessed by Spearman correlations between original HSCS-PS domains and two additional domains (n=4546)*

HSCS-PS domains	General health	Behavior
Vision	0.04 (-0.003, 0.094)	0.02 (-0.011, 0.060)
Hearing	0.09** (0.039, 0.143)	0.04 (-0.002, 0.085)
Speech	0.08** (0.047, 0.111)	0.09** (0.059, 0.126)
Mobility	0.13** (0.066, 0.187)	0.06** (0.015, 0.106)
Dexterity	0.11** (0.038, 0.178)	0.07** (0.013, 0.129)
Self-care	0.09** (0.051, 0.129)	0.17** (0.129, 0.218)
Emotion	0.00 (-0.016, 0.033)	*0.16*** (0.088, 0.221)
Learning and remembering	0.11** (0.051, 0.178)	*0.16*** (0.091, 0.228)
Thinking and problem solving	0.11** (0.056, 0.176)	*0.18*** (0.123, 0.245)
Pain and discomfort	*0.21*** (0.161, 0.250)	0.08** (0.040, 0.109)

Values presented in this table are values of Spearman correlation coefficient (CC) and 95% confidence interval of Spearman's CC. *Correlations with predefined related general health/behavior are in italics; other (spurious) are in standard font. ** When (a) 95% confidence interval is not 'across 0'; and (b) p value < 0.05, the correlation coefficient was regarded as statistically significant. HSCS-PS = Health Status Classification System-Preschool

DISCUSSION

The present study evaluated the HSCS-PS among children at three years old in a community setting using a large general population sample. The results support the feasibility, discriminant validity and concurrent validity of the HSCS-PS.

Feasibility

The HSCS-PS was well accepted by parents, as shown by the high response and relatively few missing answers. All levels of the potential answer categories were observed for five of the ten domains in this community sample: 'Speech'; 'Mobility'; 'Self-care'; 'Emotion'; 'Thinking and problem solving'. Yet, the study showed considerable ceiling effects,

specifically regarding 'Dexterity' and 'Emotion'. Such ceiling effects are a common phenomenon in community samples with a generally healthy population; they were also observed in studies with other HRQOL measures.[6, 10] The domain 'Speech' showed the highest variation in the obtained scores, which may be related to the individual differences in the development of children's speech skills.[39]

Discriminant Validity

The results support the ability of HSCS-PS to discriminate across subgroups characterized by absence/presence of adverse perinatal conditions or distinct chronic or medical conditions. The total 'disability score' showed consistent differences between the subgroups with no adverse condition/situation (the reference subgroup), and subgroups with a 'mild condition/situation' (if present), and subgroups with a 'severe condition/situation', concerning six outcomes (birth weight; gestational age at birth; wheezing in the previous year; ENT surgical procedures; behavior problem present in the last two months; total number of chronic/medical conditions), as hypothesized.

Regarding 'very low birth weight', the highest effect sizes were found in 'Self-care' and 'Learning and remembering'. A similar pattern was observed regarding 'very preterm birth'. Previous studies showed that perinatal adversity may be associated with neurodevelopmental disabilities that may cause cognitive impairment and attention problems during child development.[40] The results of our study are also supported by Msall and Tremont who measured functional outcomes in self-care in infants with very low birth weight: of children with and without neurodevelopmental impairment, 41% respectively 13% had self-care limitations.[41]

Regarding wheezing frequency, the highest effect sizes were found regarding 'Pain and discomfort' between children with at least four times of wheezing in the past year and children with no wheezing. This is in accordance with earlier reports that wheezing is associated with low HRQOL, especially in the domain of bodily pain.[42] Similarly, regarding ENT surgical procedures, the highest effect size was found regarding 'Pain and discomfort', which is consistent with studies on pain after ENT procedures.[43]
Regarding behavior problems, the highest effect sizes were found regarding 'Self-care'. This is in line with the results of previous studies that documented the impact of behavior problems on self-care.[44]

Concurrent Validity

The finding that the 5 hypothesized correlations between the HSCS-PS domains and respective parallel single-item parent reports on 'General health'/'Behavior' were higher than the 15 'non-hypothesized correlations' supports the concurrent validity of the HSCS-PS. The strength of the 5 hypothesized correlations varied. It should be noted

that 11 of the 15 'non-hypothesized correlations' were statistically significant, although they were relatively small. The correlation between 'Pain and discomfort' and 'General health' was the highest, which is consistent with previous studies; pain may play a major role in the rating of quality of life.[45] The relatively strong correlation between HSCS-PS 'Thinking and problem solving' and 'Behavior' is consistent with previous reports regarding associations between cognition deficits in children and behavior problems.[46] The observed associations to assess concurrent validity in this community sample are slightly lower than those that were found by Saigal et al. who used selected clinical cohorts. This may be explained by the relatively low prevalence of serious impairments in a general population sample such as in our study.[11]

It should be noted that relatively little is known about the acceptance and validity of parent-report single-items to describe 'General health' and 'Behavior/Mental health' of children compared to the body of knowledge regarding the validity of such measures in adult populations.[26, 27] Therefore, in the future, we recommend the concurrent validity of the HSCS-PS should be evaluated by comparing it with an accepted 'gold standard' HRQOL measure such as the Infant and Toddler Quality of Life Questionnaire (ITQOL).[6] The evaluation of the concurrent validity of the 10-domains HSCS-PS in this study is a first step and results should be interpreted with caution.

Methodological considerations

First, in this study, measurements were primarily done using parent questionnaires, including accepted validated instruments such as the Child Behavior Checklist parent questionnaire.[36] Only the birth outcomes were obtained from medical files. 'Reporting tendency' by, for example, 'optimistic' or 'pessimistic' parents may have applied to all measures in the questionnaires and may have induced relatively high statistical associations in this study. For future validation studies we recommend to use as many as possible 'objective' external measures to validate the 10-domains HSCS-PS.

Second, no formal power calculations were made with regard to the validation study, given multiple comparisons and studies of associations. However, the size of the population for analysis (n=4526) is relatively large for a validation study; therefore many associations, even with a small effect size, were statistically significant. The smallest subgroups regarding the evaluation of discriminative validity (birth weight < 1500 grams, n=28; gestational age <32 weeks, n=31) resulted in almost half of the comparisons being statistically significant. All other subgroups regarding the evaluation of discriminative validity ranged from n=104 up to n=4307.

Third, in our study, the non-participants were children from vulnerable families, who more often had single parent, and whose parents more often had lower educational level

or had an immigrant background. These children may have more health conditions/ problems than their counterparts from non-vulnerable families. This issue may impose an impact on results. For instance, the high ceiling effect may be caused by the relatively better health status of the participants. In addition, the generalizability of results in the present study may be limited due to this issue.

Fourth, while a utility-based scoring algorithm for HSCS-PS has not yet been developed, a total 'disability score' summing up the scores regarding each of the ten original domains was applied in this study.[16] Two previous studies supported the feasibility and validity of the HSCS-PS total 'disability score' in absence of a utility-based scoring algorithm, which we recommend to be developed in future studies.[15, 16, 47] Given the relative paucity of experience with the HSCS-PS system, no specific guidelines for clinically important differences are available; we recommend such guidelines to be developed. Regarding the Health Utilities Index for patients aged four years and above, it was proposed that a difference of one level within any domain may be interpreted as a clinically important difference.[12] In our case, for example, the subgroup with CBCL 'behavior problems present' and the subgroup with '≥3 chronic/medical conditions' have both a mean total 'disability score' that is more than 1 point (1 level) higher compared to the reference group, which may be interpreted as a clinically important difference. From a statistical point of view, we propose to apply Cohen's effect size (d), and to interpret 0.50 (half a standard deviation) as a meaningful difference. Effect sizes were relatively small in this study, which reflects that the general population in a society with modern and accessible health care is relatively healthy.[38, 48]

Fifth, we would like to note that regarding the procedure of developing the HSCS-PS, items were mainly derived from the HUI system and additionally two new items were based on experts' opinion. Qualitative studies, such as using focus group interviews have not been mentioned in this procedure; we recommend that qualitative research may be applied in the future, for example, to reduce the number of items, or to evaluate the content of the items.

Finally, in the present study, indicators of the reliability of the HSCS-PS, such as test-retest reliability were not evaluated. We recommend assessing this in future studies in the large varied community population.

CONCLUSION

This study is the first to apply and to evaluate the HSCS-PS in a large community sample of preschool children. This is a relevant addition to previous studies among very low birth weight children and children with cerebral palsy. For the assessment of the validity, we applied objectively measured conditions (birth weight, gestational age at birth) in

addition to validated parent-reported outcome measures (CBCL). This study supports the feasibility and validity of the HSCS-PS among preschool children in community settings. We recommend developing utility-based scoring algorithms for the HSCS-PS, and conducting empirical studies of what changes are meaningful, as well as repeated studies of reliability and validity in large varied populations with objectively measured, external benchmarks. In the meantime, the HSCS-PS may be used by clinicians and researchers as parent-reported health outcome in addition to clinical outcomes for economic evaluations, and may be used to support the development of value-based health care regarding interventions for preschool children.

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REFERENCES

1. Raat H, Mohangoo AD, Grootenhuis MA. Pediatric health-related quality of life questionnaires in clinical trials. Current Opinion in Allergy & Clinical Immunology. 2006;6(3):180-5. Epub 2006/05/04. doi: 10.1097/01.all.0000225157.67897.c2 00130832-200606000-00011 [pii]. PubMed PMID: 16670511.
2. Black N. Patient reported outcome measures could help transform healthcare. BMJ. 2013;346:f167. PubMed PMID: 23358487.
3. Kaplan RM. Quality of life measures: measurement strategies in health psychology. New York: John Wiley; 1985.
4. Patrick DL, Erickson P. Health status and health policy: quality of life in health care evaluation and resource allocation. 1993.
5. Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res. 1998;7(5):387-97. PubMed PMID: 9691719.
6. Raat H, Landgraf JM, Oostenbrink R, Moll HA, Essink-Bot ML. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. Qual Life Res. 2007;16(3):445-60. PubMed PMID: 17111231.
7. Porter ME. What Is Value in Health Care? New England Journal of Medicine. 2010;363(26):2477-81. doi: 10.1056/NEJMp1011024. PubMed PMID: 21142528.
8. Krabbe P. The Measurement of Health and Health Status: Concepts, Methods and Applications from a Multidisciplinary Perspective: Academic Press; 2016.
9. Krabbe PFM. A generalized measurement model to quantify health: the multi-attribute preference response model. PloS one. 2013;8(11):e79494.
10. Raat H, Bonsel GJ, Essink-Bot M-L, Landgraf JM, Gemke RJBJ. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. Journal of clinical epidemiology. 2002;55(1):67-76.
11. Saigal S, Rosenbaum P, Stoskopf B, Hoult L, Furlong W, Feeny D, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Quality of Life Research. 2005;14(1):243-52. doi: 10.1007/s11136-004-4228-7.
12. Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI®) system for assessing health-related quality of life in clinical studies. Annals of medicine. 2001;33(5):375-84.
13. Msall ME. Neurodevelopmental surveillance in the first 2 years after extremely preterm birth: evidence, challenges, and guidelines. Early human development. 2006;82(3):157-66.
14. Klassen AF, Lee SK, Raina P, Chan HWP, Matthew D, Brabyn D. Health status and health-related quality of life in a population-based sample of neonatal intensive care unit graduates. Pediatrics. 2004;113(3):594-600.
15. Nathan PC, Furlong W, Horsman J, Rolland M, Weitzman S, Feeny D, et al. Inter-observer agreement of a comprehensive health status classification system for pre-school children among patients with Wilms' tumor or advanced. Quality of Life Research. 2004;13(10):1707-14.
16. Nathan PC, Furlong W, De Pauw S, Horsman J, Van Schaik C, Rolland M, et al. Health status of young children during therapy for advanced neuroblastoma. Pediatric blood & cancer. 2004;43(6):659-67.
17. Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. Health-related quality of life and emotional and behavioral difficulties after extreme preterm birth: developmental trajectories. PeerJ. 2015;3:e738.
18. Vederhus BJ, Markestad T, Eide GE, Graue M, Halvorsen T. Health related quality of life after extremely preterm birth: a matched controlled cohort study. Health and quality of life outcomes. 2010;8(1):53.

19. Theunissen NCM, Veen S, Fekkes M, Koopman HM, Zwinderman KAH, Brugman E, et al. Quality of life in preschool children born preterm. Developmental medicine and child neurology. 2001;43(7):460-5.
20. Chien LY, Chou YH, Ko YL, Lee CF. Health-related quality of life among 3-4-year-old children born with very low birthweight. Journal of Advanced Nursing. 2006;56(1):9-16.
21. Schiariti V, Houbè JS, Lisonkova S, Klassen AF, Lee SK. Caregiver-reported health outcomes of preschool children born at 28 to 32 weeks' gestation. Journal of Developmental & Behavioral Pediatrics. 2007;28(1):9-15.
22. Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. European Respiratory Journal. 2012:erj00157-2012.
23. Stewart MG, Friedman EM, Sulek M, Hulka GF, Kuppersmith RB, Harrill WC, et al. Quality of life and health status in pediatric tonsil and adenoid disease. Archives of Otolaryngology–Head & Neck Surgery. 2000;126(1):45-8.
24. Richards M, Giannoni C. Quality-of-life outcomes after surgical intervention for otitis media. Archives of Otolaryngology–Head & Neck Surgery. 2002;128(7):776-82.
25. Charach A, McLennan JD, Bélanger SA, Nixon MK. Screening for Disruptive Behaviour Problems in Preschool Children in Primary Health Care Settings. Journal of the Canadian Academy of Child and Adolescent Psychiatry. 2017;26(3):172-8. PubMed PMID: PMC5642455.
26. Macias C, Gold PB, Ongur D, Cohen BM, Panch T. Are Single-Item Global Ratings Useful for Assessing Health Status? J Clin Psychol Med Settings. 2015. PubMed PMID: 26492891.
27. Ahmad F, Jhajj AK, Stewart DE, Burghardt M, Bierman AS. Single item measures of self-rated mental health: a scoping review. BMC health services research. 2014;14(1):398.
28. Jaddoe VWV, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. European journal of epidemiology. 2012;27(9):739-56.
29. General Assembly of the World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. The Journal of the American College of Dentists. 2014;81(3):14.
30. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics. 2000;105(6):1216-26. PubMed PMID: 10835060.
31. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. Jama. 2002;288(6):728-37.
32. Wardlaw TM. Low birthweight: country, regional and global estimates: UNICEF; 2004.
33. Timmermans S, Jaddoe VWV, Hofman A, Steegers-Theunissen RPM, Steegers EAP. Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation R Study. British Journal of Nutrition. 2009;102(5):777-85.
34. Sole D, Vanna AT, Yamada E, Rizzo MC, Naspitz CK. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. J Investig Allergol Clin Immunol. 1998;8(6):376-82. PubMed PMID: 10028486.
35. Mamie C, Habre W, Delhumeau C, Barazzone Argiroffo C, Morabia A. Incidence and risk factors of perioperative respiratory adverse events in children undergoing elective surgery. Pediatric Anesthesia. 2004;14(3):218-24.
36. Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms and profiles: Burlington; 2010.
37. Tick NT, Koot HM, Verhulst FC. 14-year changes in emotional and behavioral problems of very young Dutch children. Journal of the American Academy of Child & Adolescent Psychiatry. 2007;46(10):1333-40.

38. Cohen J. Statistical power analysis. Current directions in psychological science. 1992;1(3):98-101.
39. Moeller MP. Early intervention and language development in children who are deaf and hard of hearing. Pediatrics. 2000;106(3):e43-e.
40. Butler AS, Behrman RE. Preterm birth: causes, consequences, and prevention: National Academies Press; 2007.
41. Msall ME, Tremont MR. Functional outcomes in self-care, mobility, communication, and learning in extremely low-birth weight infants. Clinics in perinatology. 2000;27(2):381-401.
42. Mohangoo AD, de Koning HJ, Mangunkusumo RT, Raat H. Health-Related Quality of Life in Adolescents with Wheezing Attacks. Journal of Adolescent Health. 2007;41(5):464-71. doi: http://dx.doi.org/10.1016/j.jadohealth.2007.06.002.
43. Turan A, Emet S, Karamanlioglu B, Memis D, Turan N, Pamukcu Z. Analgesic effects of rofecoxib in ear-nose-throat surgery. Anesthesia & Analgesia. 2002;95(5):1308-11.
44. Adams H, de Blieck EA, Mink JW, Marshall FJ, Kwon J, Dure L, et al. Standardized assessment of behavior and adaptive living skills in juvenile neuronal ceroid lipofuscinosis. Developmental medicine and child neurology. 2006;48(4):259-64.
45. Arnstein P. The mediation of disability by self efficacy in different samples of chronic pain patients. Disability and rehabilitation. 2000;22(17):794-801.
46. Dodge KA. Social cognition and children's aggressive behavior. Child development. 1980:162-70.
47. Raat H, Bonsel GJ, Hoogeveen WC, Essink-Bot M-L, Dutch HUIG. Feasibility and reliability of a mailed questionnaire to obtain visual analogue scale valuations for health states defined by the Health Utilities Index Mark 3. Medical care. 2004;42(1):13-8.
48. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care. 2003;41(5):582-92.

SUPPLEMENTARY

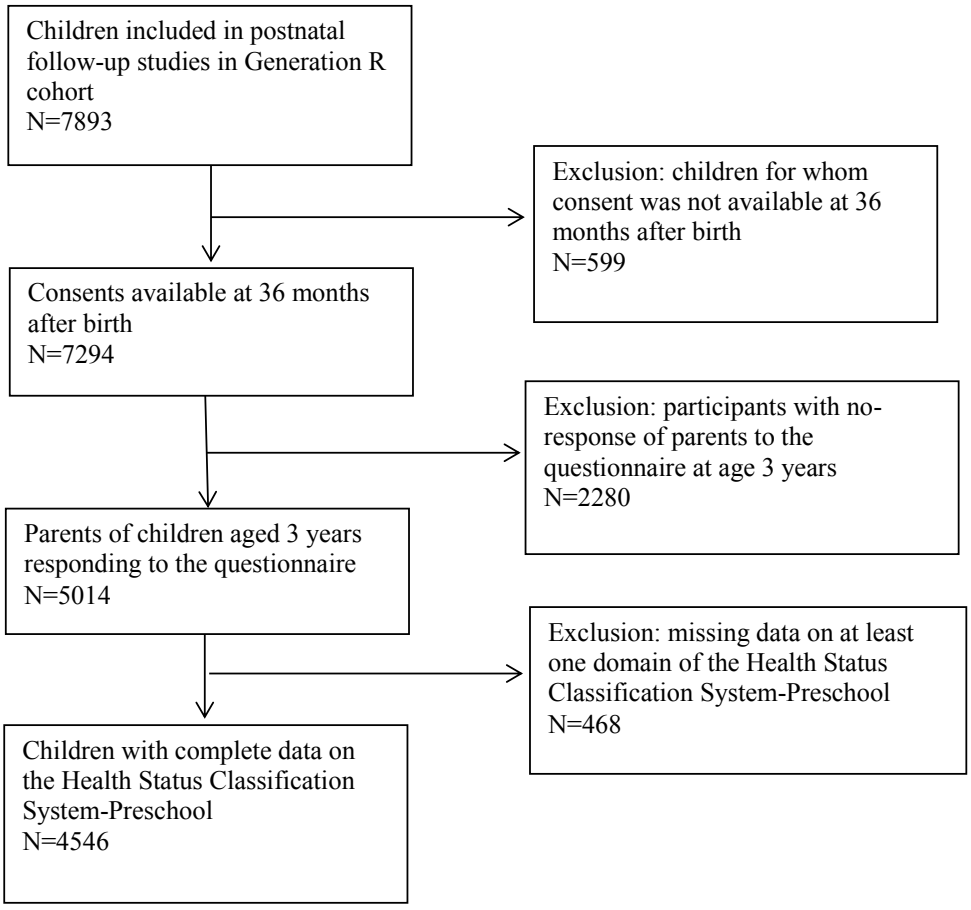

Figure S1. Flow chart of the population for analyses

Table S1. The Health Status Classification System - Preschool: domains, number of levels and score interpretation

Domains	Level	Description
Original domains		
Vision	1	Sees normally without glasses – e.g. able to see well enough to recognize small objects and familiar people at a distance.
	2	Sees normally with glasses – e.g. able to see well enough to recognize small objects and familiar people at a distance.
	3	Sees objects close to oneself – e.g. at arm's length, but has visual limitations at distance, even with glasses.
	4	Limited vision, both near and far, even with glasses.
	5	Unable to see at all.
Hearing	1	Hear what a person is saying in a usual environment with background noise and distractions without a hearing aid.
	2	Hear what a person is saying in a quiet environment when there are no competing distractions (with or without a hearing aid).
	3	Hear what a person is saying with limitations even with hearing aids.
	4	Unable to hear what a person is saying even with hearing aids.
	5	Unable to hear at all.
Speech	1	Speaks clearly and is understood by everyone.
	2	Parents understand most speech but others have some difficulty understanding the words.
	3	Speech is somewhat unclear, even to parents.
	4	Does not speak or makes only monosyllabic/unintelligible sounds (includes sounds understood by caregivers).
Mobility	1	Walks, bends, lifts, jumps and runs as well as others the same age.
	2	Walks, bends, lifts, jumps or runs with some limitations but does not require mechanical equipment or the help of another person to get around independently (e.g. a clumsy but independent walker).
	3	Walks or gets around without any help from another person, but requires mechanical equipment (this level includes independent crawlers).
	4	No independent mobility – requires the help of another person to get around and may also require mechanical equipment (e.g. stroller).
Dexterity	1	Full use of both hands and ten fingers.
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person (includes: slow, awkward but independent).
	3	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools).
	4	Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools).
Self-care	1	Eats, bathes, dresses and uses the toilet as well as others the same age.
	2	Requires a little more than usual assistance for age to eat, bathe, dress or use the toilet.
	3	Requires a lot more than usual assistance for age to eat, bathe, dress or use the toilet.
	4	Requires total care – unable to participate in self-care activities.

Table S1. Continued

Domains	Level	Description
Original domains		
Emotion	1	Usually cheerful and interested in everyday activities, but may occasionally be irritable, fretful or unhappy.
	2	Often irritable, fretful, unhappy or uninterested in everyday activities.
	3	Almost always irritable, fretful or unhappy and usually uninterested in everyday activities.
Learning and rememb-ering	1	Learns and remembers new information as well as others the same age.
	2	Learns and remembers new information a little more slowly than others the same age.
	3	Learns and remembers new information much more slowly than others the same age and may be receiving a special program for learning needs.
	4	Unable to learn and remember.
Thinking and problem solving	1	Able to think and understand how to solve everyday problems as well as others the same age.
	2	Has a little difficulty when trying to think and understand how to solve everyday problems.
	3	Has great difficulty when trying to think and understand how to solve everyday problems.
	4	Unable to think and understand how to solve everyday problems.
Pain and discomf-orts	1	None pain or discomfort (for example, generally has no earache, constipation, or toothache).
	2	Sometimes has pain but this hardly disrupts everyday activities.
	3	Has recurring pain which disrupts a lot of everyday activities.
	4	Always has pain which disrupts all everyday activities.
Two items additional to the original 10-domain HUI system		
General health	1	Generally in good health, routine use of health resources.
	2	Slightly more than usual illnesses and use of health resources.
	3	Frequent illnesses and use of health resources.
	4	Almost always ill, very frequent use of health resources and hospitalizations.
Behavior	1	Generally easy to get along with, well behaved, plays well with others even if slow to warm up (shy).
	2	Occasionally hard to get along with, disruptive, stubborn, decreased attention span, or occasionally withdrawn, apathetic, unresponsive to others.
	3	Frequently hard to get along with, disruptive, stubborn, poor attention span, or frequently withdrawn, apathetic, unresponsive to others.
	4	Requires medication and/or constant supervision by caregiver and/or special program.

Table S2. Characteristics of the study group (N=4546)*

Variable	n	%	Mean (SD)
Family characteristics			
Marital status (married/living together)	4006	92.4	
Maternal educational level			
High	1348	33.8	
Mid-high	1198	30.1	
Mid-low	1017	25.5	
Low	420	10.5	
Paternal educational level			
High	1227	39.6	
Mid-high	657	21.2	
Mid-low	763	24.6	
Low	454	14.6	
Maternal ethnic background			
Dutch	2970	65.8	
Other western	392	8.7	
Non-western	1149	25.5	
Paternal ethnic background			
Dutch	2462	73.5	
Other western	213	6.4	
Non-western	673	20.1	
Net household income (€ per month)			
<2200	1167	30.9	
≥2200	2604	69.1	
Child characteristics			
Gender (boys)	2257	49.6	
Age when questionnaire is filled out (months)			36.7 (1.5)
Birth weight (grams)			3440 (570)
≥2500	4307	94.8	
1500-2500	206	4.5	
<1500	28	0.6	
Gestational age at birth (weeks)			39.8 (1.8)
≥37	4256	94.0	
32-37	239	5.3	
<32	31	0.7	
Wheezing chest in the past one year			
No	3849	87. 3	
1-3 times	454	10.3	
≥4 times	104	2.4	
Ear-Nose-Throat (ENT) surgical procedures ever			
No	3956	88.5	
Yes	513	11.5	
CBCL borderline/non-clinical total problem score based on Dutch norms			
No	4235	94.3	
Yes	255	5.7	

* The number of missing varies across variables.

Table S3. Non-response analyses (n=7294)*

Characteristics	Population for analysis (n=4546)	Excluded population (n=2748)	P value[a]
Family characteristics			
Respondent (mother)	4196 (94.3)	416 (92.4)	0.005
Marital status mother at age 3 (married/living together)	4006 (92.4)	1815 (79.1)	<0.001
Maternal educational level[b]			
High	1348 (33.8)	74 (20.1)	<0.001
Mid-high	1198 (30.1)	79 (21.5)	
Mid-low	1017 (25.5)	124 (33.7)	
Low	420 (10.5)	91 (24.7)	
Paternaleducational level[b]			
High	1227 (39.6)	317 (24.9)	<0.001
Mid-high	657 (21.2)	210 (16.5)	
Mid-low	763 (24.6)	372 (29.2)	
Low	454 (14.6)	374 (29.4)	
Maternal ethnic background[c]			
Dutch	2970 (65.8)	869 (35.3)	<0.001
Other western	392 (8.7)	200 (8.1)	
Non-western	1149 (25.5)	1395 (56.6)	
Paternal ethnic background[c]			
Dutch	2462 (73.5)	720 (48.9)	<0.001
Other western	213 (6.4)	91 (6.2)	
Non-western	673 (20.1)	661 (44.9)	
Net household income (€ per month)			
<2200	1167 (30.9)	1068 (60.7)	<0.001
≥2200	2604 (69.1)	691 (39.3)	
Child characteristics			
Gender (boys)	2257 (49.6)	1425 (51.9)	0.068
Age when questionnaire is filled out (months)	36.7(1. 5)	36.8(1.6)	0.239
Birth weight (grams)	3440.0 (569.9)	3355.5(569.2)	<0.001
≥2500	4307 (94.8)	2566 (93.6)	0.039
1500-2500	206 (4.5)	161 (5.9)	
<1500	28 (0.6)	15 (0.5)	
Gestational age at birth (weeks)	39.8 (1.8)	39.7 (1.8)	0.016
≥37	4256 (94.0)	2532 (92.8)	0.024
32-37	239 (5.3)	183 (6.7)	
<32	31 (0.7)	13 (0.5)	
Wheezing chest in the past one year			
No	3849 (87.3)	368 (85.0)	0.364
1-3 times	454 (10.3)	52 (12.0)	
≥4 times	104 (2.4)	13 (3.0)	
Surgical procedures ever			
No	3956 (88.5)	396 (89.6)	0.499
Yes	513 (11.5)	46 (10.4)	

Characteristics	Population for analysis (n=4546)	Excluded population (n=2748)	P value[a]
CBCL borderline/non-clinical total problem score based on Dutch norms			
No	4235 (94.3)	372 (84.9)	<0.001
Yes	255 (5.7)	66 (15.1)	

*Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continues variables. Data was missing for respondent (n=2393), ethnic background of mothers (n=319), ethnic background of partners (n=2474),educational level of mother (2943), educational level of partner (2920), marital status (n=665), net household income (n=1764), age (2280), birth weight (11), gestational weeks (40), surgical procedures (n=2333),CBCL (n=2366),wheezing (n=2454). [a] Independent-sample t tests for continuous variables and Chi-square tests for categorical variables. [b] High education corresponds to university degree; mid-high level corresponds to higher vocational training, Bachelor's degree; mid-low level corresponds to more than 3 years general secondary school, intermediate vocational training; low level corresponds to no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school. [c] Ethnicity is defined according to the Dutch standard classification criteria (Statistics & Netherlands, 2004) and categorized as 'Dutch', 'Western' (other European, North-American and Oceanian) or 'non-Western' (Turkish, Moroccan, Indonesian, Cape Verdean, Surinamese and Antillean).

Table S4. Discriminative ability of the HSCS-PS between subgroups differing in the number of conditions (n=4302)

HSCS-PS domains	Number of conditions						
	No condition (n=3050)	1 condition (n=940)		2 conditions (n=262)		≥3 conditions (n=50)	
	Mean (SD)a	Mean (SD)a	Effect sizeb1	Mean (SD)a	Effect sizeb2	Mean (SD)a	Effect sizeb3
Original domains							
Vision	1.01 (0.16)	1.02 (0.19)*	0.05	1.03 (0.23)	0.09	1.08 (0.44)*	0.16
Hearing	1.01 (0.11)	1.03 (0.18)**	0.11	1.05 (0.25) ***	0.16	1.10 (0.30) ***	0.30
Speech	1.32 (0.48)	1.39 (0.53)***	0.13	1.50 (0.65) ***	0.28	1.44 (0.61)	0.20
Mobility	1.01 (0.12)	1.02 (0.17)*	0.06	1.09 (0.35) ***	0.23	1.24 (0.69) ***	0.33
Dexterity	1.00 (0.06)	1.01 (0.10)	0.10	1.03 (0.20) ***	0.15	1.16 (0.55) ***	0.29
Self-care	1.09 (0.30)	1.16 (0.40)***	0.18	1.22 (0.53) ***	0.25	1.44 (0.91) ***	0.38
Emotion	1.00 (0.05)	1.01 (0.09)**	0.11	1.03 (0.18) ***	0.17	1.02 (0.14)*	0.14
Learning and remembering	1.00 (0.07)	1.03 (0.16)***	0.19	1.10 (0.37) ***	0.27	1.12 (0.39) ***	0.31
Thinking and problem solving	1.01 (0.12)	1.03 (0.19)*	0.11	1.09 (0.38) ***	0.21	1.18 (0.56) ***	0.30
Pain and discomfort	1.08 (0.28)	1.18 (0.39)***	0.26	1.19 (0.41) ***	0.27	1.40 (0.57) ***	0.56
Disability scorec	10.55 (0.81)	10.86 (1.13) ***	0.27	11.33 (2.10) ***	0.37	12.18 (3.49) ***	0.47
Two items additonal tot he original 10-domains HUI system							
General health	1.01 (0.13)	1.09 (0.30) ***	0.27	1.17 (0.44) ***	0.36	1.54 (0.81) ***	0.65
Behavior	1.03 (0.17)	1.09 (0.32) ***	0.19	1.13 (0.36)***	0.28	1.22 (0.47) ***	0.40

Data are presented as mean or standard deviation. [a]Two-sided Mann-Whitney U-test given a non-normal distribution of the data. [b1] Difference of the means divided by the largest standard deviation between children with one condition and children with no condition. [b2] Difference of the means divided by the largest standard deviation between children with two conditions and children with no condition. [b3] Difference of the means divided by the largest standard deviation between children with three or more conditions and children with no condition. Cohen's effect size (d): 0.2≤d<0.5 indicates a small difference, 0.5≤d<0.8 indicates a moderate difference, d≥0.8 indicates a large difference. [c] Sum of the ten original domains. *p <0.05. **p<0.01. ***p<0.001. HSCS-PS: Health Status Classification System-Preschool

CHAPTER 9

General Discussion

This thesis aims to contribute to understanding maternal health-related quality of life (HRQOL) in pregnant and postpartum period, as well as children's HRQOL. Specifically, this thesis focuses on the determinants of HRQOL of mothers and children, the link between maternal HRQOL during pregnancy and infant health, and on an instrument to measure HRQOL in very young children.

In this chapter, the main findings of the studies presented in this thesis and the interpretations of these findings are summarized, the methodological considerations are discussed, and recommendations for practice and directions for future research are given. Finally, an overall conclusion is provided.

MAIN FINDINGS AND INTERPRETATIONS

Determinants of maternal health-related quality of life

The first research question was: To what extent are nausea, vomiting and fatigue in early pregnancy independently associated with maternal HRQOL? This question was addressed in **Chapter 2**. We found that nausea, vomiting and fatigue are very common symptoms in early pregnancy. 83% of women in our study reported the presence of nausea; 43% reported vomiting and 98% reported fatigue. Compared with women who reported no presence of nausea, vomiting and fatigue, women who reported daily presence of at least one of these symptoms had significantly worse physical and mental HRQOL in early pregnancy. Our findings are consistent with other studies, which found that nausea and vomiting of pregnancy adversely affect a woman's daily activities, role performance, self-concept and interpersonal relationships at home, at work and in social life.[1-3] Reportedly, women felt their unpleasant experience of having nausea and vomiting in early pregnancy was trivialized by health professionals.[4] This may be related to the commonness of nausea and vomiting in early pregnancy and its self-limiting nature. In accordance with the guidelines from the American College of Obstetricians and Gynecologists,[5] we suggested health professionals to help pregnant women manage these symptoms. In addition, our study also showed the independent association between a more frequent presence of fatigue and worse physical and mental HRQOL in early pregnancy; a finding that contributes to the thus far limited body of literature on this issue.

The second research question was: What are trajectories of HRQOL during pregnancy and what are predictors of these trajectories? This question was addressed in **Chapter 3.** We have applied the Latent Class Mixture Modeling to identify the distinct trajectories regarding physical and mental HRQOL, respectively. Four physical HRQOL trajectories during pregnancy were identified: a healthy trajectory ('healthy') in 63% of subjects, a

trajectory with consistently low HRQOL scores ('vulnerable') in 11%, a small increase ('recovering') in 13% and a large decrease ('at risk') in 13%. Three mental HRQOL trajectories during pregnancy were identified: a healthy trajectory ('healthy') in 86% of subjects, an increasing trajectory ('recovering') in 8% and a decreasing trajectory ('at risk') in 6%. Overall, we found that most women in the study population reported a healthy level of physical and mental HRQOL during pregnancy, which is a positive finding. Characteristics of women with suboptimal trajectories differed from those with healthy trajectories. The notable factors for the suboptimal physical and mental HRQOL trajectories in this study were pregnancy-related physical symptoms and pregnancy-specific anxiety. In practice, the impact of these symptoms/conditions may be underestimated by health professionals.[4, 6] For instance, care providers do not routinely screen for pregnancy-specific anxiety during pregnant. Our study highlighted the relevance of managing pregnancy-related symptoms and pregnancy-specific anxiety in an early stage of pregnancy, given that these symptoms/conditions may predict the suboptimal development of HRQOL during pregnancy. In particular, we suggested health professionals to pay more attention to women who report the daily presence of physical symptoms. In addition to the above-mentioned predictors, we also like to note the finding that low household income, unplanned pregnancy and maternal smoking in early pregnancy were predictors for a decreasing trajectory of mental HRQOL during pregnancy, which confirms findings of other studies in smaller samples.[7, 8] Our study provides insights in the profile of characteristics of women who may be at risk for the suboptimal HRQOL trajectory during pregnancy. Some of these characteristics are modifiable. We recommend that future interventions can target the modifiable risk factors that were identified in this study.

The third research question was: What are the determinants of maternal HRQOL after childbirth? This question was addressed in **Chapter 4**. We have assessed an extensive set of potential determinants of maternal HRQOL at two months after delivery in a large general population sample of women in the Netherlands. We found multiple factors associated with postpartum physical and mental HRQOL. More specifically, we found that older maternal age, shorter time after delivery, elective/emergency cesarean delivery, loss of energy, maternal psychopathology, and the hospital admission of the baby were significantly associated with worse physical HRQOL; older maternal age, non-western background, low household income, loss of energy and maternal psychopathology were significantly associated with worse mental HRQOL. Our finding provide insights into the characteristics of women who may be at risk for suboptimal HRQOL after delivery. In particular, maternal psychopathology was profoundly associated with postpartum mental HRQOL. As Emmanuel et al. reported in their studies, the psychopathological symptoms in early postpartum phase may disturb women's ability to function, mental health, social engagement, inter-personal relationships and overall quality of life.[9, 10]

These women may need support. We therefore call for awareness among health care professionals.

Associations between maternal health-related quality of life during pregnancy and birth outcomes

The fourth research question was: To what extent is maternal HRQOL during pregnancy associated with birth outcomes? This question was addressed in **Chapter 5**. Our study did not confirm the hypotheses that worse mental HRQOL in early, mid- and late pregnancy were associated with more preterm birth, shorter gestational duration, low birth weight and more often small-for-gestational-age birth in the total sample. Unlike our findings, the study by Wang et al showed that women reporting better mental health in pregnancy (25-29 gestational weeks) had a lower risk of having low-birth-weight infants.[11] Our study showed only small effects regarding a relatively low average birth weight and more frequent small-for-gestational-age birth in the subgroup with worst mental HRQOL compared with the subgroup with the best mental HRQOL. This confirm the above-mentioned finding by Wang et al.[11] A potential explanation is that poor mental HRQOL is an indicator of psychological symptoms and disorders, such as maternal depression, that may be related to impaired fetal growth. [12] However, given the small effect sizes, we recommend further studies in other populations to confirm or reject our findings.

Determinants of health-related quality of life among school-aged children in the Netherlands

The fifth research question was: What are the determinants of HRQOL among school-aged children in the Netherlands? This question was addressed in **Chapter 6**. Consistent with our hypotheses, the strongest determinants of children's HRQOL were factors that directly or indirectly related to children's health. Regarding physical HRQOL, these variables were the number of chronic conditions and health complaints and the use of health care; regarding psychosocial HRQOL, the variable was the number of behavioral/ learning disorders. To a small extent, children's HRQOL was dependent on demographic, socioeconomic and to family and environmental factors. These findings confirm those of other studies.[13-16] Compared with previous studies, our study addressed a relatively extensive set of potential determinants of children's HRQOL. Since the study population was a large, randomly selected sample from national data, we consider the findings in our study generalizable to the whole Dutch population of school-aged children.

The sixth research question was: To what extent do the prevalent chronic conditions in childhood impact HRQOL of school-aged children in the Netherlands? This question was addressed in **Chapter 7**. Based on the data of the Dutch Health Interview Survey (2009-2013), the five most prevalent chronic conditions among school-aged children were

asthma, eczema, dyslexia, attention deficit hyperactivity disorder (ADHD) and migraine/severe headache. Our study showed that the parent-reported HRQOL of children with one of the above-mentioned conditions was worse than the parent-reported HRQOL of children without any chronic condition. Asthma and eczema were mainly associated with worse physical HRQOL; dyslexia and ADHD were mainly associated with worse psychosocial HRQOL; and migraine/severe headache was negatively associated with both physical and psychosocial HRQOL. These findings can be explained by characteristics of each condition, and were consistent with previous findings in clinical population.[17-24] In addition, we observed a gender difference in HRQOL of children with eczema. Parent-reported psychological HRQOL of girls indicated more behavior concerns and lower self-esteem than boys. Perhaps the visible appearance of eczema has a stronger impact on girls than on boys. Our study also demonstrated that HRQOL of children with the studied chronic condition and comorbidities was generally worse than HRQOL of children with only one of the studied conditions, which is consistent with findings from two population-based studies.[25, 26] The above-mentioned chronic conditions may affect parents and families as well. For instance, parents may experience more emotional worries and have less personal time as a result of the child's health condition(s). The family activities and cohesion may be adversely affected by children's chronic condition(s).

Validation of an instrument to measure health-related quality of life among preschool children

The seventh research question was: What are the feasibility and validity of the Health Status Classification System-Preschool (HSCS-PS) a large community-dwelling sample of preschool children? This question was addressed in **Chapter 8**. HSCS-PS is a preference-based measure of HRQOL of the preschool-aged children (defined as children aged 0-4 years in the Netherlands). In a large sample of relatively healthy children aged around three years, HSCS-PS showed a good feasibility, according to the high response and relatively few missing answers. As a result of the population being relatively healthy, we observed considerable ceiling effects. Such ceiling effects are a common phenomenon in community samples with a generally healthy population.[27, 28] Our study supports a good discriminant validity of HSCS-PS. Specifically, 'very preterm birth' and 'very low birth weight' were mainly associated with worse health status in the domains 'self-care' and 'learning and remembering'. This finding is consistent with a study that indicated a significant association between premature birth with neurodevelopmental impairment. [29] We found wheezing and ear-nose-throat surgery to be mainly associated with worse health status in the domain 'pain and discomforts'. This could be explained by the nature of these conditions.[30, 31] The relatively strong correlation between HSCS-PS 'Thinking and problem solving' and 'Behavior' is consistent with previous reports regarding associations between cognition deficits in children and behavior problems. [32]

Table 1. Overview of main results

Chapter	Main exposure	Main outcomes	Main results
2	Nausea, vomiting and fatigue in early pregnancy	Maternal HRQOL in early pregnancy	Compared with women who never reported nausea, vomiting and fatigue, women with daily presence of at least one of these symptoms had significantly lower physical and mental HRQOL in early pregnancy, after adjusting for potential confounders.
3	Multiple exposures	Distinct trajectories of maternal HRQOL during pregnancy	Four distinct trajectories of physical HRQOL during pregnancy and three distinct trajectories of mental HRQOL during pregnancy were identified. Healthy physical and mental HRQOL trajectories were most common. Predictors indicative of suboptimal HRQOL trajectories included pregnancy-related symptoms and pregnancy-specific anxiety in early pregnancy.
4	Multiple exposures	Maternal HRQOL measured at at two months postpartum	Multiple factors are associated with maternal postpartum HRQOL. Maternal psychopathology was profoundly associated with postpartum mental HRQOL. These women may need support. Therefore, we call for awareness from health professionals.
5	Maternal HRQOL in early, mid- and late pregnancy	Preterm birth, gestational weeks at birth, (low) birth weight, small size for gestational age	In the total study population, our findings did not confirm the hypotheses that worse maternal physical and mental HRQOL in early, mid- and late pregnancy were associated with worse birth outcomes. Our study showed small effects regarding a relatively low average birth weight and more frequent small-for-gestational-age birth in the subgroup with worst mental HRQOL compared with the subgroup with the best mental HRQOL.
6	Multiple exposures	HRQOL of children aged 4-11 years	Our study shows that HRQOL of school-aged children is mainly associated with the number of disorders and health complaints and the use of health care. Demographic, socio-economic and family/environmental characteristics are associated with HRQOL to a small extent.
7	Five most prevalent chronic conditions	HRQOL of children aged 4-11 years	Compared with children without any chronic conditions, children with at least one prevalent chronic conditions were reported with worse physical and/or psychosocial HRQOL by their parents.
8	Not applicable	Not applicable	This study supports the feasibility and validity of Health Status Classification System-Preschool (HSCS-PS) in a large community-dwelling sample of preschoolers.

CONTRIBUTIONS TO THE KNOWLEDGE GAPS

We contributed to the body of scientific literature in the following ways.
First, we contributed to the limited data on the 'normal' HRQOL of women during pregnancy and the postpartum period, and the 'normal' HRQOL of children at both preschool and school age, based on a large community-dwelling population and a randomly-selected national population in the Netherlands. The HRQOL data presented in this thesis can be used for comparison by other studies that measure HRQOL using the same instrument.

Second, we contributed to the innovation of methodology by applying Latent Class Mixture Modeling (LCMM) to identify the trajectories of maternal HRQOL during pregnancy. This is the first study to apply LCMM in a large community-dwelling pregnant population, which may include different subgroups of individuals sharing a common, underlying pattern of HRQOL change over time (distinct trajectories). LCMM enables to identify these distinct trajectories.

Third, we assessed the feasibility and validity of a preference-based measure of HRQOL for preschoolers (HSCS-PS) in a large community-dwelling sample of preschool children (aged three years), in addition to the existing evidence in clinical populations. Our study supports the feasibility and validity of HSCS-PS when it is applied in a general population setting.

METHODOLOGICAL CONSIDERATIONS

There are some methodological considerations that need to be considered when interpreting the study findings in this thesis.

Selection bias

The studies described in Chapter 2-5 and Chapter 8 were embedded in the Generation R Study, a prospective population-based birth cohort. In this study we have to consider the presence and impact of selection bias. Selection bias may occur when individuals or groups that participate in a study differ systematically from the 'population of interest'; selection bias may induce errors in the associations that are being studied.[33] Two types of selection bias need to be considered in our study: sampling bias and loss to follow-up. In the entire Generation R Study, the overall response rate was 61% among all eligible pregnant women living in the predefined area in Rotterdam. In general, women participating in the Generation R Study were relatively healthy, more often had a higher educational level and less often had a minority ethnic background than the women who did not participate in the Generation R study.[34] But it is hard to estimate the entire population.

In large cohort studies such as the Generation R Study, biased estimates mainly arise from loss to follow up. One notable characteristic of the population of respondents is that women had relatively high educational level which is an indicator of better health or better HRQOL. Therefore, our results need to be interpreted with caution.

Regarding the missing data among the respondent population, we applied multiple imputation in Chapter 2 and Chapter 4. The results based on the imputed dataset are similar to the results based on the non-imputed dataset (i.e. complete cases).

Most of mothers and children participating in the Generation R Study are relatively healthy. There is a relatively small number of participants with severe health conditions or symptoms. Therefore, we recommend to repeat our studies in clinical populations.

Information bias

In the Generation R Study, we have measured a wide range of variables, such as demographic and social determinants, symptoms/health conditions in antepartum and postpartum period, before the outcome measures. This may reduce the risk of recall bias. In this thesis, children's HRQOL was reported by parents. According to Barks et al., HRQOL of children as reported by parents may differ from HRQOL as reported by children themselves.[35-38] For instance, parents may overestimate the impact of mental health disorders on children's school experience and social functioning, whereas children may estimate their HRQOL similar to their peers.[14]

Confounding

Confounders are variables that influence both the determinant and outcome variable under study. Ignoring confounders may result in overestimating or underestimating the true association between determinant and outcome.[39] Though we have adjusted the potential confounders as many as possible in our studies, residual confounding might still be an issue due to unmeasured or insufficiently measured determinants.

The impact of time trend in health survey

The Dutch Health Interview Survey (DHIS) is a cross-sectional survey, conducted yearly, amongst the community-dwelling population in the Netherlands. The response rate of parents of children aged 4-11 years is approximately 75%. In the DHIS, a stratified two-step-sample of persons is taken from the Dutch Municipal Personal Records every month, which maximizes the representability of the participating population. In **Chapter** 6, a 9-year set of surveys was used (from 2001 to 2009). To detect whether time trends may have affected our findings, we applied additional bivariate analyses to assess the impact of the variable 'Year of data collection'. The analyses showed that the year of data collection did not significantly affect HRQOL scores (see **Chapter** 6).

Measurement of maternal HRQOL

In this thesis, maternal HRQOL during pregnancy and the postpartum period was measured by SF-12 which is a generic instrument. With regard to the measures of HRQOL in antepartum and postpartum period, a systematic review by Mogos et al. showed that 57% of the included studies applied only generic tools; SF-12, SF-36, WHOQoL-BREF (World Health Organization's Quality of Life Scale- BREF) were most frequently used. [40] Mogos also noted that the tools specific for pregnancy context were used in only 20% studies, while the combination of generic and specific tools were used in 23% of the analyzed studies.[40] In general, compared with the generic HRQOL measures, specific measures may be more sensitive to the small changes in disease-specific outcomes or functioning.[41] In the maternity care setting, there is a relatively small body of specific quality of life measures;[42] the examples were Mother-Generated Index (MGI),[43] Maternal Postpartum Quality of Life (MAPP-QoL),[44] Health-Related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL).[45] In the recent decade, the number of specific tools to measure HRQOL of pregnant and postpartum women has increased. Examples of these newly-developed tools are QOL-GRAV,[46] Short Form Postpartum Quality of Life Questionnaire (SF-PQOL),[47] Patient-reported Outcome-Maternity,[48] and Patient-reported Outcome Measure Information System Global Short Form (PROMIS-GSF) in pregnancy.[49]

RECOMMENDATIONS

First, we have identified multiple risk factors that are associated with the suboptimal HRQOL in antepartum and postpartum periods. Some of these risk factors may be modifiable or manageable, such as pregnancy-related physical symptoms (e.g., nausea, vomiting, fatigue, back pain), pregnancy-specific anxiety, and postpartum psychopathological symptoms. We recommend health professionals to support women to manage these symptoms. We also recommend to refer women to evidence-based interventions that can relieve the above-mentioned symptoms/conditions and to improve their HRQOL. For example, mindfulness practice has been proposed as an effective approach to relief maternal physical and psychological stress.[50-52] We suggest to investigate how mindfulness-based intervention can be applied in maternal intervention programs.

Second, given that chronic condition in childhood is an important determinant of HRQOL, we suggest health professionals to pay attention to the potential impacts of chronic conditions on both children and their families.

Third, regarding the measurement of maternal HRQOL, we suggest to apply both generic and maternity-specific HRQOL measures in HRQOL studies, in order to better

understand women's evaluation of their health during pregnancy and after delivery. Regarding the measurement of children's HRQOL, we recommend to apply children self-reported measures of HRQOL when children are capable to evaluate their health. In addition, we recommend further studies regarding the agreement between parent-reported and children self-reported HRQOL.

Fourth, some of our findings need replication. In Chapter 3, we applied the Latent Class Mixture Modeling to identify distinct trajectories of maternal HRQOL during pregnancy. Preferably this study will be repeated in large community populations of pregnant women with heterogeneous backgrounds. In Chapter 5, we did not find significant associations between worse maternal HRQOL in pregnancy and worse birth outcomes, which is in contrast with our hypothesis. We found an unexpected association between better physical HRQOL in late pregnancy with higher chance of having small-for-gestational-age birth. Therefore, we suggest to repeat this analysis in the future studies. In Chapter 8, we evaluated the feasibility and validity of a preference-based HRQOL measure (HSCS-PS) for the first time among a large sample of preschool children (3 years old) from general population. According to the report from UNICEF (The United Nations Children's Fund), children in the Netherlands have the best well-being in the 29 nations of the industrialized world. [53] This may impact the performance of HSCS-PS when it was applied to the general population, for instance, the big ceiling effect. We recommend to validate HSCS-PS in other cultures and countries regarding the feasibility, reliability and validity of the instrument. In addition, as a preference-based measure of HRQOL, no algorithm has been developed for HSCS-PS to calculate the utility score. We propose further research on this issue.

Fifth, we would like to address the potential benefits of applying the qualitative research approaches to HRQOL studies. Compared with quantitative research, qualitative research can provide details about human behavior, emotion and personality characteristics.[54] For instance, qualitative study can help to obtaining information in depth regarding how women perceive the impacts of pregnancy and childbirth on their health and life. We recommend to combine the qualitative approaches with quantitative approaches in future studies.[54]

OVERALL CONCLUSIONS

In the thesis, we demonstrated the knowledge and insights regarding maternal and children's HRQOL. Several conclusions can be drawn. In the Generation R Study, most women had healthy trajectories of both physical and mental HRQOL during pregnancy. We found multiple determinants of suboptimal HRQOL in antepartum and postpartum

periods. Some of these risk factors may be modifiable, such as pregnancy-related physical symptoms, pregnancy-specific anxiety, and postpartum psychopathological symptoms. We can conclude that HRQOL of school-aged children in the Netherlands is mainly associated with children's health indicators, such as the number of chronic conditions and health complaints, behavioral/learning disorders and health care visits. Therefore, our findings may provide opportunities for targeting women and children who may be at risk for suboptimal HRQOL, and for developing customized health interventions.

In addition, our study demonstrated the feasibility and validity of a preference-based measure of HRQOL of preschoolers (HSCS-PS), in a large sample of community-dwelling population.

REFERENCES

1. Chou FH, Avant KC, Kuo SH, Fetzer SJ. Relationships between nausea and vomiting, perceived stress, social support, pregnancy planning, and psychosocial adaptation in a sample of mothers: a questionnaire survey. Int J Nurs Stud. 2008;45(8):1185-91. PubMed PMID: 17905253.
2. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? Bjog. 2008;115(12):1484-93. PubMed PMID: 18752585.
3. İsbir GG, Mete S. Experiences with Nausea and Vomiting During Pregnancy in Turkish Women Based on Roy Adaptation Model: A Content Analysis. Asian Nursing Research. 2013;7(4):175-81. doi: https://doi.org/10.1016/j.anr.2013.09.006.
4. Heitmann K, Svendsen HC, Sporsheim IH, Holst L. Nausea in pregnancy: attitudes among pregnant women and general practitioners on treatment and pregnancy care. Scand J Prim Health Care. 2016;34(1):13-20. PubMed PMID: 26854395.
5. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126(3):e12-24. PubMed PMID: 26287788.
6. Ross LE, McLean LM. Anxiety disorders during pregnancy and the postpartum period: A systematic review. J Clin Psychiatry. 2006;67(8):1285-98. PubMed PMID: 16965210.
7. Tsai SY, Lee PL, Lin JW, Lee CN. Cross-sectional and longitudinal associations between sleep and health-related quality of life in pregnant women: A prospective observational study. Int J Nurs Stud. 2016;56:45-53. PubMed PMID: 26803171.
8. Holtrop JS, Meghea C, Raffo JE, Biery L, Chartkoff SB, Roman L. Smoking among pregnant women with Medicaid insurance: are mental health factors related? Matern Child Health J. 2010;14(6):971-7. PubMed PMID: 19838777.
9. Emmanuel E, St John W. Maternal distress: a concept analysis. J Adv Nurs. 2010;66(9):2104-15. PubMed PMID: 20626484.
10. Emmanuel E, St John W, Sun J. Relationship between social support and quality of life in childbearing women during the perinatal period. J Obstet Gynecol Neonatal Nurs. 2012;41(6):E62-70. PubMed PMID: 22861382.
11. Wang P, Liou SR, Cheng CY. Prediction of maternal quality of life on preterm birth and low birthweight: a longitudinal study. BMC Pregnancy Childbirth. 2013;13:124. PubMed PMID: 23725558.
12. Alder J, Fink N, Bitzer J, Hosli I, Holzgreve W. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med. 2007;20(3):189-209. PubMed PMID: 17437220.
13. Schulpen TW. Migration and child health: the Dutch experience. Eur J Pediatr. 1996;155(5):351-6. PubMed PMID: 8741029.
14. Ruijsbroek A, Wijga AH, Kerkhof M, Koppelman GH, Smit HA, Droomers M. The development of socio-economic health differences in childhood: results of the Dutch longitudinal PIAMA birth cohort. BMC Public Health. 2011;11:225. PubMed PMID: 21486447.
15. Mansour ME, Kotagal U, Rose B, Ho M, Brewer D, Roy-Chaudhury A, et al. Health-related quality of life in urban elementary schoolchildren. Pediatrics. 2003;111(6 Pt 1):1372-81. PubMed PMID: 12777555.
16. Ludwig DS, Rouse HL, Currie J. Pregnancy weight gain and childhood body weight: a within-family comparison. PLoS Med. 2013;10(10):e1001521. PubMed PMID: 24130460.
17. Merikallio VJ, Mustalahti K, Remes ST, Valovirta EJ, Kaila M. Comparison of quality of life between asthmatic and healthy school children. Pediatr Allergy Immunol. 2005;16(4):332-40. PubMed PMID: 15943597.
18. Sawyer MG, Spurrier N, Whaites L, Kennedy D, Martin AJ, Baghurst P. The relationship between asthma severity, family functioning and the health-related quality of life of children with asthma. Qual Life Res. 2000;9(10):1105-15. PubMed PMID: 11401043.

19. Klassen AF, Miller A, Fine S. Agreement between parent and child report of quality of life in children with attention-deficit/hyperactivity disorder. Child Care Health Dev. 2006;32(4):397-406. PubMed PMID: 16784495.
20. McNulty MA. Dyslexia and the life course. J Learn Disabil. 2003;36(4):363-81. PubMed PMID: 15490908.
21. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006;155(1):145-51. PubMed PMID: 16792766.
22. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract. 2006;60(8):984-92. PubMed PMID: 16893440.
23. Danckaerts M, Sonuga-Barke EJ, Banaschewski T, Buitelaar J, Dopfner M, Hollis C, et al. The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. Eur Child Adolesc Psychiatry. 2010;19(2):83-105. PubMed PMID: 19633992.
24. Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses. Pediatrics. 2003;112(1 Pt 1):e1-5. PubMed PMID: 12837897.
25. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev. 2008;34(4):418-29. PubMed PMID: 19154551.
26. Lee SL, Cheung YF, Wong HS, Leung TH, Lam TH, Lau YL. Chronic health problems and health-related quality of life in Chinese children and adolescents: a population-based study in Hong Kong. BMJ Open. 2013;3(1). PubMed PMID: 23293240.
27. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. J Clin Epidemiol. 2002;55(1):67-76. PubMed PMID: 11781124.
28. Raat H, Landgraf JM, Oostenbrink R, Moll HA, Essink-Bot ML. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. Qual Life Res. 2007;16(3):445-60. PubMed PMID: 17111231.
29. Institute of Medicine Committee on Understanding Premature B, Assuring Healthy O. 2007. PubMed PMID: 20669423.
30. Mohangoo AD, de Koning HJ, Mangunkusumo RT, Raat H. Health-related quality of life in adolescents with wheezing attacks. J Adolesc Health. 2007;41(5):464-71. PubMed PMID: 17950166.
31. Turan A, Emet S, Karamanlioglu B, Memis D, Turan N, Pamukcu Z. Analgesic effects of rofecoxib in ear-nose-throat surgery. Anesth Analg. 2002;95(5):1308-11, table of contents. PubMed PMID: 12401617.
32. Dodge KA. Social cognition and children's aggressive behavior. Child Dev. 1980;51(1):162-70. PubMed PMID: 7363732.
33. Catalogue of Bias Collaboration, Nunan D, Bankhead C, Aronson JK. Selection bias. Catalogue Of Bias 2017: http://www.catalogofbias.org/biases/selection-bias/
34. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. Eur J Epidemiol. 2012;27(9):739-56. PubMed PMID: 23086283.
35. Burks ML, Brooks EG, Hill VL, Peters JI, Wood PR. Assessing proxy reports: agreement between children with asthma and their caregivers on quality of life. Ann Allergy Asthma Immunol. 2013;111(1):14-9. PubMed PMID: 23806454.
36. Bastiaansen D, Koot HM, Ferdinand RF, Verhulst FC. Quality of life in children with psychiatric disorders: self-, parent, and clinician report. J Am Acad Child Adolesc Psychiatry. 2004;43(2):221-30. PubMed PMID: 14726730.

37. Davis E, Nicolas C, Waters E, Cook K, Gibbs L, Gosch A, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. Qual Life Res. 2007;16(5):863-71. PubMed PMID: 17351822.
38. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007;5:2. PubMed PMID: 17201923.
39. Rothman K, Greenland S, Lash LL. Validty in epidemiological studies. Modern Epidemiology (3rd edition). Philadelphia: Lippincott, Willams, & Wikinsl; 2008.
40. Mogos MF, August EM, Salinas-Miranda AA, Sultan DH, Salihu HM. A Systematic Review of Quality of Life Measures in Pregnant and Postpartum Mothers. Applied research in quality of life. 2013;8(2):219-50. PubMed PMID: PMC3667203.
41. Wells GA, Russell AS, Haraoui B, Bissonnette R, Ware CF. Validity of quality of life measurement tools--from generic to disease-specific. J Rheumatol Suppl. 2011;88:2-6. PubMed PMID: 22045972.
42. Symon A. A review of mothers' prenatal and postnatal quality of life. Health and Quality of Life Outcomes. 2003;1(1):38. doi: 10.1186/1477-7525-1-38.
43. Symon A, MacDonald A, Ruta D. Postnatal quality of life assessment: introducing the Mother-Generated Index. Birth. 2002;29(1):40-6.
44. Hill PD, Aldag JC. Maternal perceived quality of life following childbirth. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2007;36(4):328-34.
45. Lacasse A, Bérard A. Validation of the nausea and vomiting of pregnancy specific health related quality of life questionnaire. Health and Quality of Life Outcomes. 2008;6:32-. doi: 10.1186/1477-7525-6-32. PubMed PMID: PMC2396154.
46. Vachkova E, Jezek S, Mares J, Moravcova M. The evaluation of the psychometric properties of a specific quality of life questionnaire for physiological pregnancy. Health and quality of life outcomes. 2013;11(1):1.
47. Nikan F, Jafarabadi MA, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M. Designation and psychometric properties of the Short Form Postpartum Quality of Life Questionnaire (SF-PQOL): an application of multidimensional item response theory and genetic algorithm. Health Promotion. 2018;8(3):215-24.
48. Mahmud A, Morris E, Johnson S, Ismail KM. Developing core patient-reported outcomes in maternity: PRO-Maternity. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121(s4):15-9. doi: doi:10.1111/1471-0528.12901.
49. Lundsberg LS, Schwarz EB, Vilardo NA, Yonkers KA, Gariepy AM. Clinical Validation of PROMIS Global Short Form in Pregnancy. Applied Research in Quality of Life. 2018;13(1):89-103. doi: 10.1007/s11482-017-9507-x.
50. Vieten C, Astin J. Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: results of a pilot study. Archives of women's mental health. 2008;11(1):67-74.
51. Beddoe AE, Yang C-PP, Kennedy HP, Weiss SJ, Lee KA. The effects of mindfulness-based yoga during pregnancy on maternal psychological and physical distress. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2009;38(3):310-9.
52. Dunn C, Hanieh E, Roberts R, Powrie R. Mindful pregnancy and childbirth: effects of a mindfulness-based intervention on women's psychological distress and well-being in the perinatal period. Archives of Women's Mental Health. 2012;15(2):139-43.
53. Child Wellbeing in Rich Countries. 2013. UNICEF. Retrieved 19 August, 2018. From https://www.unicef-irc.org/Report-Card-11/
54. Carr LT. The strengths and weaknesses of quantitative and qualitative research: what method for nursing? Journal of advanced nursing. 1994;20(4):716-21.

CHAPTER 10

Summary and Samenvatting

SUMMARY

Health-related quality of life (HRQOL) is an essential issue for maternal and child health. This thesis aims to extend the understanding of maternal HRQOL during pregnancy and after childbirth, as well as HRQOL of children. The following specific research questions were formulated:

1. To what extend are nausea, vomiting, and fatigue in early pregnancy independently associated with maternal HRQOL?
2. What are trajectories of HRQOL during pregnancy and what are predictors of these trajectories?
3. What are the determinants of maternal HRQOL after childbirth?
4. To what extent is maternal HRQOL during pregnancy associated with birth outcomes?
5. What are the determinants of HRQOL among school-aged children?
6. To what extent do prevalent chronic conditions in childhood impact HRQOL of school-aged children in the Netherlands?
7. What are the feasibility and validity of the Health Status Classification System-Preschool (HSCS-PS) in a large community-dwelling sample of preschool children?

The studies presented in this thesis were embedded in the Generation R Study and the Dutch Health Interview Survey in the Netherlands. The Generation R Study is a prospective population-based mother- and child cohort study. It has been designed for identifying the early environmental and genetic factors for normal and abnormal growth, development and health from fetal life onwards until the adulthood. The Dutch Health Interview Survey, conducted by Statistics Netherlands, is a cross-sectional national health survey among the population living in private households in the Netherlands. The purpose of the Dutch Health Interview Survey is to give an overview of the developments in health, medical contacts, lifestyle and preventive behavior of the Dutch population.

Chapter 2 shows that nausea, vomiting and fatigue are very common in early pregnancy. Compared with women who never reported nausea, vomiting and fatigue in early pregnancy, women with daily presence of at least one of these symptoms had significantly worse physical and mental HRQOL.

Chapter 3 describes the distinct trajectories of physical and mental HRQOL during pregnancy, identified by Latent Class Mixture Modeling. Healthy physical and mental HRQOL trajectories during pregnancy were most common. Predictors indicative of suboptimal HRQOL trajectories included pregnancy-related physical symptoms and pregnancy-specific anxiety.

Chapter 4 presents the multiple determinants of maternal HRQOL assessed at two months after delivery. Worse physical HRQOL was associated with older maternal age, shorter time after delivery, cesarean delivery, loss of energy, maternal psychopathology, and the hospital admission of the baby; worse mental HRQOL was associated with older maternal age, non-western background, low household income, loss of energy and maternal psychopathology. In particular, maternal psychopathology is a profound determinant of worse mental HRQOL after delivery.

In Chapter 5, our findings did not confirm the hypotheses that worse maternal physical and mental HRQOL in early, mid- and late pregnancy are associated with more preterm birth, shorter pregnancy duration, and lower birth weight in the total study population. In contrast, in late pregnancy, we saw that a relatively better physical HRQOL is associated with a higher chance of having a small-for-gestational-age birth. This requires further study. Our study showed only small effects regarding a relatively low average birth weight and more frequent small-for-gestational-age birth in the subgroup with worst mental HRQOL compared with the subgroup with the best mental HRQOL. The importance of mother's mental HRQOL during pregnancy and the potential consequences for the child requires further study.

Chapter 6 presents determinants of HRQOL among school-aged children in the Netherlands. Having a non-western immigrant background, parents who did not work, more health conditions/disorders and using more healthcare were associated with poorer physical HRQOL. Boys, single-parent family, obesity and having more health conditions/disorders were associated with poorer psychosocial HRQOL.

Chapter 7 demonstrates lower HRQOL of children with a prevalent chronic condition (asthma, eczema, dyslexia, attention deficit hyperactive disorder, or migraine/severe headache) compared with children without any chronic conditions. The pattern of impaired HRQOL is specific across these conditions. When comorbidity was taken into account, the HRQOL were lower than when the comorbidity was excluded from analyses.

In **Chapter 8**, the feasibility and validity of an instrument to measure HRQOL among preschool children was assessed. This is the first study to validate Health Status Classification System-Preschool (HSCS-PS) in a large general population. The results support the feasibility, concurrent validity, and discriminant validity of the HSCS-PS.

Chapter 9 presents a general discussion, including a description and interpretation of the main findings, methodological considerations, recommendations for practice, and directions for future research.

In conclusion, this thesis demonstrates that there are medical, social and psychological determinants of maternal HRQOL during pregnancy and after childbirth, as well as determinants of children's HRQOL. Among these determinants, some factors are modifiable, which provides opportunities for targeted health interventions. We recommended health professionals to include measures of maternal HRQOL in antenatal and postnatal visits. In addition, we suggested future research to repeat the assessment of links between maternal HRQOL during pregnancy and birth outcomes, as well as to repeat the evaluation of validity of the instrument HSCS-PS in other large general population of preschool children.

SAMENVATTING

Gezondheidsgerelateerde kwaliteit van leven (KvL) is een essentieel aspect van de gezondheid van moeders en kinderen. Dit proefschrift heeft als doel om meer inzicht te krijgen in maternale Gezondheidsgerelateerde KvL tijdens de zwangerschap en na de bevalling, alsook in Gezondheidsgerelateerde KvL van kinderen. De volgende specifieke onderzoeksvragen werden geformuleerd.

1. In hoeverre zijn de meest voorkomende zwangerschaps-gerelateerde symptomen vroeg in de zwangerschap (misselijkheid, overgeven en vermoeidheid) geassocieerd met Gezondheidsgerelateerde KvL van vrouwen?
2. Wat zijn trajecten voor Gezondheidsgerelateerde KvL tijdens de zwangerschap, en wat zijn voorspellers van deze trajecten?
3. Wat zijn de determinanten van maternale Gezondheidsgerelateerde KvL na de bevalling?
4. In hoeverre is maternale Gezondheidsgerelateerde KvL tijdens de zwangerschap onafhankelijk geassocieerd met geboorte-uitkomsten?
5. Wat zijn de determinanten van Gezondheidsgerelateerde KvL in schoolgaande kinderen?
6. Wat voor impact hebben de meest voorkomende chronische aandoeningen op Gezondheidsgerelateerde KvL van schoolgaande kinderen in Nederland?
7. Wat is de haalbaarheid en validiteit van een instrument om Gezondheidsgerelateerde KvL te meten bij peuters?

Het onderzoeken die worden gepresenteerd in dit proefschrift zijn ingebed in het Generation R onderzoek en de Nederlandse Gezondheidsenquête. Het Generation R onderzoek is een prospectief cohortonderzoek waarin moeders en kinderen uit de algemene populatie worden gevolgd vanaf het foetale leven tot aan de volwassenheid. Het onderzoek is opgezet om vroege omgevingsfactoren en genetische factoren te identificeren die een rol spelen bij normale en abnormale groei, ontwikkeling en

gezondheid. De Nederlandse Gezondheidsenquête, welke wordt uitgevoerd/afgenomen door het Centraal Bureau voor de Statistiek (CBS) is erop gericht een dwarsdoorsnede van de Nederlandse bevolking in kaart te brengen. Dit gebeurt door middel van een landelijke enquête onder particuliere huishoudens in Nederland. Het doel van de Nederlandse Gezondheidsenquête is om een overzicht te geven van de ontwikkelingen in gezondheid, medische contacten, leefstijl en preventief gedrag van de Nederlandse bevolking.

Hoofdstuk 2 laat zien dat misselijkheid, overgeven en vermoeidheid heel vaak voorkomen tijdens de vroege zwangerschap. In vergelijking met vrouwen die nooit misselijkheid, overgeven of vermoeidheid rapporteerden tijdens de vroege zwangerschap, hadden vrouwen die dagelijks last hadden van ten minste één van deze symptomen een significant slechtere fysieke en mentale Gezondheidsgerelateerde KvL.

Hoofdstuk 3 beschrijft verschillende trajecten van fysieke en mentale Gezondheidsgerelateerde KvL tijdens de zwangerschap, welke zijn geïdentificeerd met behulp van Latent Class Mixture Modeling. Gezonde fysieke en mentale Gezondheidsgerelateerde KvL trajecten tijdens de zwangerschap kwamen het meest voor. Voorspellers van suboptimale Gezondheidsgerelateerde KvL trajecten waren onder andere zwangerschapsgerelateerde fysieke symptomen, en zwangerschaps-specifieke angst.

Hoofdstuk 4 presenteert verschillende determinanten van maternale Gezondheidsgerelateerde KvL rond twee maanden na de bevalling. Slechtere fysieke Gezondheidsgerelateerde KvL was geassocieerd met een hogere leeftijd van de moeder, kortere tijd na levering, bevalling via een keizersnede, verminderde energie, psychische problematiek, and de ziekenhuisopname van de baby. Slechtere mentale Gezondheidsgerelateerde KvL was geassocieerd met een hogere leeftijd van de moeder, niet-westerse achtergrond, een laag gezinsinkomen, en verlies van energie and psychische problematiek. Vooral maternale psychologische problematiek was sterk geassocieerd met de postnatale mentale Gezondheidsgerelateerde KvL.

In **Hoofdstuk 5** werden de associaties van maternale Gezondheidsgerelateerde KvL – vroeg, midden en laat in de zwangerschap – met geboorte-uitkomsten onderzocht. Moeders met slechtst mentale Gezondheidsgerelateerde KvL vroeg, midden en laat in de zwangerschap kregen kinderen met een gemiddeld lager geboortegewicht en was de prevalentie van Small for Gestational Age (SGA) hoger dan met moeders met het beste mentale Gezondheidsgerelateerde KvL.

Hoofdstuk 6 presenteert determinanten van Gezondheidsgerelateerde KvL van schoolgaande kinderen in Nederland. Het hebben van een niet-westerse migrantenachtergrond,

ouders die niet werken, meer gezondheidsproblemen/aandoeningen en het gebruiken van meer gezondheidszorg waren geassocieerd met een slechtere fysieke Gezondheidsgerelateerde KvL. Mannelijk geslacht, éénoudergezin, obesitas en het hebben van meer gezondheidsproblemen/aandoeningen waren geassocieerd met een slechtere psychosocialeGezondheidsgerelateerde KvL.

Hoofdstuk 7 laat zien dat kinderen met een veel voorkomende chronische aandoening (astma, eczeem, dyslexie, ADHD of migraine/ernstige hoofdpijn) slechtere Gezondheidsgerelateerde KvL rapporteerden dan kinderen zonder een chronische aandoening. Het patroon van verminderde Gezondheidsgerelateerde KvL is specifiek voor deze aandoeningen. Wanneer rekening werd gehouden met comorbiditeit, was de Gezondheidsgerelateerde KvL slechter dan wanneer de comorbiditeit werd uitgesloten van de analyses.

In **hoofdstuk 8** werd de haalbaarheid en validiteit onderzocht van een instrument om Gezondheidsgerelateerde KvL te meten bij peuters. Dit is het eerste onderzoek dat de Health Status Classification System-Preschool (HSCS-PS) valideert in een grote, algemene populatie. De resultaten ondersteunen de haalbaarheid, concurrente validiteit en discriminerende validiteit van de HSCS-PS.

Hoofdstuk 9 presenteert een algemene discussie, inclusief een beschrijving en interpretatie van de belangrijkste bevindingen, methodologische overwegingen, aanbevelingen voor de praktijk en richtingen voor toekomstig onderzoek.

Samenvattend laat dit proefschrift zien dat er medische, sociale en psychologische determinanten zijn van maternale Gezondheidsgerelateerde KvL tijdens de zwangerschap en na de bevalling, evenals determinanten van de Gezondheidsgerelateerde KvL van kinderen. Een aantal van deze determinanten is veranderbaar, wat kansen biedt voor gerichte gezondheidsinterventies. Wij raadden gezondheidsprofessionals aan om metingen van maternale Gezondheidsgerelateerde KvL op te nemen in prenatale en postnatale bezoeken. Daarnaast stelden we voor om in de toekomst het onderzoek naar de verbanden tussen maternale Gezondheidsgerelateerde KvL tijdens de zwangerschap en geboorte-uitkomsten te herhalen, alsook om de evaluatie van de validiteit van het instrument HSCS-PS te herhalen in een andere grote algemene populatie van peuters.

APPENDICES

Author's Affiliations
Publications and Manuscripts
About the Author
PhD Portfolio
Words of Gratitude

AUTHOR'S AFFILIATIONS

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David Feeny

Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
Saroj Saigal

PUBLICATIONS AND MANUSCRIPTS

Published articles-English (n=7; in reverse chronological order)

1. Xinye Fang, **Guannan Bai**, Dafna A Windhorst, David Feeny, Saroj Saigal, Liesbeth Duijts, Vincent WV Jaddoe, Shanlian Hu, Chunlin Jin, Hein Raat. Feasibility and validity of the Health Status Classification System-Preschool (HSCS-PS) in a large community sample: The Generation R Study. *Accepted by BMJ Open, Oct 2018*.

2. **Guannan Bai,** Hein Raat, Vincent V.W. Jaddoe, Eva Mantner, Ida J Korgage. Trajectories and predictors of women's health-related quality of life during pregnancy: A large longitudinal cohort study. *PLoS ONE*. 2018. 13(4): e0194999. DOI: https://doi.org/10.1371/journal.pone.0194999.

3. **Guannan Bai,** Marieke Houben-van Herten, Jeanne M Landgraf, Ida J Korfage, Hein Raat. Chronic conditions in school-aged children and health-related quality of life: findings from a large population-based study. *PLoS ONE, 2017; 12 (6): e0178539*. DOI: https://doi.org/10.1371/journal.pone.0178539.

4. **Guannan Bai,** Ida J Korfage, Esther Hafcamp, Vincent V.W. Jaddoe, Eva, Mautner, Hein Raat. Associations between nausea, vomiting, fatigue and health-related quality of life of women in early pregnancy: the Generation R Study. *PLoS ONE 2016; 11(11): e0166133*. DOI: https://doi.org/10.1371/journal.pone.0166133.

5. Marieke Houben-van Herten, **Guannan Bai,** Esther Hafcamp, Jeanne M Landgraf, Hein Raat. Determinants of Health-Related Quality of Life in School-Aged Children: A General Population Study in the Netherlands. *PLoS ONE 2015; 10 (5): e0125083*. DOI: https://doi.org/10.1371/journal.pone.0125083.

6. **Guannan Bai,** Yufeng Wang, Li Yang, Wenyi Niu. Effectiveness of a focused brief psychoeducation program for parents of ADHD children: improvement on the medication adherence and symptoms. *Neuropsychiatr Dis Treat. 2015; 11: 2721–2735*. DOI: https://doi.org/10.2147/NDT.S88625.

7. Wang Wei, Guo XiaoHui, Shen Guiju; **Bai Guannan,** Wei Zheng, Liu Junhao, Strauss Kenneth, Hirsch Laurence. Skin and Subcutaneous Thickness at Insulin Injection Sites in Chinese Patients with Diabetes: Clinical Implications. *Diabetes & Metabolism, 2016; 42 (5): 374-377*.DOI: https://doi.org/10.1016/j.diabet.2016.04.010.

Processing articles-English (n=2; in reverse chronological order)

1. **Guannan Bai,** Ida J Korfage, Eva Mantner, Hein Raat. Associations between maternal health-related quality of life during pregnancy and birth outcomes: The Generation R Study. *Submitted.*

2. **Guannan Bai,** Ida J Korfage, Eva Mantner, Hein Raat. Determinants of Postpartum Health-related Quality of Life: The Generation R Study. *Draft to be submitted.*

Published articles on Chinese core journals (n=8; in reverse chronological order)

1. Wei Wang, Xiaohui Guo, Guiju Shen, **Guannan Bai**, Zheng Wei. Effect of needle reuse on blood glucose in diabetic patients treated with insulin. *Chinese Journal of Diabetes*. 2018, 26 (2): 101-103. DOI: 10.3969/j.issn.1006-6187.2018.02.003.

2. Zheng Ren, Wenyi Niu, Yufeng Wang, Li Yang, **Guannan Bai**. Application of Delphi method in core information selection for improving medication adherence among children with attention deficit hyperactivity disorder. *Chinese Journal of Health Education*. 2015, 31 (3): 252-255. DOI: 10.16168/j.cnki.issn.1002-9982.2015.03.003.

3. Ying Qian, Xueni Li, **Guannan Bai,** Huipu Li, Jin Yi, Cuilin Song, Qingmei Kong, Shuxia Geng, Chaozhong Liu, Darong Zhang. Qualitative study of effect of open group psychotherapy for inpatients with eating disorder. *Chinese Mental Health Journal*. 2014, 28 (1): 28-34. DOI: 10.3969/j.issn.1000-6729.2014.01.005.

4. **Guannan Bai**, Wenyi Niu, Yufeng Wang. A thematic framework analysis of medication adherence for children with attention-deficit/hyperactivity disorder: What do parent say? *Chinese Mental Health Journal*. 2013, 27(7): 529-533. DOI:10.3969/j.issn.1000-6729.2013.07.009.

5. **Guannan Bai,** Wenyi Niu. The review of parent training programs of ADHD children: methods and evaluation. *Chinese Journal of Health Education*. 2013, 29 (2): 158-162.

6. **Guannan Bai**, Mengmeng Cui, Wenyi Niu. Correlation between psychosomatic health and time perspective among undergraduates in Beijing. *Chinese Journal of School Health*. 2013, 34 (12): 1450-1452. 10.16835/j.cnki.1000-9817.2013.12.017

7. **Guannan Bai**, Wenyi Niu. A thematic framework analysis of messages posted to an online "AIDS postbar". 2013. *Chinese Journal of AIDS & STD*. 2013, 118(07) 482-484+491. DOI: 10.13419/j.cnki.aids.2013.07.002.

8. **Guannan Bai**, Wenyi Niu. A content analysis of one-month messages posted to an online "AIDS bar". 2012. *Chinese Journal of Health Education*. 2012, 28 (8): 649-652. DOI: 10.16168/j.cnki.issn.1002-9982.(2012) 08-0649-04.

ABOUT THE AUTHOR

Guannan Bai was born on 2nd February, 1989, in Liaocheng, in the province of Shandong, P.R. China. She followed primary education and secondary education in her hometown, and then she followed high school education in Liaocheng No.1 High School from 2003 to 2006. In 2006, she was accepted by the School of Public Health in Shandong University. In July 2011, she graduated from Shandong University with a bachelor degree in preventive medicine. During her bachelor study, she has participated in various social and academic projects, and was granted with the President Scholarship in 2010, which was the highest honor for students in Shandong University.

In September 2011, Guannan started the Master project in the School of Public Health in Peking University with examination waived. During her master study, she has been trained in health education and social medicine. Her main research interest was on health education strategies for parents whose children had attention deficit hyperactivity disorder (ADHD). She has developed a psychoeducation program for parents to improve children's ADHD symptoms and to improve the adherence to medication. The parent manual and posters are still widely used in clinical practice for parent education in hospitals. She was actively involved in the international youth communication. She was selected as a youth delegate to attend the 3rd Saudi-Chinese Youth Dialogue Forum in 2012. She coauthored a letter to Dr. Margaret Chan (the former Director-General of World Health Organization), together with Saudi Arabic youth delegates. In this letter, she proposed an online platform for communications and exchanging knowledge/expertise on health-science-related issues globally. This proposal, together with inspirations from the subsequent Saudi International Youth Dialogue Forums, have emerged a new digital communications technology platform UNDP Digital Good (launched in Sep 2015) to enable individuals worldwide to help achieve Sustainable Development Goals. In November 2012, she was selected for the India-China Youth Exchange Program. In July 2014, she received a Master of Science diploma from Peking University with a cum laude.

In August 2014, she started her PhD project at Erasmus MC-University Medical Center Rotterdam in the Netherlands. The PhD project was supported by the PhD fellowship from China Scholarship Counsil (CSC). From 2014 to 2018, she worked under the supervision of Prof. Hein Raat and Dr. Ida J Korfage in the Department of Public Health and the Generation R Group. Her research is mainly focused on health-related quality of life (HRQOL) of mothers and children in the general population. She has built up a social network with excellent researchers from China, Europe and North America via international collaborations and via attending and presenting at the international congresses. In the future, Guannan would like to continue in academia or develop her career in the international organizations, such as World Health Organization and UNICEF. She would like to devote herself in the research and public health practice to improve maternal, infant and child health globally. If possible, she also would like to extend her research / public health practice to the elderly population.

PHD PORTFOLIO

Name PhD student	Guannan Bai
Departments	Public Health, Erasmus Medical Center Rotterdam
Research school	Netherlands Institute for Health Sciences (NIHES), Rotterdam
PhD period	September 2014-December 2018
Promotor	Prof. dr. Hein Raat
Co-promotor	Dr. Ida J Korfage

	Year	Workload (ECTS)
1. PhD training		
Courses		
Biostatistical Methods I: Basic Principles	2014	5.7
Topics in Meta-analysis	2015	0.7
Principles of Genetic Epidemiology	2015	0.7
Genomics in Molecular Medicine	2015	1.4
Social Epidemiology	2015	0.7
Advances in Genomics Research	2015	0.4
Advances in Epidemiology Analysis	2015	0.4
The Practices of Epidemiological Analysis	2015	0.7
Quality of Life Measurement	2016	0.9
Causal Mediation Analysis	2016	0.7
Scientific Writing	2016	3.0
Endnote, Medical Library, Erasmus MC	2014	0.3
Scientific Integrity, Erasmus MC	2015	0.3
Seminars and workshops		
Seminar, Institute of Social and Preventive Medicine, University of Bern, Switzerland	2018	1.0
Seminar, West China School of Public Health, Sichuan Univeristy, Chengdu, China	2018	1.0
Seminars, Department of Public Health	2014-2018	4.0
Generation R Research Meeting	2014-2018	2.8
Generation R maternal and child health meetings	2014-2018	1.0
PhD Day, Erasmus MC	2015-2018	1.1
Career Guidance Program	2017-2018	1.4

	Year	Workload (ECTS)
Inter(national) conferences		
ISOQOL (International Society of Quality of Life Research) 22nd Annual Conference, Vancouver, BC, Canada	2015	1.1
ISOQOL (International Society of Quality of Life Research) 23rd Annual Conference, Copenhagen, Denmark	2016	1.1
ISOQOL (International Society of Quality of Life Research) 24th Annual Conference, Philadelphia, United States	2017	1.1
Swiss Public Health Conference, Basel, Switzerland	2017	0.6
West China Preventive Medicine Annual Conference, Chengdu, China	2018	0.6
Swiss Public Health Congress, Neuchâtel, Switzerland	2018	0.6
2. Scholarships and grants		
CSC (Chinese Scholarship Council) PhD Fellowship	2014-2018	
Student and New Investigator Traveling Scholarship, ISOQOL	2015	
Trustfunds Erasmus Universiteit Rotterdam Grants	2015-2016	
3. Teaching activities		
Teaching at NIHES course: Quality of Life Measurement	2017	0.6
Supervision of visiting researcher project "Validation of an instrument HSCS-PS to measure preschooler's health-related quality"	2016-2018	5.0

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours

WORDS OF GRATITUDE

If there is a word to describe how wonderful to have PhD training in the Department of Public Health and the Generation R Group at Erasmus MC, I think this word should be **MAGIC**!

It is like MAGIC that I moved to Rotterdam and worked at Erasmus MC, then I found out the unbelievable bond between my family and Erasmus University, which I did not know when I applied for the PhD position. Therefore, I give my first words of gratitude to no one but **The Lord of Love and Life** for leading my path to Erasmus MC. On 22 September, 1999, my aunt, Jiefen Yao, my mom's cousin, defended her PhD thesis entitled "Three-Dimensional Echocardiography in Coronary Artery Disease" at Erasmus University Rotterdam. After getting her PhD degree, she moved to United States. That is why I had seldom heard from her for many years. Even my family knew little about her experience in Europe. Twenty years ago, the Netherlands, Rotterdam and Erasmus University, were known by very few of people in China, especially people living in a very small city, for example, the city where my aunt and I grew up. When I started my PhD project in Erasmus MC, by coincidence, I checked the Linkedin profile of my aunt, I was shocked when I saw her education experience as a PhD candidate in the Department of Cardiology at Erasmus University Rotterdam from 1997-1999. At that moment, I was pretty sure that it was not a coincidence that I came to Erasmus MC, it is my **DESTINY**.

Therefore, I present this thesis, especially to my aunt, Dr. Jiefen (Yao) Munley, and to the incredible connection of my family with Erasmus University.

To make this magic happen in the real world, I would like to thank my promotor professor Dr. Hein Raat, for offering me the opportunity to conduct my PhD research in the Generation R Group. Dear Hein, I cannot thank you more for your unconditional trust, support and care. Thank you for the extremely valuable supervision of my research in the past years. The luckiest thing during education is being guided by a noble soul. I am very lucky to have you as my promotor.

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