# TRAJECTORIES OF PICKY EATING

## From normal rite of passage to a developmental problem

Sebastian Cardona Cano

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Trajectories of Picky Eating

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# Trajecten van Picky Eating

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Trajectories of picky eating during childhood: A general population study. **Cardona Cano S**, Tiemeier H, Van Hoeken D, Tharner A, Jaddoe VW, Hofman A, Verhulst FC, Hoek HW. Int J Eat Disord 2015 Sep;48(6):570-579. doi: 10.1002/eat.22384.

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Are parents' anxiety and depression related to child fussy eating? De Barse LM, **Cardona Cano S**, Jansen PW, Jaddoe VVW, Hofman A, Verhulst FC, Franco OH, Tiemeier H, Tharner A. Arch Dis Child 2016 Jun;101(6):533–538. doi:10.1136/archdischild-2015-309101.

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CHAPTER 1

# General introduction

# Introduction

Rare is the child who will eat pretty much anything. Most toddlers develop specific favorite foods and, of more concern, absolute no-go foods. The latter is of major concern for parents [1], who find picky eating one of the most-difficult-to-deal-with feeding problems [2]. Mothers even go as far as feeling inadequate as a parent if their child refuses to eat [3]. Unfortunately, feeding is a complex interplay between several factors which parents cannot always influence; i.e. genetics, different neural pathways influencing eating behavior, child and parental factors, as well as peer and other environmental factors all contribute to whether a child chooses to eat a specific food.

Picky eating research in its current form is relatively new, with most entries of picky eating (including fussy eating and selective eating) in online literature search engines dating predominantly from the last two decades. However, from a historical perspective picky eating was subsumed under the umbrella term "feeding problems" since the start of last century; i.e. one of the first feeding problem entry in Pubmed dates from 1923 [4], where different problematic eating behaviors are described, and the largest group being the children with food refusal problems without underlying somatic problems. The thought that "children will eat if they are hungry", and that treatment should primarily focus on mealtime hygiene and increased discipline in feeding patterns from parents is herein promoted [4-5]. This line of thought still persists to this day.

At present picky eating is considered by health professionals to be a normal rite of passage [6]; i.e. typically an infant transits from breastfeeding or formula to consuming a variety of solid foods in the first two years. During this time, children can put various edible and nonedible objects in their mouth, but this is considered part of normal development. Thereafter, when the child becomes more mobile, children tend to become pickier about what they eat. It has been postulated that this is an evolutionary adaptation meant to reduce the chance of an intoxication by ingestion of unsafe foods [7]. When the child gets older, the picky eating phase usually remits. Thus health professionals' advice a watchful waiting approach, and reassure parents "that the child will not starve themselves". This holds true for the majority of children in the general population. However, picky eating can also lead to a poor nutritional status, faltering weight gain and growth, and is associated with unfavorable health outcomes (such as anxiety and pervasive developmental problems). The extreme forms of picky eating can be classified as an avoidant/restrictive food intake disorder (ARFID). ARFID is a new diagnostic category in the DSM-5 replacing the feeding disorder of infancy and early childhood, and its core symptom is picky eating leading to somatic and/or psychosocial dysfunction [8]. In contrast to anorexia and bulimia nervosa, ARFID lacks the fear of weight gain. Surprisingly, little is known about the etiology, course and outcome of ARFID [8] and picky eating [9]. Thus picky eating

embodies two (possibly distinct) trajectories, which both are of major concern for parents, but could possibly be diametrically opposed in clinical relevance; i.e. one that remits and has little to no clinical consequences and one that has major health impacts. Therefore, it is important to be able to differentiate between individuals in the general population with transient or mild picky eating behaviour, which could be regarded as part of normal development or functioning, and more extreme picky eaters whose eating behavior is associated with adverse health or psychosocial outcomes.

However, picky eating research, although there is a growing body of literature in recent years, is hampered by several limitations [10]. Not in the least, because several terms are interchangeably used for the same concept; i.e. picky/ fussy/ faddy/ selective eating (disorder), and food neophobia. This reaffirms that the concept of picky eating is still in its infancy, and no clear definition is established [10].

The core of this thesis focuses on picky eating in the general population, trying to establish a better working concept by differentiating between normal and problematic trajectories of picky eating. This thesis also contains a chapter on a specific hormone (ghrelin) which influences the neurobiology of eating behaviour. As a clinician I started my thesis with translational research studying the possible relation between ghrelin and eating disorders, before my focus shifted to a more epidemiological approach on picky eating.

# This thesis

The aim of this thesis is to extend on the existing knowledge on picky eating to identify determinants in order to differentiate between picky eating as part of normal development, and picky eating at risk for adverse (mental) health outcomes.

The specific aims were to study:

1. Further conceptualization of the construct of picky eating
2. The prevalence of picky eating
3. Risk factors associated with different trajectories of picky eating
4. Adverse mental health outcomes associated with different trajectories of picky eating

## Systematic reviews

For the systematic reviews literature searches were performed within the online search engines Ovid medline, Embase and PsychInfo, and extended with a manual search and complemented with cross-referencing.

## Setting

The research was partially embedded within the Generation R Study, a population-based cohort in Rotterdam, the Netherlands [11], that aims to identify environmental and genetic causes of normal and abnormal growth, development, and health from early fetal life onward. Pregnant women residing in Rotterdam with an expected delivery date between April 2002 and January 2006 were invited to participate. Information about sociodemographic factors was collected using postal questionnaires.

## Outline

**Chapter 2** reviews the current body of literature regarding picky eating and examines the conceptualization of this construct, risk factors and treatment options. In **Chapter 3 & 4**, we explore the child, parental and sociodemographic risk factors associated with different trajectories of picky eating. In **Chapter 5**, we study the associations between different trajectories of picky eating and emotional, behavioral and pervasive developmental problems to indicate which trajectories are at risk for adverse mental health outcomes, and which trajectories are most likely part of normal development. **Chapter 6** reviews the hormone ghrelin, and the changes of this hormone in different eating disorders, while also discussing new potential treatment options. **Chapter 7** discusses the main findings of these studies, together with methodological considerations, clinical implications, and recommendations for future research.

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## CHAPTER 2

# Picky eating: the current state of research

Sebastian Cardona Cano
Hans W. Hoek —Rachel Bryant-Waugh

Curr Opin Psychiatry 2015; 28:448-454

# Abstract

## Purpose of review

In this review an overview of literature on picky eating is given with the focus on recently published studies.

## Recent findings

Papers on picky eating published over the last 2 years broadly covered three themes: characterization of picky eating; factors contributing to the development of picky eating in children; and management of picky eating. Findings suggest that picky eating is a reasonably robust concept, comprising food neophobia, eating a limited variety of food, and other specific features related to food and eating (e.g. low enjoyment of food, slowness in eating and higher satiety responsiveness). Picky eating has a higher prevalence in preschool children and seems to decrease thereafter. Studies investigating factors influencing the development of picky eating in childhood have examined a range of child factors, parent factors and parent-child interactions. Only very limited guidance has emerged regarding the management of picky eating.

## Summary

Picky eating is a descriptive term with greater emerging clarity about its core characteristics and associations. Research remains limited with ongoing difficulties related to lack of standardized assessment measures, and poor ability to differentiate between normal and clinically significant picky eating.

## Key points

- Characteristics of picky eating include food neophobia, eating a limited variety of foods, less enjoyment of food, slowness in eating, and higher satiety responsiveness.
- Prevalence of picky eating is highest in preschool children, and seems to decline at 6 years of age.
- Risk factors associated with picky eating include parental (age, maternal negativity, parenting styles), child (gender, weight at birth) and sociodemographic (socioeconomic status and birth order) characteristics.
- Management of picky eating focusses on reducing parental anxiety and continued exposure of foods to reduce food neophobia.

# Introduction

'Picky eating' is a widely used descriptive term, but without a clear or consistent definition. This lack of operationalization has contributed to limitations in existing research [1]. Picky eating is often considered to be characterized by food refusal, food neophobia (unwillingness to try new food) and other aberrant eating behaviors [1]. There has been discussion in the literature about the nature of picky eating and main contributory factors; for example, Boquin and colleagues note, "it is difficult to discern if picky eating is an independent construct or a result of genetic predisposition, food exposure, parental modeling, or parenting style" [2]. Picky eating in early childhood is often recognized as part of normal development reflected by a high prevalence and incidence rates which begin to decline by around 4 to 5 years of age [3-5], but may persist through to adulthood in some individuals [6]. Picky eating is often a major concern for parents of young children [5, 7-9], who may express frustration that their concerns are dismissed when consulting health care professionals [10].

In this paper we use the term picky eating not as a clinical or diagnostic category, but as a description of eating behavior in line with common usage. More extreme variants of picky eating that are associated with clinically significant distress or impairment to development or functioning may meet diagnostic criteria for Avoidant Restrictive Food Intake Disorder (ARFID) [11]. Picky eating and ARFID are not synonymous terms. ARFID is a new diagnostic category in the DSM-5 [12-13], and also likely to be included in ICD-11, currently scheduled for publication in 2017 [14].

If picky eating behavior is understood as occurring on a continuum, it is important to be able to differentiate between individuals in the general population with transient or mild picky eating behavior, which could be regarded as part of normal development or functioning, and more extreme picky eaters, whose eating behavior is associated with adverse health or psychosocial outcomes as in a feeding or eating disorder such as ARFID. A small but growing literature currently exists on ARFID. In theory, picky eating in early childhood could in some cases be a precursor for ARFID. More research is required to build an adequate understanding of aetiology, development, course and outcome of ARFID [12]. Picky eating behavior has also been found to predict symptoms of anorexia nervosa [15]. And picky eating is often associated with children with autism, possibly leading to nutritional inadequacies [16], and thus extending to ARFID-like behavior.

In this review we aim to provide an overview of recently published studies on picky eating. First we discuss papers addressing the current status of the concept of picky eating, addressing: common parent identified characteristics of picky eating in children; research on possible interactions between picky eating in children and parental factors; studies on tactile sensitivity and picky eating; and picky eating in adults. We then focus on recent literature regarding assessment, epidemiology (including risk factors), and management. We conclude with suggestions for further research.

Literature searches were performed within the electronic search engines Ovid medline, Embase and PsycInfo, using the search terms “picky eating”, “selective eating”, and “fussy eating” for the last 24 months up to January 2015, extended with a manual search and complemented with cross-referencing.

# Characterization of picky eating

## Parent identified characteristics of picky eating

In an attempt to further operationalize the picky eating concept several recent studies [2, 17-18] have used qualitative study designs and semi-structured focus groups. These studies have involved parents of children in the general population describing aspects of eating which they associate with pickiness. One study [18] focussed on self-identified adult picky eaters, which is described separately. Findings are summarized and discussed below with the aim of contributing to the establishment of a better working concept of picky eating.

Boquin and colleagues [2] found food neophobia and consuming a limited variety of foods to be the most important reported factors characterizing picky eating. Rigid behavior regarding foods, avoiding mealtimes, slowness in eating, and less enjoyment of food were also reported as behaviors associated with picky eating. The parents of picky eaters additionally reported extreme hypersensitivity, negative reactions to sensory properties of foods, more problems before and during the meals such as struggles to get the child at the table, and “crying, cringing or gagging” [2, 19]. Johnson’s study of low income mothers of preschoolers revealed that children displaying picky eating were also described as being “overwhelmed” at mealtimes [17].

## Interactions between parental factors and picky eating

It has been demonstrated that picky eating in children is associated with several parental behaviors both in relation to child feeding and own eating. These include: greater parental pressure to eat and overall control of the child’s intake [20-21]; higher maternal dietary restraint [22]; and more recently, higher maternal externally cued eating (such as eating more when more food is accessible and wanting to eat when watching others eat) [23]. In another study, mothers of picky eaters reported lower expectations regarding the amount and range of foods that their child would eat compared to good eaters [17]. Maternal anxiety about the child eating too little resulted in serving specific foods that the mothers thought the child would eat. As most studies have a cross-sectional design, caution is needed in interpreting causality [24].

Recent work has confirmed previous findings of an association between child

picky eating behavior and maternal mental health and self-esteem; “seeing their child eat (enough) was central to being a successful parent” [17]. Picky eating in children has been associated with negative maternal affect [25-27], with Hafstad and colleagues [28] finding that negative maternal affect predicted picky eating in early childhood in a longitudinal study. A bidirectional effect between parental pressure and negative affect increasing the picky eating behavior due to a problematic parent-child interaction is possible. For example, parental pressure to eat could be a reaction to a child’s picky eating behavior, or could result in increasing picky eating behavior by reducing enjoyment of food [29-30].

## Tactile sensitivity and picky eating

Picky eating has also been found to be associated with tactile sensitivity [31-33]. Coulthard and colleagues [34] found associations between tactile sensitivity, food neophobia and eating a limited variety of food in a general population sample as well as in picky eaters [33-34]. However as these findings were based on parental report, Nederkoorn and colleagues [32] used in vivo behavioral experiments to study whether tactile sensitivity is associated with picky eating in schoolchildren between 4 and 10 years of age. Participants were presented with 10 different foods and 10 tactile stimuli. Picky eating was assessed by two different measures; the number of foods eaten and reported enjoyment of those items. A positive association was found between the two components of picky eating and tactile sensitivity only in the younger children (4 - 7.5 years of age). The authors therefore propose that picky eating is promoted through not only taste sensitivity (disliking the taste of food), but also through tactile sensitivity (disliking the texture or feel of foods). In a subsequent study, color, texture and taste were investigated in relation to picky eating [31]. Children between 30 and 48 months from day care centers were offered well-liked yoghurt as baseline. Thereafter the yoghurt was manipulated in one of the three modalities (color, taste, texture) and the number of accepted spoons was used as the outcome measure. Children were rated on picky eating using the Child Eating Behavior Questionnaire (CEBQ) ‘food fussiness’ subscale [35]. Only the texture modality reduced the amount of intake but this was not found to be associated with picky eating. Nevertheless the authors [31] comment on the importance of tactile sensitivity as a key characteristic of picky eating. They suggest that their lack of finding a clear association between tactile sensitivity and picky eating could reflect a shortcoming in the assessment method of picky eating.

### Picky eating in adults

Most research has focussed on picky eating in children, but research on adult picky eating is emerging [6, 18, 36]. In a qualitative study self-identified adult picky eaters reported that their restricted eating behavior had existed since childhood and despite trying to broaden their diet on several occasions, they continued to consume a limited variety of food, had a dislike for certain food groups, and engaged in aberrant eating behaviors [18]. Some described a "strong physical and emotional reaction" to disliked foods, making them feel "physically sick" [18]. This may mirror the crying/gagging reaction reported in children [2]. Furthermore, some adult picky eaters described their picky eating behavior as part of their identity, reporting that in some instances it could negatively influence psychosocial functioning, such as problems with eating out or even problems with eating with the family.

## Assessment

### Questionnaire measures

Research into picky eating is complicated by the use of different assessment methods [1]. There is currently no gold standard for the assessment of picky eating. Some studies over the last decade have determined the existence of picky eating by a single question; "is your child a picky eater" [37], a method which is still being used [19].

Independently of each other, two recent studies [23, 38] performed class analyses on the CEBQ to define picky eaters. Both identified picky eaters as children with high food fussiness, high satiety responsiveness, emotional undereating, slowness in eating, and less enjoyment of food. These findings overlap with the qualitative results regarding the aspects of picky eating reported by parents [2]. Indeed, low eating enjoyment was found to be a an important factor in the concept of picky eating [29].

Another approach has been to use the items "did not eat well", and "refused to eat" of the Child Behavior Checklist (CBCL) [3, 28]. When comparing non-picky vs. picky eaters defined with the CBCL on eating styles measured with the CEBQ [3], picky eaters were found to demonstrate the profile of high fussiness, satiety responsiveness, emotional underrating, and less enjoyment in eating. The CBCL defined picky eaters had a lower variety of accepted foods (specifically less vegetables, fish and meat and whole grain) and a lower caloric intake. In picky eaters identified from the latent class analyses of the CEBQ a lower caloric intake and lower variety of foods was also found [38].

Taken together these findings suggest that although there is no gold standard for measuring picky eating, the operationalizations used approximate the consensus-based concept of picky eating.

### Parental report

As the assessment of picky eating is usually based on parental report, it is possible that the identification of picky eating is – at least partially – a result of parental (mis)perceptions [39], rather than an objectively quantifiable behavior. Nevertheless, several studies have found behavioral validation for picky eating [27, 40-41]. A recent study used standardized in-home meals in children from 2 to 4 years of age to reduce informant bias, and to investigate whether parental perceived picky eating correctly reflected their child mealtime behavior [19]. Picky eaters were found to have a lower variety of accepted foods, and had a lower intake compared to non-picky eaters as measured with the standardized home meal. These results emphasize that parental reports are valid in assessing picky eating status.

## Epidemiology

Prevalence estimates of picky eating are inconsistent, with a reported range between 14% - 50% in early childhood [3, 5, 37, 42] with peak prevalence at 2 years of age [37]. A recent birth cohort study in the Netherlands of children measured at 1, 3 and 6 years of age [3] revealed that prevalence was highest in early childhood (27.6%), where after it declined to 13.2% at six years of age. Almost half of the children (45.5%) were found to have picky eating problems, the amount of new picky eating cases declined at 6 years of age, and the majority of the picky eaters (32%) remitted within 3 years of age [3], which is in accordance with an earlier study [5]. A relatively small but nevertheless substantial group (4% of the general population) showed persistent picky eating problems from 1 to 6 years of age [3].

## Risk factors

Several risk factors have been identified for picky eating. Cross-sectionally lower birth weight and lower socioeconomic status were found to be associated with picky eating [42], while longer duration of exclusive breastfeeding (>6 months) and introduction of complementary foods after 6 months of age were found to reduce the risk of developing picky eating [43]. Two recent longitudinal studies in the general population further expanded the available information in this field. A study with children from 1.5 to 4.5 years of age found that lower maternal age, maternal negative affectivity, higher child emotionality, and birth order predicted picky eating [28]. In a cohort followed from pre-birth up to 6 years risk differences became clear between children with different picky eating trajectories [3]; children with picky eating problems that persisted from 1 to 6 years of age were more likely to be boys, had a lower birth

weight, and lower socioeconomic status compared to children who never had picky eating problems. The same risk factors were found for children with an onset of picky eating problems at 6 years, with the exception of gender. Children with picky eating problems between the ages of 1 and 4, but for whom the picky eating remitted before 6 years of age did not differ on risk factors compared to children who never had picky eating problems, with the exception of a modest effect on birth order. These findings suggest that birth order has a limited effect on picky eating development. The observation that, in the remitting group, no other risk factor was found, suggests that this trajectory resembles the never picky eating trajectory and therefore may be seen as part of normal development. However, longer-term outcome studies are needed to elucidate these relationships.

### Gender

There seems to be some discrepancy regarding the contribution of gender in picky eating. Most previous studies found no gender differences [5, 27, 37]. A landmark paper of 25 years ago reported higher picky eating in girls [15]. More recent trajectory analysis of picky eating [3] revealed that for the majority of picky eaters (the remitting picky eaters; 32% of the general population) gender was equally distributed, but that boys were more prevalent in the group of persisting picky eating problems. Males were also found to be more prevalent in children presenting with ARFID-like disorders [44-45]. It is possible that boys are more at risk than girls for the more problematic forms of picky eating and/or ARFID-like behavior, but in picky eating behavior that is part of normal development, as is suggested in the "remitting picky eaters", gender distribution is more equal.

## Management

### Parental considerations

As many picky eaters do not develop a clinical feeding problem, they do not receive professional help. Parents of picky eaters often turn to friends, family and media for advice [46]. However, as picky eating is a major concern for parents [5, 7], they may try different methods to get their child to eat "the right (amount of) food", such as disguising healthy foods in preferred foods, negotiating with the picky eater, using pressure to eat, giving food rewards, using coercion, or preparing separate meals altogether [2, 17, 46-47]. Several of these methods could be counterproductive: disguising foods and similar methods can in some cases increase intake [48], but in the long term could "limit opportunities for the child to become familiar with the

individual flavors of healthy and nutritious foods" and/or "reinforces the notion that healthy foods are not palatable or desirable" [47]. Also, pressure to eat has been proposed to increase picky eating behavior by reducing food enjoyment [29]. Mitchell and colleagues [46] propose that coercion and distraction undermine the ability to recognize and respond to feelings of hunger and fullness, and can even lead to over-eating. They found that methods such as restriction and using food as rewards were associated with a higher BMI and/or emotional over-eating. However, parents of picky eaters seem to be more concerned about the amount of food intake of the child [17, 46], and more often give in [47]. Parents of older picky eaters are reported to accept the picky eating behavior as a part of the child's identity, and therefore attempt to avoid struggles, by teaching the picky eater how to make their own meals to avoid interpersonal difficulties [2].

## Professional help

The most common approach to the management of picky eating is to start with nutritional education (for an elaborate review see Mitchell [46]). Summarizing; Educational group programmes for parents of children with non-clinical feeding problems focus on increasing parental knowledge, improving parenting feeding styles, and reducing negative parent-child interactions, such as coercion and parental anxiety. This, in turn has been found to reduce child feeding problems [46]. Several treatment options using internet and mobile apps are in development, with some developed by commercial parties. Overall, evidence of effectiveness for abovementioned interventions is currently lacking, thus some caution is necessary when recommending these treatment options [46].

Most treatment options regarding picky eating tend to focus on feeding disorders or feeding problems in combination with autism [49-51]. However a recent study focussed on treatment of picky eating in the general population; this so-called "Tiny Tastes" programme has a starting scientific basis to increase food acceptance in children by using small rewards to encourage children to eat novel foods [52-53]. A recent randomized control trial tested whether this intervention could be performed without direct health professional contact in preschoolers [54]. Participating families (n = 442) were randomized into the intervention arm or no treatment control condition. The intervention group received a leaflet with instructions, a progress chart, and stickers. Parents were asked to give the child a tiny piece of one vegetable daily outside mealtimes for a period of 2 weeks, introducing it as a game. If the child tried the vegetable they were rewarded with a sticker. The leaflet also increased parental knowledge and focussed on "patience and persistence". If needed an instruction video was made available online. The results showed an increase in acceptance of disliked foods. Thus, this study reaffirms the importance of repeated exposure to reduce food

neophobia, but extends on the relatively inexpensive method of leaflets to achieve this without direct intervention from a health professional. This method has the potential to be used in the educational guidelines. However, as this method has been described primarily by the authors themselves, there is a need for independent research.



# Conclusion

There has been an increase in research on picky eating in recent years. A consistent concept of picky eating is beginning to emerge, comprised of food neophobia, eating a limited variety of foods, and aberrant eating behaviors often associated with less enjoyment of food, slowness in eating, higher satiety responsiveness, and possibly tactile sensitivity. Although recent studies propose a predisposition [3, 42] to picky eating, etiology of picky eating is likely to be multifactorial. Parental anxiety, parenting stress and feeding styles probably have a bi-directional association with picky eating. Management of picky eating mostly focusses on reducing parental anxiety by nutritional education, and reducing food neophobia by repeated food exposure in the child.

## Suggestions for future research

As the concept of picky eating becomes more operationalized with greater clarity about its core characteristics, a validated gold standard measure is necessary to advance research. Additionally, more longitudinal research is needed to elucidate the causes and consequences of picky eating in order to distinguish between clinically significant problem behavior and behavior that can be considered part of normal development. Lastly, educational guidelines and treatment strategies need to be developed and assessed for their effectiveness in particular for picky eaters at risk for adverse health outcomes, but also for picky eating in general as this is a major parental concern.

# References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest


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2. * Boquin M, Moskowitz HR, Donovan SM, Lee S. Defining perceptions of picky eating obtained through focus groups and conjoint analysis. J Sens Stud 2014; 29:126-138.

   Qualitative study design to explore parental beliefs of core characteristics of picky eating.

3. * Cardona Cano S, Tiemeier H, Van Hoeken D, et al. Trajectories of picky eating during childhood: a general population study. Int J Eat Disord 2015; 48:570-579.

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This paper expands on earliers studies of the same workgroup which demonstrates that repeated exposure reduces food neophobia in the general population. This study demonstrates a cost-effective intervention method which is easily appliable in the general population.

CHAPTER 3

# Trajectories of picky eating during childhood: a general population study

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# Abstract

## Objective

This cohort study describes the prevalence of picky eating and examines prognostic factors for picky eating trajectories during childhood.

## Methods

4,018 participants of a population-based cohort with measurements from pregnancy onwards were included. Picky eating was assessed by maternal report when children were 1.5, 3 and 6 years old. The associations of child and family characteristics with trajectories of picky eating were examined using logistic regression. Never picky eaters were used as the reference group.

## Results

Prevalence of picky eating was 26.5% at 1.5 years of age, 27.6% at the age of 3 and declined to 13.2% at 6 years. Four main picky eating trajectories were defined: 1) never picky eating at all three assessments (55% of children) 2) remitting (0 - 4 years, 32%) 3) late-onset (6 years only, 4%) 4) persistent (all ages, 4%) This implies that almost two thirds of the early picky eaters remitted within 3 years. Male sex, lower birth weight, non-Western maternal ethnicity and low parental income predicted persistent picky eating. More often late-onset picky eaters were children of parents with low income and non-Western ethnicity.

## Discussion

We found that nearly half (46%) of children were picky eaters at some point during early childhood. However, remittance was very high. This suggests that picky eating is usually a transient behavior and part of normal development in preschool children. However, a substantial group of persistent picky eaters, often from a socially disadvantaged background, continues to have problems beyond the preschool age.

# Introduction



"Picky eating" is a construct that reflects eating and feeding problems, most often in children. It is a common problem during childhood [1-2]. Prevalence estimates of picky eating are inconsistent and range between 14% - 50% in preschool children [3-4], and 7% - 27% in later childhood [1-2; 5]. New onset picky eating occurs in 13% of the preschool children and decreases to 3% at age 6 years [2].

Although there is great variation in the definitions of picky eating, consuming a limited variety of foods, unwillingness to try new foods (food neophobia) and aberrant eating behaviors are accepted as characteristics of picky eating [6]. Picky eating is associated with increased behavioral problems [7], parental stress [8], anxiety and psychosocial problems in childhood [9], and in some but not all [10] studies with a higher risk of anorexia nervosa [1]. The term picky eating has also been used to describe feeding disorders such as infantile anorexia nervosa and sensory food aversion as proposed by Chatoor [11]. Recent studies [5; 7] concluded that picky eating in children of school age must be seen as a risk factor or marker for general psychopathology, rather than a precursor of an eating or feeding disorder; i.e. picky eating was cross-sectionally associated with internalizing and externalizing child behavioral problems, but not with factors associated with disturbed eating.

If the current definitions of picky eating are applied, the group of children with picky eating problems in the general population is very heterogeneous; it encompasses children for whom the picky eating could be considered as developmentally normal behavior, but also children for whom the disordered eating behavior could be classified as an avoidant/restrictive food intake disorder (ARFID) according to the criteria in DSM-5. ARFID is a new diagnostic category in the DSM-5 replacing the feeding disorder of infancy and early childhood. The main diagnostic criterion of ARFID is avoidance or restriction of food intake. It is important to differentiate between children with transient picky eating behavior and picky eaters who are at risk for a feeding or eating disorder. We hypothesize that transient picky eating is part of normal development, whereas persistent picky eaters will most likely be at risk for underlying or subsequent disorders. However, data on trajectories of picky eating throughout childhood are mostly lacking. There is a need to evaluate picky eating in the context of the child's developmental age. From a clinical point of view it is important to determine prognostic factors that allow the differentiation between transient and persistent picky eating.

Several characteristics, such as ethnicity, gender, maternal characteristics and socioeconomic status, are associated risk factors for feeding and eating disorders [12-15]. However, very few studies focused on determinants of picky eating. Shim and colleagues [16] showed that a short duration of exclusive breastfeeding and early introduction of complementary foods (4 - 6 months) were associated with the development of picky eating symptoms in preschool children. Other studies have demonstrated that low birth weight, number of siblings, low maternal age, maternal negative affectivity, and

socioeconomic status were associated with presence or persistence of picky eating in the preschool period [3; 17]. Because picky eating may be part of normal development at this age, it is important to look longitudinally beyond early childhood to determine whether these determinants also predict persistent picky eating later in childhood.

This longitudinal prospective cohort study aimed to determine the prevalence of picky eating, to identify trajectories beyond early childhood, and to determine which child and family characteristics were associated with the different groups of picky eaters. We hypothesized that prevalence is high in early childhood but has decreased by 6 years of age, and that low socioeconomic status and low birth weight are prognostic factors for picky eating problems that persist throughout childhood, but not for remitting picky eating. The definition of picky eating is not well defined, currently there is no gold standard for its measurement and validated diagnostic instruments are lacking [6]. Therefore additional analyses were performed to evaluate whether our method approximated "picky eating" as discussed by Dovey and colleagues [6].

# Method

## Study design and population

This study was embedded within the Generation R Study, a prospective population-based cohort in Rotterdam, The Netherlands [18]. Its goal is to identify environmental and genetic causes of normal-abnormal growth, development and health from fetal life onwards. All pregnant women residing in Rotterdam with an expected delivery date between April 2002 and January 2006 were invited to participate. The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, approved the study. Information about child and family characteristics was obtained by postal questionnaires filled out by parents, and from medical records of hospitals, midwives, and community Child Health Centers.

Picky eating was assessed by parental report questionnaires when children were 1.5, 3 and 6 years old [18]. Only children who were assessed for picky eating both at 6 years and at least one earlier time point (1.5 and/or 3 years) were included. Twin births (n = 179) were excluded from analysis. For 5,700 children mothers completed questionnaires at their child's age of 1.5 or 3 years. Of those, a total of 4,018 children also had an assessment at 6 years of age and thus were included in the present study (retention rate of 70.5%) (complete data on picky eating at all three waves, N = 3,227, 56.6%).

# Measures

## Identification of groups of picky eating



Previous studies have identified picky eating using a variety of instruments [6]. Currently there is no gold standard. Several studies have operationalized picky eating using a single question of the Child Feeding Questionnaire (CFQ) [2; 4; 19]; "is your child a picky eater" with the answer categories "sometimes" and "always". Dubois and colleagues [3] operationalized picky eaters as children who 1) "always" ate different meals from that eaten by other members of the family, 2) "often" refused to eat the right food or 3) "often" refused to eat. Other studies identified picky eaters [20-21] by the endorsement of the three items of the CFQ pickiness subscale; "1) my child's diet consists of only a few foods, 2) my child is unwilling to eat any of the foods that our family eats at mealtimes and 3) my child is fussy or picky about what he/she eats". The Child Behavior Checklist (CBCL) has been used previously to identify picky eaters [17].

In this study, we operationalized picky eating by two items of the CBCL that were assessed at all three measurement points. The CBCL (1.5 - 5 years) is a 99-item parent report questionnaire that assesses child emotional and behavioral problems. The Dutch CBCL has been reported to have good reliability and validity [22]. In the current study picky eating was assessed at ages 1.5, 3 and 6. Mothers were asked to indicate whether their child "does not eat well" and "refuses to eat" on a 3-point Likert scale of (1) not at all applicable, (2) sometimes, (3) often applicable. Both "refuses to eat" and "doesn't eat well" have been used and/or approximate items established in different questionnaires to identify picky eaters [3-4]. Item scores were summed (sum range: 2 - 6) and, based on previous studies [2; 4; 19], children with a score of sometimes and/or often on both items (score of $\geq 4$) were classified as "picky eater" at that age (see Supplement 3.1 for prevalence based on different cut-offs). The cut-off of 4 was chosen to include all different types of picky eating; i.e. picky eating in the general population ranging from normal behavior to subclinically or clinically significant problem behavior (possibly ARFID). Groups of picky eaters over time were defined using the CBCL cut-off. Five picky eating groups were created as follows: 1) **never picky eaters**: those who were never identified as picky eaters 2) **remitting picky eaters**: those who were picky eaters at one or both preschool assessments (1.5 and/or 3 years), but not at 6 years of age, 3) **late-onset picky eaters**, defined as new cases of picky eaters at 6 years of age, 4) **persistent picky eaters**: those who were picky eaters during all assessment waves (1.5, 3 and 6 years), 5) a **remainder category** that consisted of children who did not fit one of these trajectories: children assessed as picky eaters at 1.5 year and 6 years, but not at 3 years, and children that were picky eaters at 3 and 6 years, but not at 1.5 years. Prior to our main analyses we compared the CBCL-defined picky eaters on attributes of picky eating.

## Additional analyses

To determine whether the assessment method used at the three measurement points approximated the concept of picky eating as defined by Dovey and colleagues [6], we studied the relation of picky eating, as defined by the CBCL, to the variety of accepted foods and eating styles. The relations between picky eating to lower caloric intake and number of foods consumed were also measured, as in earlier studies [6; 19; 21], these were suggested as patterns of picky eating. When children were 14 months old their dietary intake was assessed with the Food Frequency Questionnaire (FFQ) [23] completed by parents. This measure assesses children's food intake based on the frequency and type of food consumed over the past 4 weeks. The food items were classified into 12 different food groups: refined grain products, wholegrain products, dairy products, formula, pasta/rice/potatoes, vegetables, fruit, fish/seafood, meat, confectionary, savory snacks, and composite dishes (see Supplement 3.2). The item scores were combined to indicate variety and total number of foods consumed, as well as total caloric intake following the approach of Kiefte-de Jong et al [24]. When children were 4 years old, their eating behavior was assessed with the Dutch version of the Children's Eating Behavior Questionnaire (CEBQ [25], for a description of the Dutch version used in the current study see Jansen et al.) [26], completed by parents. The CEBQ is a 35-item instrument designed to assess variation in eating style among children. The items are scored on a 5-point Likert scale from 1 'never' to 5 'always'. The CEBQ consists of seven subscales, four of which measure food approach behaviors: emotional overeating, enjoyment of food, food responsiveness, and desire to drink. The other three subscales quantify food-avoidant behavior: emotional undereating, satiety responsiveness, and fussiness. Higher scores on each subscale indicate more of the respective behavior assessed by the subscale. The CEBQ has good psychometric properties, such as good internal consistency (Cronbach's alpha 0.72 - 0.91), construct validity and test-retest reliability (correlation coefficient 0.52 - 0.87) [27].

Picky eaters defined with the CBCL differed significantly on variability of food intake from non-picky eaters in a number of food groups measured at the age of 14 months (see Table 3.1). Picky eaters ate fewer whole grain products ($\chi^2$ = 16.42, $p$ < 0.001), rice and pasta ($\chi^2$ = 15.89, $p$ < 0.001), vegetables ($\chi^2$ = 30.21, p < 0.001), fish ($\chi^2$ = 4.93, $p$ = 0.026), meat ($\chi^2$ = 9.46, $p$ = 0.002) and confectionary ($\chi^2$ = 6.24, $p$ = 0.013). No difference was found on refined grain products, dairy, formula, fruit, savory snacks and composite dishes. Picky eaters also ate a lower total number of foods (t = 4.8, $p$ < 0.001) and had a lower total caloric intake (t = 2.8, $p$ = 0.02).

Table 3.1 | Eating variability of picky eaters

| Age 1 | Non-picky eaters n=2,421 | Picky eaters n=840 | $Chi^2$ |
|---|---|---|---|
| Refuses | Percentage [a] | Percentage [a] | p-value |
| Refined grain | 58.9 | 58.8 | 0.95 |
| Whole grain | 10.6 | 15.8 | **<0.001** |
| Dairy | 29.3 | 32.5 | 0.08 |
| Formula | 31.4 | 29.2 | 0.22 |
| Rice/Pasta | 16.6 | 22.8 | **<0.001** |
| Vegetables | 36.0 | 46.7 | **<0.001** |
| Fruit | 3.8 | 4.9 | 0.19 |
| Fish | 86.0 | 89.1 | **0.03** |
| Meat | 58.7 | 64.8 | **0.002** |
| Confectionary | 4.1 | 6.2 | **0.01** |
| Savoury snacks | 87.0 | 87.1 | 0.91 |
| Composite dishes | 21.9 | 24.1 | 0.20 |
| | Mean (SE) | Mean (SE) | |
| Number of foods | 15.8 (0.11) | 14.7 (0.19) | **<0.001** |
| Total caloric intake | 1,329 (8.15) | 1,293 (14.05) | **0.02** |

Food intake measured with the Food Frequency Questionnaire at 1 yr of age over the past 4 weeks.
Picky eating measured at 1.5 yrs of age.
[a] Results are given as the percentage of children who did not eat at least 10 grams in that specific subgroup.

As expected picky eating was associated with aberrant eating styles measured at the age of 4 years. Picky eaters were found to be more fussy ($t = -57.8$, $p < 0.001$), had a higher satiety response ($t = -57.1$, $p < 0.001$), and a lower enjoyment of food ($t = 42.3$, $p < 0.001$). They also were found to have more emotional under eating ($t = -17.6$, $p < 0.001$), a higher desire to drink ($t = -4.3$, $p < 0.001$), and a lower food responsiveness ($t = 12.6$, $p < 0.001$) (see Table 3.2).

Our results demonstrate that picky eaters identified with the CBCL indeed showed a pattern of fussy eating with avoidance of specific food types and consumption of limited amounts of foods. This is in accordance with earlier studies [5; 7]. The picky eating status defined by the CBCL correlates well with other measures of picky eating. Unlike another study [4] picky eaters in our study had fewer difficulties with mixed dishes. We must be cautious in speculating about clinical implications as our definition of picky eating includes children with “sometimes” picky eating problems and/or transient picky eating behavior.

Table 3.2 | Eating behavior of picky eaters

| | Non-picky eaters n=3,798 | Picky eaters n=1,127 | $Chi^2$ |
|---|---|---|---|
| | Mean(SD) | Mean (SD) | p-value |
| Food fussiness | 2.67 (0.66) | 3.91 (0.56) | <0.001 |
| Satiety response & Slowness in eating | 2.88 (0.51) | 3.82 (0.41) | <0.001 |
| Enjoyment of food [a] | 3.57 (0.63) | 2.66 (0.64) | <0.001 |
| Food responsiveness [a] | 1.85 (0.71) | 1.56 (0.55) | <0.001 |
| Emotional undereating [a] | 2.64 (0.82) | 3.13 (0.81) | <0.001 |
| Emotional overeating [a] | 1.46 (0.61) | 1.47 (0.61) | 0.525 |
| Desire to drink [a] | 2.50 (0.91) | 2.64 (1.05) | <0.001 |

Eating behavior measured with the CEBQ at 4 yrs of age.

Picky eating measured at 3 yrs of age.

[a] Due to missings, n differed slightly between groups.

Enjoyment of food n=4,912;, Food responsiveness n=4,923; Emotional undereating n=4,895; Emotional overeating n=4,869; Desire to drink n=4,890.

## Child and parental characteristics and sociodemographic information

Information about child's sex and birth weight was obtained from midwife and hospital registries. Parental BMI, ethnicity, age at intake, educational level, family income, child's birth order, duration of breastfeeding, introduction of fruits/vegetables, and maternal smoking habits during pregnancy were assessed by postal questionnaire. Birth weight is given in kilograms, gestational age at birth in weeks, and BMI in body-weight/height2 ($kg/m^2$). Birth order was defined as firstborn or later born. Maternal ethnicity was coded as Dutch, Moroccan, Turkish, a combined code (Sur/Ant/Cape) for mothers with a Surinamese, Dutch Antillean or Cape Verdian ethnicity, other Western and other non-Western. Maternal educational level was coded as high (some college or university education), middle (secondary education), or low (primary education or none). Family income per month was coded as high (above median income; >2200 euro), middle (1200-2200 euro), or low (<1200 euro). Duration of breastfeeding was coded as shorter or longer than 6 months. Introduction of fruits/vegetables was defined as before or after 6 months. Maternal smoking was coded as no (no smoking during pregnancy), stopped (stopped smoking when pregnancy was known), and continued (continued smoking during pregnancy).

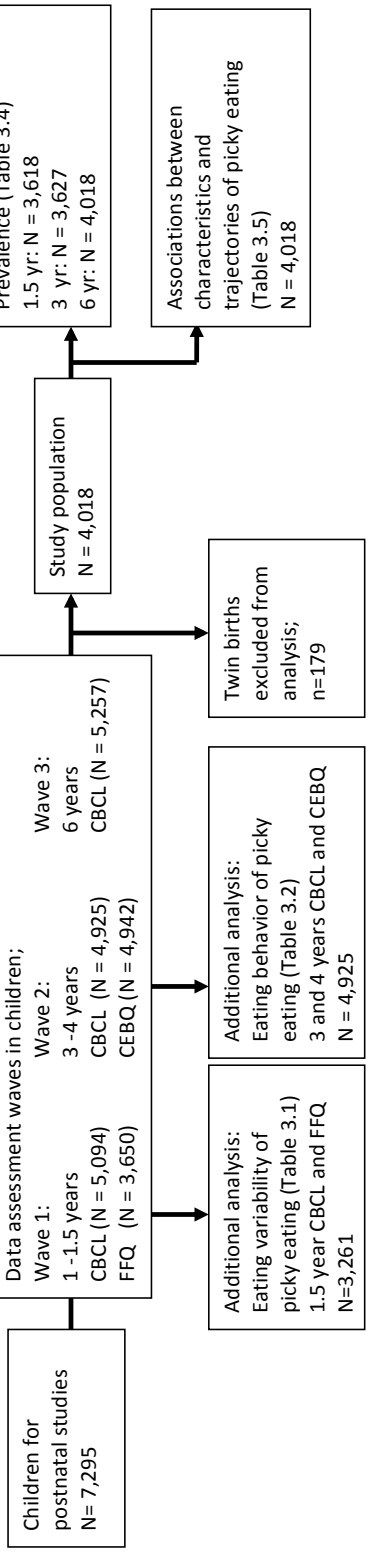


Figure 3.1 | Flow diagram of this study

## Statistical analysis

See Figure 3.1 for a flow diagram of the study design and analyses.

Prevalence was defined as the percentage of picky eaters at each wave (N = 3,618, N = 3,627 and N = 4,018 at ages 1.5, 3 and 6 years respectively). New cases were defined as picky eaters at wave 2 or 3 who had not previously been identified as such. Prevalence of the trajectories was defined as the percentage of children in a picky eating group out of the total study population (N = 4,018, including the remainder category).

We then used multivariate multinomial logistic regression analyses to identify child and family characteristics that predict different trajectories of picky eating during childhood. The groups of trajectories of picky eating were used as the dependent variable, with the exception of the remainder category (n = 199; 5.0% of the study population), which was excluded. Child's sex, birth weight, BMI of mother, maternal ethnicity, maternal educational level, family income, birth order and smoking during pregnancy were used as independent variables. Because birth weight is strongly associated with gestational age at birth, the latter was included in the model as a confounder. Other variables such as paternal age and breastfeeding were not included in the final model as the observed effects did not change when controlling for these variables. The number of missings ranged from 2 for weight at birth to 977 for BMI of mother before pregnancy. Missing values on the covariates were estimated using multiple imputation techniques. Analysis as complete case analysis (N = 2,168) gave similar results compared to analysis after multiple imputation (results not shown). The presented results are based on pooled estimates of five imputed datasets. Analyses were performed using STATA/SE 12.0.

# Results

## Study population and non-response analysis

Child and family characteristics are presented in Table 3.3. Fifty percent of the sample consisted of boys. Compared to the ethnic population in Rotterdam [18], our study population had a higher percentage of Dutch mothers (66.6%), while Moroccan mothers (2.7%) were more underrepresented compared to Turkish (5.2%) and mothers of Surinamese, Antillean or Cape Verdian origin (8.7%). As described earlier [18] household income and education levels on average were higher than in the whole study area as is common in large scale cohort studies.

Comparison of responders and non-responders indicated that data on picky eating were more often missing in children with mothers of non-Dutch origin, ($\chi^2$ = 609, $p$ < 0.001) with lower education ($\chi^2$ = 369, $p$ < 0.001), lower income ($\chi^2$ = 444, $p$ <

Table 3.3 | Population characteristics

| N=4,018 | | Percentage or mean |
|---|---|---|
| Child characteristic | | (unless otherwise indicated) |
| Sex | Boy | 50.3 |
| | Girl | 49.7 |
| Birth weight | Normal weight | 80.5 |
| | Underweight | 3.8 |
| | Overweight | 15.7 |
| Gestational age at birth | Aterm | 88.1 |
| | Preterm | 4.5 |
| | Postterm | 7.4 |
| Birth order | Firstborn | 58.6 |
| | Later born | 41.4 |
| Parental characteristic | | |
| Age mother (years) [a] | Mean (SD) | 31.6 (4.5) |
| Age father (years) [a] | Mean (SD) | 33.8 (5.1) |
| BMI mother (weight/length$^2$) [b] | Normal | 67.5 |
| | Underweight | 4.5 |
| | Overweight | 28.0 |
| Maternal ethnicity | Dutch | 66.6 |
| | Moroccan | 2.7 |
| | Turkish | 5.2 |
| | Sur/Ant/Cape [c] | 8.7 |
| | Other Western | 8.9 |
| | Other non-Western | 7.8 |
| Maternal educational level [d] | High | 67.6 |
| | Middle | 29.5 |
| | Low | 3.0 |
| Family income | High | 68.0 |
| | Middle | 22.6 |
| | Low | 9.4 |
| Duration of breastfeeding | Shorter than 6 months | 62.2 |
| | Longer than 6 months | 37.8 |
| Introduction of fruits/vegetables | Before 6 months | 97.1 |
| | After 6 months | 2.9 |
| Smoking during pregnancy | No | 78.9 |
| | Stopped at pregnancy | 9.2 |
| | Yes | 12.0 |

[a] At intake.

[b] Before pregnancy.

[c] Suriname / Antillean / Cape Verdean.

[d] Highest followed.

0.001), smoking during pregnancy ($\chi^2$ = 51, $p$ < 0.001), a higher BMI before pregnancy (t = 5.1, $p$ < 0.001), and younger age (t = -21.4, $p$ < 0.001). Children with missing data were less often firstborn ($\chi^2$ = 29, $p$ < 0.001), and were lighter at birth (t = -9.1, $p$ < 0.001). No differences were found with respect to child's sex.

## Prevalence

Prevalence of picky eating was 26.5% at 1.5 years of age and 27.6% at the age of 3 years; at 6 years of age it declined to 13.2% ($\chi^2$ = 293, $p$ < 0.001) (see Table 3.4). Among the 2,389 children who were not defined as picky eaters at 1.5 years, 474 new cases were found at 3 years. At 6 years 111 new cases were found among the remaining 1,915 non picky eaters. No difference was found in prevalence by child's sex.

The proportion of never picky eaters was 54.5% (95% CI 53.0 - 56.1%), 4.2% (95% CI 3.6 – 4.8%) were persistent picky eaters, 4.0% (95% CI 3.4 – 4.6%) were late onset picky eaters, 5.0% (95% CI 4.3 – 5.7%) formed the remainder category, and 32.3% (95% CI 30.8 – 33.7%) were remitting picky eaters. Of the latter group most children remitted within three years; 12.2% of the total population were picky eaters at 1,5 years and remitted before 3 years, and 11.3% of the total population were picky eaters at 3 years but remitted before 6 years. Only a small portion of children (8.8% of the total population) had picky eating problems throughout early preschool; those children were picky eaters at both 1.5 and 3 years but not at 6 years of age. Thus 72.8% of the remitting picky eaters, and 64.1% of the early preschool picky eaters (persistent and remitting picky eaters combined), remitted within three years.

Table 3.4 | Prevalence of picky eating

| Age (yrs) | Sex | Total (N) | Picky eaters (n) | Prevalence (95% CI) |
|---|---|---|---|---|
| 1.5 | Boy | 1,811 | 477 | 26.3 (24.4-28.4) |
| | Girl | 1,807 | 480 | 26.6 (24.6-28.7) |
| | Total | 3,618 | 957 | 26.5 (25.1-27.9) |
| 3 | Boy | 1,813 | 515 | 28.4 (26.4-30.5) |
| | Girl | 1,814 | 485 | 26.7 (24.8-28.8) |
| | Total | 3,627 | 1,000 | 27.6 (26.1-29.1) |
| 6 | Boy | 2,022 | 282 | 14.0 (12.5-15.3) |
| | Girl | 1,996 | 248 | 12.4 (11.1-16.2) |
| | Total | 4,018 | 530 | 13.2 (12.2-14.3) |

N= total population; n=number of prevalent cases; CI = confidence interval.

Table 3.5 | Multinomial regression table – Associations of child, parental and sociodemographic determinants with picky eating trajectories

| | | | PICKY EATING TRAJECTORIES | | |
|---|---|---|---|---|---|
| | | Never N= 2,192 | Remitting N=1,296 | Late-onset N=161 | Persistent N=169 |
| | | | Relative Risk Ratio (95% CI) | Relative Risk Ratio (95% CI) | Relative Risk Ratio (95% CI) |
| Sex | Girl | Ref | 1 | 1 | 1 |
| | Boy | Ref | 1.00 (0.86-1.17) | 1.06 (0.74-1.52) | **1.43 (1.01-2.04)*** |
| Weight at birth | | Ref | 0.85 (0.71-1.01) | 1.25 (0.85-1.84) | **0.54 (0.35-0.82)**** |
| Age mother | | Ref | 0.99 (0.98-1.01) | 1.03 (0.99-1.07) | 1.01 (0.97-1.05) |
| BMI before pregnancy | | Ref | 1.01 (0.99-1.03) | 1.00 (0.96-1.05) | 1.01 (0.97-1.06) |
| Maternal ethnicity | Dutch | Ref | 1 | 1 | 1 |
| | Moroccan | Ref | 1.10 (0.68-1.79) | 2.38 (0.98-5.89) | **2.37 (1.02-5.53)*** |
| | Turkish | Ref | 1.23 (0.81-1.51) | **2.55 (1.11-5.87)*** | **6.43 (3.48-11.86)***** |
| | Sur/Ant/Cape [p] | Ref | 1.14 (0.86-1.51) | **2.38 (1.35-4.17)**** | **1.97 (1.11-3.49)*** |
| | Western | Ref | 0.99 (0.75-1.32) | 1.57 (0.87-2.83) | 1.56 (0.86-2.85) |
| | Other non-Western | Ref | 1.15 (0.86-1.54) | 1.41 (0.70-2.85) | **2.04 (1.04-3.97)*** |

Table 3.5 (continued)

| | | PICKY EATING TRAJECTORIES | | | |
|---|---|---|---|---|---|
| | | Never<br>N= 2,192 | Remitting<br>N=1,296<br>Relative Risk Ratio<br>(95% CI) | Late-onset<br>N=161<br>Relative Risk Ratio<br>(95% CI) | Persistent<br>N=169<br>Relative Risk Ratio<br>(95% CI) |
| Education mother | Low | Ref | 1.24 (0.53-2.89) | 1.30 (0.52-3.27) | 0.94 (0.37-2.38) |
| | Middle | Ref | 1.03 (0.87-1.24) | 1.14 (0.73-1.77) | 1.14 (0.75-1.72) |
| | High | Ref | 1 | 1 | 1 |
| Income | Low | Ref | 1.15 (0.82-1.62) | 2.41 (1.37-4.24)** | **2.53 (1.35-4.72)**** |
| | Middle | Ref | 1.11 (0.89-1.38) | 1.37 (0.80-2.33) | **1.75 (1.13-2.70)*** |
| | High | Ref | 1 | 1 | 1 |
| Birth order | Firstborn | Ref | 1 | 1 | 1 |
| | Later born | Ref | **0.79 (0.67-0.92)**** | 1.14 (0.79-1.65) | 1.01 (0.70-1.45) |
| Smoking | No | Ref | 1 | 1 | 1 |
| | Stopped | Ref | 0.92 (0.70-1.20) | 1.06 (0.58-1.91) | 0.74 (0.38-1.46) |
| | Continued | Ref | 1.03 (0.81-1.31) | 1.34 (0.62-2.90) | 1.17 (0.64-2.12) |

### Comparison of trajectory groups of picky eating

The results of the multinomial regression analysis are given in Table 3.5. The never picky eating group was used as the reference group.

The persistent picky eating group differed on child, parental and sociodemographic characteristics compared to never picky eaters. Boys were more likely to be persistent picky eaters (relative risk ratio [RRR] = 1.43, $p = 0.05$). With every kilogram increase in birth weight the odds of being a persistent picky eater was reduced by a factor of 0.54 (RRR = 0.54, $p < 0.01$). Non-Western maternal ethnicity was more often associated with persistent picky eating (RRR = 6.42, $p < 0.001$ for Turkish vs. Dutch; RRR = 2.37, $p = 0.045$ for Moroccan vs. Dutch; RRR = 1.97, $p = 0.02$ for Suriname / Antillean/ Cape Verdian vs. Dutch; RRR = 2.04, $p = 0.04$ for non-Western vs. Dutch), as was lower parental income (RRR = 2.53, $p < 0.01$ for low vs. high income; RRR = 1.75, $p = 0.01$ for middle vs. high income). The remitting picky eating group did not differ except on birth order. Being a younger sibling reduced the odds of being a remitting picky eater (RRR = 0.79, $p < 0.01$ for later born vs. firstborn). Late-onset picky eating differed only on sociodemographic determinants; i.e. for a low versus a high parental income the relative risk for late-onset picky eating was increased (RRR = 2.41, $p < 0.01$). The relative risk for Turkish and Suriname / Antillean/ Cape Verdian versus Dutch mothers was increased for late-onset picky eater (RRR = 2.55, $p = 0.03$ for Turkish vs. Dutch; RRR = 2.38, $p < 0.01$ for Sur/Ant/Cape vs. Dutch).

## Discussion

Our results demonstrate that using two eating-related items of the CBCL approximates the concept of picky eating. Picky eating was found to be very common in preschool age children. Prevalence of picky eating was highest at 3 years of age (27.6%) and lowest at 6 years of age (13.2%). Almost two thirds of the early picky eaters remitted within 3 years. This suggests that picky eating in preschool children is a transient behavior which may be seen as part of normal development. More than half of the children never had picky eating problems. However, a group of picky eaters continues to have problems at the age of 6. A substantial group of children (4.2%) shows persistent picky eating. Also, a similar percentage (4.0%) starts to be picky after the preschool period.

Our data confirm earlier findings on prevalence [1; 4-5] showing that picky eating is predominantly present in preschool children. The prevalence estimates vary greatly in literature. The use of different methods for identifying picky eating may explain this. Furthermore, Mascola et al. [2] demonstrated that the incidence of picky eating decreases after preschool age, and that although the incidence was low, the prevalence remained relatively stable thereafter. The latter implies that late-onset picky eating could be a more persistent behavior.

The lack of predictive risk factors for remitting picky eating is another indication that picky eating in the preschool age is part of normal development. No differences were found between the remitting and never picky eaters on child's sex, birth weight, parental ethnicity or family income. The risk of remitting picky eating was not predicted by any of the child and family characteristics we tested. Only birth order differed modestly between these groups: firstborns were more often remitting picky eaters. Older siblings may have a small but protective effect on younger siblings in becoming picky eaters. Siblings who have passed the picky eating phase may function as a role model for younger siblings. Or younger children could be "modeled" to follow the preferred family routine. The protective effect of older siblings is consistent with earlier studies that showed that siblings and peers have a positive effect on children's eating behavior [28-30]. Another explanation for this effect may be found in the reporting pattern of the mother. Maternal overprotection is known to decrease with the number of children [31]. Thus, maternal worry about her child's eating in a younger sibling may decrease due to the experience gained with an older child. It is also important to note that mothers could also have changed their feeding practice in order to improve food intake of their child, as an earlier study [32] demonstrated that mothers were not likely to give their children disliked foods. This could result in an incorrect classification of some children as "remitting"; i.e. a child may still have picky eating problems, but parents manage this by offering accepted food types.

During early childhood the child is transitioning from non-solid foods to different types of solid foods and textures. Early taste experiences such as food flavors transmitted through breast milk and the introduction of solid foods [16; 33] may influence eating behaviors. However, a child's food preferences and food neophobia seem highly heritable [34-36]. It has been postulated that for toddlers there is an evolutionary advantage to being a picky eater [37]. When the child becomes more mobile being a picky eater reduces the chance of an intoxication by ingestion of unsafe foods. When the child is older, it develops more cognitive capacities and is capable of more top-down control. The child can then safely expand his food preferences. When this process is disturbed, children may develop persistent picky eating.

We found that several child and family factors predicted the risk of persistent picky eating. Child's sex had a small but significant association with persistent picky eating: among the persistent picky eaters there were relatively more boys compared to the never picky eaters. This could be an indication that boys are more at risk of severe picky eating; it has been observed that boys are overrepresented in a sample of selective eaters [38]. Our study also confirms the findings of Dubois [3] that a lower birth weight and insufficient income were associated with persistent picky eating in preschool children (2.5-4.5 years of age). One possible explanation is that a low income may lead to a reduced access to fruit and vegetables [39], which in turn can lead to insufficient familiarity with those food types, thus promoting picky eating. Also, a lower birth weight could fuel unrealistic feeding expectations of concerned mothers,

who will then more easily assess their child as a picky eater. Another possibility is that, as Dubois mentioned [3] a low birth weight could be an indication of a biological predisposition or alteration that promotes picky eating.

Although low family income and maternal ethnicity were also found to predict late-onset picky eating, no child characteristics were found to be a risk factor. We propose that late-onset picky eating might reflect the influence of child-parent interactions and environmental factors rather than a child's predisposition to food aversion and food refusal as seen in persistent picky eaters. Indeed, child-parent interaction and different parenting styles can influence feeding behavior [40] and can be an important risk factor. One study found that picky eating between 5 - 7 years was associated with more emotional, behavioral and somatic functional problems [5]. Against this background, we carefully speculate that children with picky eating problems at 6 years (both the persistent and late-onset picky eaters) are at higher risk of adverse health outcomes than non-picky eaters. This could include more behavioral problems and/or feeding and eating disorders in later childhood [1; 5; 7]. More research is needed to elucidate this.

Finally, an intriguing finding was that the children with a non-Western background, particularly those of Turkish descent, had the highest relative risk of persistent picky eating. Various studies in different countries have demonstrated consistently that migrant status affects dietary feeding patterns e.g. children with a migration background in Germany showed different eating habits than the native population [41-42]. In the Netherlands, non-Western migrants were found to have less favorable micronutrient intake than Dutch children [43]. Migrant children with traditional cultural orientations were less likely to be overweight or obese than children who had an integrated or marginalized cultural orientation [44]. Migration thus seems related to dietary eating habits through acculturation and cultural identity. In this case both migration and picky eating, while usually associated with a lower weight, could lead to obesity; i.e. non-Western picky eaters eat a smaller variety of foods, yet have an increased caloric intake leading to obesity. This is strengthened by the fact that prevalence of picky eating in Turkish children in their native country was similar to that found in other prevalence studies [45]. Genetic make-up, parental feeding practices, environmental influences and/or cultural and migration problems are all potential mediating factors of this ethnicity effect. As yet, the underlying mechanisms for a higher risk for persistent and late-onset picky eating in children with a non-Western ethnicity, and more specifically why Turkish children have an increased relative risk compared to other non-Western ethnicities, remain unclear.

## Strengths and limitations

The strengths of this study are the large sample size of children included, its population-based longitudinal design and the extensive data collection on many potential determinants of the trajectories of picky eating. Some limitations should also be discussed.

First, we used a new method (2 items on the CBCL) to identify picky eating. Currently there is no gold standard for picky eating, and different studies have identified picky eaters using different methods, most relying on 1 to 3 questions [6]. We compared our measure of picky eating with other instruments used for this purpose. Parental endorsement of the CBCL-items "my child refuses to eat" and "my child doesn't eat well" correlated well with our other, single-point, measures of picky eating. The convergence indicates that our definition is a valid approximation of the concept.

A second limitation is that the non-response analysis showed a selective non-response of Non-Dutch and low income families. The generalizability of our findings to different populations might therefore be limited.

## Clinical implications

There seems to be a discrepancy between parents' experienced concern about picky eating and health professionals' views. Commonly, health professionals tend to regard picky eating as a transient phase of the development of the preschool child [9]. However, many parents of picky eaters seek medical help for their children's pickiness [46-47], and express frustration with physicians for dismissing their concerns [48]. We argue that indeed picky eating between the ages of 0 and 4 years may in general be considered as part of normal development. For the majority of picky eaters in preschool age picky eating will remit by the age of 6. However, we emphasize that there is a non-negligible group of persistent and late-onset picky eaters who deserve the attention and consideration of clinicians. Although male sex, low birth weight, low income and non-Western maternal origin were found to be risk factors, those are not specific enough to be used in a clinical setting. As a guideline, health care professionals could focus on a duration > 3 years of picky eating, non-Dutch (non-Western) descent and low family income to monitor for risk at becoming a persistent picky eater. The consequences of persistent and late onset picky eating for (adverse) health outcomes, including the degree of distress it causes, are yet to be determined.

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# Supplementary material

Supplement 3.1

S3.1 | Prevalence of picky eating with different cut-offs

| Age (yrs) | Total N | Cut-off ≥4 n (%) | Cut-off ≥5 n (%) | Cut-off =6 n (%) |
|---|---|---|---|---|
| 1.5 | 3,618 | 957 (26.5) | 159 (4.4) | 57 (1.6) |
| 3 | 3,627 | 1,000 (27.6) | 218 (6.0) | 76 (2.1) |
| 6 | 4,018 | 530 (13.2) | 148 (3.7) | 39 (1.0) |

N= total population;, n=number of prevalent cases.

Supplement 3.2

| Food group | Included food item |
|---|---|
| Refined grain products | Waffles, rusk, crackers, currant bread, currant buns, white buns croissant, white bread or baguette, cornflakes, low fiber breakfast cereal |
| Whole grain products | Whole-bran bread or baguette, whole-bran buns, oatmeal, muesli, multi-grain breakfast cereal |
| Dairy | All cheeses, milk (except soy milk), yoghurt, French cheese, custard (excluding chocolate milk or sweetened yoghurt drinks) |
| Formula | All formula |
| Pasta/rice/potatoes | Pasta, rice, and potatoes (boiled, baked or mashed) |
| Vegetables | Vegetables (raw, boiled, or baked) |
| Fruit | Fruit and fruit compote (excluding juice) |
| Fish/seafood | Fish and seafood (excluding fishfingers, which are included in the “savory snacks” category) |
| Meat | All processed and non-processed meat (except meat-containing snacks such as chicken-nuggets which are included in the “savory snacks” category) |
| Confectionary | Dutch spiced honey cake. sweetened or chocolate containing desserts, chocolate containing sandwich spread, ice cream, cakes, cookies, biscuits, chocolate, pastries, pancakes, candy |
| Savory snacks | Chips, toast with cheese or pâté, sausage rolls, spring rolls, meat rolls, meat croquettes, sate, salted peanuts and nuts, hamburgers, chicken nuggets, fried chips and fried potatoes (i.e. French fries) |
| Composite dishes | Ready to eat infant meals, and ready to eat cooled or frozen meals |

CHAPTER 4

# Are parents' anxiety and depression related to child fussy eating?

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# Abstract

## Objective

To examine the association between parental anxiety and depression with child fussy eating – that is, consistent rejection of particular food items.

## Method

This study was embedded in Generation R, a prospective cohort from fetal life onwards in the Netherlands.
SETTING: Population-based.
PARTICIPANTS: 4,746 four-year-old children and their parents.
EXPOSURE: Parental internalizing problems (i.e. symptoms of anxiety and depression) were assessed with the Brief Symptoms Inventory during pregnancy and the preschool period (child age three years).
MAIN OUTCOME MEASURE: The food fussiness scale of the Children's Eating Behaviour Questionnaire.

## Results

Maternal anxiety during pregnancy and during the child's preschool period was related to higher food fussiness sum-scores in children. For instance, per point on the anxiety scale in pregnancy, children had on average a 1.02 higher sum-score (95% CI 0.59 - 1.46) on the food fussiness scale, after adjustment for confounders. Likewise, mothers' depressive symptoms at both time points were associated with fussy eating behavior in their children (e.g. in the antenatal period: per point on the depression scale, children had a 0.91 point higher on the food fussiness scale, 95% CI 0.49 - 1.33). We found largely similar associations between fathers' internalizing problems and children's fussy eating. However, fathers' anxiety during the antenatal period was not related to child fussy eating.

## Conclusions

Maternal and paternal internalizing problems were prospectively associated with fussy eating in preschoolers. Healthcare practitioners should be aware that non-clinical symptoms of anxiety and depression in parents are risk factors for child fussy eating.

## Key points

### *What is already known*

- Fussy eating behavior, characterized by consistently rejecting particular food items, is a common problem in childhood causing major concerns among parents.
- Maternal postnatal anxiety and depressive symptoms have been related to child fussy eating.
- It is unclear whether maternal internalizing problems are risk factors for child fussy eaters or rather a result of child fussy eating behavior.

### *What this study adds*

- Mothers' antenatal anxiety symptoms predict child fussy eating independent of mothers' postnatal anxiety symptoms
- Also mothers depressive symptoms during pregnancy and three years later were associated with more fussy eating in their children.
- We found indications that fathers' internalizing problems are related to children's fussy eating.

# Introduction

Fussy eating is characterized by consistent rejection of particular foods, which results in a restricted diet variety [1], causing major concerns among parents [2]. Child fussy eating has been associated with functional constipation [3], weight problems [4], and behavioral problems [5]. Previous research suggested parental controlling feeding [4], and parental physical and mental health problems [6] as potential risk factors for fussy eating (also called 'picky' or 'selective' eating). However, the etiology of fussy eating is not well understood [6].

It is well known that internalizing psychiatric problems of parents (i.e. anxiety and depression) are related to problematic child development [7], including disturbed eating behaviors [8, 9]. A complex interplay of multiple factors such as genetics, disturbed parent-child interaction, and modeling of parent behavior account for the increased risk of problems in children [7], and may also affect children's fussy eating. Maternal internalizing problems have been related to fussy eating in preschool-aged children in population-based studies [6, 10]. Maternal internalizing problems during the child's preschool period have been found to be predictive for persistent fussy eating at a later age [11]. Farrow and Blissett, however, have reported that antenatal and postnatal maternal psychiatric symptoms did not predict fussy eating in six-month-old children [12].

Most studies focused on symptoms during the child's preschool period. This is a sensitive period in development, but the Barker hypothesis [13] highlights the need to also study antenatal anxiety and depression. Another advantage of studying internalizing problems in the antenatal period is that the association with children's fussy eating is less prone to reverse causation – that is, children's fussy eating is not likely to affect their mothers' problems during pregnancy. In addition, most previous studies were limited in their reliance on maternal reports of both exposure (internalizing problems) and outcome (child fussy eating) [6, 10, 11, 14]. Consequently, reported associations may be overestimated due to reporter bias as the depression-distortion hypothesis states that mothers with psychiatric problems might have a biased perception of their child's behavior [15]. Last, most studies focused on mothers' anxiety and depression, without studying the effects of fathers' symptoms.

The current study's objective was to examine whether maternal and paternal internalizing problems are prospectively associated with children's fussy eating, using multiple informants of child eating behavior. More specifically, we aimed to evaluate the role of anxiety and depressive symptoms in the antenatal and preschool period.

# Material and methods

## Study design and procedure

This study was embedded in Generation R, a population-based prospective cohort from fetal life onwards [16, 17]. Pregnant women living in Rotterdam, the Netherlands, with a delivery date between April 2002 and January 2006 were invited to participate (response rate: 61%). The local medical ethics committee has approved the study. Sociodemographic information was collected by postal questionnaires during pregnancy and from medical birth records completed by gynecologists and midwives. Parental internalizing problems were assessed by postal questionnaire during mid-pregnancy, and again when the child was three years old. At three and four years of age, parents filled in postal questionnaires including an assessment of their children's eating behavior. More detailed information about the design and procedure is available elsewhere [16].



## Participants

Parents of 7295 children gave full consent for the preschool phase of Generation R. Those with missing data on the food fussiness scale of the Children's Eating Behaviour Questionnaire (CEBQ) were excluded (N = 2355). Of the remaining parent-child dyads, 194 participants had missing values of maternal anxiety or depression during pregnancy and three years later, yielding a sample size of 4746 children and mothers. The population for analysis with fathers' anxiety or depression was smaller (N = 4144), as 602 participants had missing values for fathers' anxiety or depression on both time points.

# Measures

## Parental anxiety and depressive symptoms

Anxiety and depressive symptoms of both mothers and fathers were assessed with the Brief Symptom Inventory (BSI) at two time points: during mid-pregnancy and three years later. The BSI is a validated 53-item self-report questionnaire assessing a spectrum of psychological problems in the preceding seven days [18, 19]. We used the anxiety scale (e.g. 'feeling fearful') and the depression scale (e.g. 'feeling lonely'). Each scale consists of six items rated on a 5-point Likert-scale from 0 (not at all) to 4 (extremely). For each scale, mean-scores were calculated, with higher scores indicating more problems.

## Child fussy eating behavior

At age four years, fussy eating was assessed with the CEBQ, a validated parent report questionnaire [20]. The CEBQ consists of eight subscales, containing 35-items on which parents rate the frequency of their children's eating behaviors. We used the subscale food fussiness, which consists of six items covering children who are difficult to please with meals, who display food neophobia (e.g. 'My child refuses new foods at first'), and who have a limited diet variety (e.g. 'My child enjoys a wide variety of foods', reverse coded). Each item was answered on a Likert-type scale from 1 (never) to 5 (always). Scale sum-scores were calculated, with higher scores indicating more food fussiness (range: 6 - 30). To facilitate comparison with other studies, we also calculated the mean score of this scale.

As most CEBQs were filled out by mothers (~88%), we also used the Child Behavior Checklist for toddlers (CBCL / 1 ½ - 5) [21] for which we had multiple informants. Two items were used as a proxy for fussy eating: (1) 'does not eat well' and (2) 'refuses to eat' in the past two months. These questions were answered by both mothers and fathers when the children were three years old. Items were rated on a 3-point Likert scale from 1 (not true) to 3 (often true). Sum-scores were calculated (range 2 - 6) and children with a score of ≥ 4 were classified as 'fussy eaters' [22].

## Confounders

During pregnancy, questionnaires were used to assess sociodemographic characteristics: parental age, family income, parental ethnic background (based on country of birth of parents and grandparents), parental educational level, marital status, and parity (defined as number of live births mothers delivered before birth of the participating child). Mode of delivery, sex of child, and birth characteristics (birth weight and gestational age) were obtained from medical records.

## Statistical analysis

We used separate linear regression analyses to test whether higher scores of mothers' anxiety and depression on the BSI at each time point (during pregnancy, and at three years postnatal) were related to higher sum-scores on the CEBQ's food fussiness scale. We also tested the independent effects of maternal internalizing problems on child food fussiness by analyzing the two time points in the same model. In addition, we explored whether fathers' anxiety and depression scores at each time point were related to food fussiness, using separate linear regression analyses. All antenatal models were adjusted for sociodemographic characteristics. All models with postnatal

internalizing symptoms were additionally adjusted for mode of delivery, sex of child, and birth characteristics.

We performed several sensitivity analyses. As the CEBQ's food fussiness scale was mainly reported by mothers, the associations of maternal anxiety and depression with this outcome measure may be prone to reporter bias. Therefore, we additionally examined the associations of mothers' anxiety and depression scales (continuously) with the CBCL data on fussy eating, as obtained by multiple informants. Separate logistic regression analyses were conducted for mother reports and father reports on the CBCL. Second, using linear regression analyses, we compared the food fussiness scores of the following three groups of children: (1) children of mothers who had average or below average anxiety or depression scores (reference group); (2) children of mothers who had above average anxiety scores (0.50 and higher but below clinical cut-off) or above average depression scores (0.33 and higher but below clinical cut-off); (3) children of mothers who had clinically significant anxiety scores (0.71 and higher) or clinically significant depression scores (0.80 and higher). The Dutch cut-offs for the BSI were used to categorize the mothers [23]. All sensitivity analyses were adjusted for the same potential confounders as described above.

Multiple imputation techniques were used to impute missing values on confounders and exposure [24]. The reported B-values are pooled from 20 imputed datasets. In addition, we repeated our main analyses in complete cases. All statistical analyses were performed with SPSS V.21.0.

# Results

## Sample characteristics

Sample characteristics are presented in Table 4.1. The food fussiness sum-score at age four was 17.7 (SD = 4.9) and the mean was 3.0 (SD = 0.8). Using the CBCL as proxy for fussy eating, ~30% of all children were classified as fussy eaters at age three. In total, agreement of mothers and fathers about their child being a fussy or non-fussy eater was 76.7%. We calculated Yule's Y [25] to be 0.47, indicating moderate agreement between mothers and fathers.

Table 4.1 | Sample characteristics of 4746 parent-child dyads in the Generation R Study

| Characteristics | | N [a] | Percentage or mean[b] |
|---|---|---|---|
| Family | | | |
| Maternal age (years) | | 4746 | 31.6 (4.5) |
| Paternal age (years) | | 4746 | 34.0 (5.4) |
| Family income | <€2000 monthly | 1262 | 26.6 |
| Mothers' ethnic background | Dutch | 3113 | 65.6 |
| | Moroccan | 139 | 2.9 |
| | Surinamese & Dutch Antillean | 335 | 7.1 |
| | Turkish | 276 | 5.8 |
| | Other Western (mainly European) | 414 | 8.7 |
| | Other non-Western | 469 | 9.9 |
| Fathers' ethnic background | Dutch | 3148 | 66.3 |
| | Moroccan | 174 | 3.7 |
| | Surinamese & Dutch Antillean | 354 | 7.5 |
| | Turkish | 258 | 5.4 |
| | Other Western (mainly European) | 320 | 6.7 |
| | Other non-Western | 492 | 10.4 |
| Mothers' educational level [c] | Low | 678 | 14.3 |
| | Medium | 1324 | 27.9 |
| | High | 2744 | 57.8 |
| Fathers' educational level [c] | Low | 850 | 17.9 |
| | Medium | 1241 | 26.2 |
| | High | 2655 | 55.9 |
| Marital status | Single parent | 373 | 7.9 |
| Parity | Multipara | 1964 | 41.4 |
| Mode of delivery | Cesarean section | 650 | 13.7 |
| Parents' anxiety scale scores (BSI) | | | |
| Mothers' anxiety during pregnancy | | 4746 | 0.23 (0.38) |
| Mothers' anxiety at 3 years postnatal | | 4746 | 0.18 (0.32) |
| Fathers' anxiety during pregnancy | | 4144 | 0.16 (0.29) |
| Fathers' anxiety at 3 years postnatal | | 4144 | 0.15 (0.25) |

Table 4.1 | (continued)

| Characteristics | N [a] | Percentage or mean[b] |
|---|---|---|
| Parents' depression scale scores (BSI) | | |
| Mothers' depression during pregnancy | 4746 | 0.17 (0.38) |
| Mothers' depression at 3 years postnatal | 4746 | 0.14 (0.33) |
| Fathers' depression during pregnancy | 4144 | 0.10 (0.26) |
| Fathers' depression at 3 years postnatal | 4144 | 0.10 (0.27) |
| Child | | |
| Sex (Boy) | 2363 | 49.8 |
| Birth weight (g) | 4746 | 3442 (568) |
| Gestational age (weeks) | 4746 | 40 (2) |
| Fussy eating | | |
| Food fussiness at 4 years (CEBQ sum-score, range 6-30) | 4746 | 17.7 (4.9) |
| Food fussiness at 4 years (CEBQ mean-score, range 1-5) | 4746 | 3.0 (0.8) |
| Fussy eating proxy at 3 years (CBCL) | | |
| Fussy eaters as reported by mother | 944 | 27.7 |
| Fussy eaters as reported by father | 1047 | 30.7 |

[a] N=4746 as this table represents imputed data for covariates. N=4144 for fathers' anxiety and depression. Reports of fussy eating on the CBCL by both mother and father were available for 3409 parent-child dyads.

[b] Values are percentages for categorical variables and mean (SD) for continuous variables.

[c] Low: ranging from no education to high school level; medium: lower vocational training; high: higher vocational training and higher academic training.

BSI, Brief Symptom Inventory; CBCL, Child Behavior Checklist; CEBQ, Children's Eating Behaviour Questionnaire.

Table 4.2 | Parental anxiety symptoms and fussy eating in four-year-old children (CEBQ)

| Parental anxiety symptoms (BSI) | N | Food fussiness sum-score [a] regression coefficients (95% CI) [b] | p-value |
|---|---|---|---|
| Maternal anxiety scale scores | 4746 | | |
| Anxiety during pregnancy | | 1.02 (0.59-1.46) | <0.001 |
| Anxiety at 3 years postnatal | | 0.88 (0.43-1.33) | <0.001 |
| Paternal anxiety scale scores | 4144 | | |
| Anxiety during pregnancy | | 0.10 (-0.49-0.69) | 0.74 |
| Anxiety at 3 years postnatal | | 0.88 (0.26-1.49) | 0.01 |

a The food fussiness sum-scores range from 6-30.

b All reported regression coefficients are unstandardized B-values and quantify the difference in food fussiness score per 1 point higher parental anxiety score, adjusted for child age when the CEBQ was completed and sociodemographic characteristics(parental age, family income, parental ethnic background, parental educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, sex of child, and child's birth characteristics (birth weight and gestational age) in the postnatal models.

BSI, Brief Symptom Inventory; CEBQ, Children's Eating Behaviour Questionnaire.

## Parental anxiety symptoms and children's fussy eating behavior

Maternal anxiety symptoms during pregnancy and during the preschool period were related to fussy eating in their four-year-old children (Table 4.2). For instance, per point on the anxiety scale in pregnancy, children had a 1.02 higher food fussiness sum-score (95% CI 0.59 - 1.46). By additionally analyzing maternal anxiety at both time points in the same model, we found that mothers' anxiety during pregnancy (B = 0.81, 95% CI 0.33 - 1.29) and during the preschool period (B = 0.54, 95% CI 0.05 - 1.03) were both independently related to child fussy eating (not shown in tables). Fathers' anxiety in the preschool period, but not during the antenatal period, was related to fussy eating in their child (Table 4.2).

Sensitivity analyses showed that not only children of mothers with clinically significant anxiety had elevated food fussiness scores (e.g. antenatal model; B = 1.06, 95% CI 0.46 - 1.67), but children of mothers with anxiety scores above average also had higher food fussiness scores than children of mothers with average or below average anxiety scores (e.g. antenatal model; B = 0.72, 95% CI 0.21 - 1.22) (see Supplementary table S4.1).

Table 4.3 | Parental depressive symptoms and fussy eating in four-year-old children (CEBQ)

| Parental depressive symptoms (BSI) | N | Food fussiness sum-score [a] regression coefficients (95% CI) [b] | p-value |
|---|---|---|---|
| Maternal depression scale scores | 4746 | | |
| Depression during pregnancy | | 0.91 (0.49-1.33) | <0.001 |
| Depression at 3 years postnatal | | 0.81 (0.35-1.26) | <0.001 |
| Paternal depression scale scores | 4144 | | |
| Depression during pregnancy | | 0.72 (0.07-1.36) | 0.03 |
| Depression at 3 years postnatal | | 0.68 (0.08-1.28) | 0.03 |

[a] The food fussiness sum-scores range from 6-30.

[b] All reported regression coefficients are unstandardized B-values and quantify the difference in food fussiness score per 1 point higher parental depression score, adjusted for child age when the CEBQ was completed and sociodemographic characteristics (parental age, family income, parental ethnic background, parental educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, sex of child, and child's birth characteristics (birth weight and gestational age) in the postnatal models.

BSI, Brief Symptom Inventory; CEBQ, Children's Eating Behaviour Questionnaire.



## Parental depressive symptoms and children's fussy eating behavior

Table 4.3 shows that higher maternal depressive symptoms in the antenatal period as well as at three years postnatal were related to more fussy eating in their four-year-old children (e.g. per point antenatal depression score, children had a 0.91 higher food fussiness sum-score, (95% CI 0.49 - 1.33)). Likewise, the associations between fathers' depressive symptoms at both time points and children's food fussiness were in the same direction (Table 4.3).

Similar to the independent effects of mothers' anxiety at both time points, we also found that mothers' depressive symptoms during pregnancy and three years later were independently related to child fussy eating (data not shown). Supplementary table S4.2 shows that mothers' depression scores above average already predicted fussy eating, especially during pregnancy (B = 0.87, 95% CI 0.41 - 1.33 for above average scores and B = 0.87, 95% CI 0.22 - 1.51 for clinically significant depression).

## Mothers' internalizing problems and children's fussy eating across informants

Table 4.4 shows that maternal internalizing problems were also associated with both mother and father reports of children's fussy eating on the CBCL. ORs were very similar regardless of whether mothers or fathers reported their three-year-olds' fussy eating behavior (e.g. for antenatal anxiety OR = 1.50 (95% CI 1.18 - 1.89) as reported by mothers and OR = 1.44 (95% CI 1.13 - 1.83) as reported by fathers).

## Additional sensitivity analyses

Results of our full case analyses (see Supplementary tables S4.3-S4.5) were very similar to our main findings (Tables 4.2 and 4.3). For instance, mothers' internalizing problems were also related to child food fussiness at age four (e.g. for antenatal anxiety B = 1.15 (95% CI 0.69 - 1.61)). Only the associations of fathers' internalizing problems in the preschool period with fussy eating were no longer statistically significant, probably because of reduced power, although the magnitude of the associations was also slightly reduced (e.g. for anxiety B = 0.69 (95% CI -0.14 - 1.52)).

Table 4.4 | Maternal internalizing problems and a proxy for fussy eating at age 3 years as independently reported by both parents on the CBCL

| | | Fussy eater [a] reported by mother | | Fussy eater [b] reported by father | |
|---|---|---|---|---|---|
| Maternal internalizing symptoms (BSI) | N | OR (95% CI) [c] | p-value | OR (95% CI) [c] | p-value |
| Maternal anxiety scale scores | 3409 | | | | |
| Anxiety during pregnancy | | 1.50 (1.18-1.89) | 0.001 | 1.44 (1.13-1.83) | 0.003 |
| Anxiety at 3 years postnatal | | 1.65 (1.27-2.13) | <0.001 | 1.59 (1.23-2.05) | <0.001 |
| Maternal depression scale scores | 3409 | | | | |
| Depression during pregnancy | | 1.24 (0.96-1.61) | 0.10 | 1.28 (1.00-1.64) | 0.05 |
| Depression at 3 years postnatal | | 1.38 (1.05-1.79) | 0.02 | 1.29 (0.99-1.67) | 0.06 |

[a] Values are ORs for fussy eaters (N=944) compared with non-fussy eaters (N=2465), reported by mothers.

[b] Values are ORs for fussy eaters (N=1047) compared with non-fussy eaters (N=2362), reported by fathers.

[c] Adjusted for child age when the CBCL was completed and sociodemographic characteristics (maternal age, family income, maternal ethnic background, maternal educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, sex of child, and child's birth characteristics (birth weight and gestational age) in the postnatal models.

BSI, Brief Symptom Inventory; CBCL, Child Behavior Checklist.

# Discussion

Higher maternal internalizing problems during pregnancy and at three years postnatal were prospectively and both independently related to child fussy eating in a large population-based cohort. We also found indications that fathers' internalizing problems are related to child fussy eating.

The finding that maternal internalizing problems predicted more fussy eating in children is largely consistent with previous research [6, 9-11, 26-28], although conflicting studies exist [12, 29]. Importantly, we found that mothers' antenatal internalizing symptoms predicted four-year-olds' fussy eating independent of mothers' symptoms at three years postnatal. This strongly suggest that the direction of the associations with mothers' antenatal symptoms is from mother to child. Coulthard and Harris [30] found that infants' persistent food refusal was related to mothers' concurrent state anxiety, but not to their trait anxiety, which is more general and stable. Consequently, they concluded that maternal anxiety is probably a consequence rather than a cause of child food refusal. However, in the present study, child fussy eating at age three and four cannot be an antecedent of mothers' symptoms during pregnancy. Moreover, our results suggest that not only clinically significant anxiety has an effect on child fussy eating, but also slightly elevated anxiety symptoms.

The inclusion of both mothers' and fathers' anxiety and depression as contrasting exposures allows us to speculate about underlying mechanisms. Mothers' anxiety during both pregnancy and during the child's preschool period predicted fussy eating in the child. In contrast, fathers' anxiety during pregnancy was not associated with children's fussy eating. Thus, a genetic explanation is unlikely, whereas these results provide some support for fetal programming [13]. The association between fathers' anxiety during the preschool period and child fussy eating can be explained by parenting factors. Possibly, fathers' anxiety affects children's fussy eating via controlling feeding practices such as pressure to eat [31, 32]. Such feeding practices could have counterproductive effects by contributing to negative affective reactions to food [33], thereby increasing the risk of food rejection by the child. Parental anxiety may also influence children's fussy eating by affecting difficulties in parent-child interactions.

Like mothers' depressive symptoms, fathers' depressive symptoms during pregnancy were related to children's fussy eating. Thus for these associations, fetal programming seems unlikely. Shared heritability of depression and fussy eating could underlie this association pattern, especially bearing in mind genetic influences on fussy eating [34]. Possibly, lifestyle or socioeconomic factors impact both parental and child behaviors, although we carefully adjusted for education and income. Parenting factors may mediate the associations of both mothers' and fathers' depressive symptoms at three years postnatal with child fussy eating. Also, maternal depression has been related to difficulties in the mother-child interaction [35] and, in

turn, these problematic interactions could mediate the associations with children's fussy eating [36].

Strengths of our study were its large population-based sample, prospective design, and multiple informant ratings. It is noteworthy that our results were similar for mother and father reports of fussy eating at age three, suggesting that mothers with internalizing problems do not overrate their children's eating behavior. This also supports the validity of previous findings that relied on mothers' reports of child eating behavior [6, 10, 11, 14]. However, we did not know whether maternal and paternal reports of fussy eating were completely independent of each other, although two separate questionnaires were mailed. The BSI was used to assess psychiatric symptoms. Although a well-validated instrument [19], its brief character may limit the extent to which it captures all aspects of internalizing problems. As with all cohort studies, some selective loss to follow-up among families from low socio-economic status and non-Western origin occurred in Generation R [16].

In conclusion, we observed that maternal and paternal internalizing problems were prospectively associated with fussy eating in preschoolers. For effective prevention and management of children's fussy eating, the role of parents' internalizing problems should be considered. Clinicians should be aware that not only severe anxiety and depression, but also milder forms of internalizing problems can affect child eating behavior.

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# Supplementary material

Supplement 4.1

S4.1 | Above average and clinically significant anxiety in mothers and fussy eating in four-year-old children (CEBQa)

| Maternal anxiety symptoms (BSI[a]) | N | Food fussiness sum-score[b] regression coefficients (95% CI)[c] | p-value |
|---|---|---|---|
| Anxiety during pregnancy | 4746 | | |
| Average or below (score <0.50) | 3893 | Reference | |
| Above average (score ≥ 0.50) | 475 | 0.72 (0.21; 1.22) | .006 |
| Clinical cut off (score ≥ 0.71) | 378 | 1.06 (0.46; 1.67) | .001 |
| Anxiety at 3 years postnatal | 4746 | | |
| Average or below (score <0.50) | 4164 | Reference | |
| Above average (score ≥ 0.50) | 359 | 0.61 (0.05; 1.17) | .03 |
| Clinical cut off (score ≥ 0.71) | 223 | 0.87 (0.19; 1.55) | .01 |

[a] CEBQ, Children's Eating Behaviour Questionnaire; BSI, Brief Symptom Inventory.

[b] The food fussiness sum-sores range from 6-30.

[c] All reported regression coefficients are unstandardized B-values and quantify how the food fussiness score for children of mothers with either 'above average' or 'clinically significant' anxiety scores differs from children of mothers with 'average or lower' anxiety scores, adjusted for age child when CEBQ was filled out and socio-demographic characteristics (maternal age, family income, maternal ethnic background, maternal educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, child sex, and child's birth characteristics (birth weight and gestational age) in the postnatal models.

Supplement 4.2

S4.2 | Above average and clinically significant depression in mothers and fussy eating in four-year-old children (CEBQa)

| Maternal depressive symptoms (BSI[a]) | N | Food fussiness sum-score[b] regression coefficients (95% CI)[c] | p-value |
|---|---|---|---|
| Depression during pregnancy | 4746 | | |
| Average or below (score <0.33) | 3833 | Reference | |
| Above average (score ≥ 0.33) | 604 | 0.87 (0.41; 1.33) | <.001 |
| Clinical cut off (score ≥ 0.80) | 309 | 0.87 (0.22; 1.51) | .01 |
| Depression at 3 years postnatal | 4746 | | |
| Average or below (score <0.33) | 3949 | Reference | |
| Above average (score ≥ 0.33) | 582 | 0.48 (0.03; 0.93) | .04 |
| Clinical cut off (score ≥ 0.80) | 215 | 1.11 (0.38; 1.84) | .003 |

[a] CEBQ, Children's Eating Behaviour Questionnaire;, BSI, Brief Symptom Inventory.

[b] The food fussiness sum-sores range from 6-30.

[c] All reported regression coefficients are unstandardized B-values and quantify how the food fussiness score for children of mothers with either 'above average' or 'clinically significant' depression scores differs from children of mothers with 'average or lower' depression scores, adjusted for age child when CEBQ was filled out and socio-demographic characteristics (maternal age, family income, maternal ethnic background, maternal educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, child sex, and child's birth characteristics (birth weight and gestational age) in the postnatal models.

Supplement 4.3

S4.3 | Full case approach: Sample characteristics of 4746 parent-child dyads in Generation R

| Characteristics<br>Family | | N [a] | Percentage or mean[b] |
|---|---|---|---|
| Maternal age (years) | | 4746 | 31.6 (4.5) |
| Paternal age (years) | | 4317 | 34.0 (5.4) |
| Family income | < €2000 monthly | 1012 | 25.2 |
| Mothers' ethnic background | Dutch | 3111 | 65.8 |
| | Moroccan | 139 | 2.9 |
| | Surinamese & Dutch Antillean | 321 | 6.8 |
| | Turkish | 275 | 5.8 |
| | Other Western (mainly European) | 413 | 8.7 |
| | Other non-Western | 466 | 9.9 |
| Fathers' ethnic background | Dutch | 3113 | 67.5 |
| | Moroccan | 163 | 3.5 |
| | Surinamese & Dutch Antillean | 315 | 6.8 |
| | Turkish | 252 | 5.5 |
| | Other Western (mainly European) | 307 | 6.7 |
| | Other non-Western | 464 | 10.1 |
| Mothers' educational level[c] | Low | 636 | 13.9 |
| | Medium | 1270 | 27.7 |
| | High | 2677 | 58.4 |
| Fathers' educational level[c] | Low | 508 | 15.2 |
| | Medium | 838 | 25.1 |
| | High | 1989 | 59.6 |
| Marital status | Single parent | 348 | 7.6 |
| Parity | Multipara | 1908 | 41.3 |
| Mode of delivery | Cesarean section | 568 | 13.6 |

Supplement 4.4

S4.4 | Full case approach for the associations between parental anxiety symptoms and fussy eating in four-year-old children (CEBQa)

| Parental anxiety symptoms (BSI[a]) | N | Food fussiness sum-score[b] regression coefficients (95% CI)[c] | p-value |
|---|---|---|---|
| Maternal anxiety scale scores | | | |
| Anxiety during pregnancy | 3458 | 1.15 (0.69; 1.61) | <.001 |
| Anxiety at 3 years postnatal | 3165 | 1.15 (0.57; 1.72) | <.001 |
| Paternal anxiety scale scores | | | |
| Anxiety during pregnancy | 2826 | 0.11 (-0.56; 0.77) | .75 |
| Anxiety at 3 years postnatal | 2198 | 0.69 (-0.14; 1.52) | .10 |

[a] CEBQ, Children's Eating Behaviour Questionnaire; BSI, Brief Symptom Inventory.

[b] The food fussiness sum-sores range from 6-30.

[c] All reported regression coefficients are unstandardized B-values and quantify the difference in food fussiness score per 1 point higher parental anxiety score, adjusted for child age when CEBQ was filled out and socio-demographic characteristics(parental age, family income, parental ethnic background, parental educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, child sex, and child's birth characteristics (birth weight and gestational age) in the postnatal models.

Supplement 4.5

S4.5 | Full case approach for the associations between parental depressive symptoms and fussy eating in four-year-old children (CEBQa)

| Parental depressive symptoms (BSI[a]) | N | Food fussiness sum-score[b] regression coefficients (95% CI)[c] | p-value |
|---|---|---|---|
| Maternal depression scale scores | | | |
| Depression during pregnancy | 3458 | 1.04 (0.57; 1.52) | <.001 |
| Depression at 3 years postnatal | 3166 | 1.06 (0.48; 1.63) | <.001 |
| Paternal depression scale scores | | | |
| Depression during pregnancy | 2822 | 0.69 (-0.11; 1.48) | .09 |
| Depression at 3 years postnatal | 2198 | 0.48 (-0.39; 1.34) | .28 |

[a] CEBQ, Children's Eating Behaviour Questionnaire; BSI, Brief Symptom Inventory.

[b] The food fussiness sum-sores range from 6-30.

[c] All reported regression coefficients are unstandardized B-values and quantify the difference in food fussiness score per 1 point higher parental depression score, adjusted for child age when CEBQ was filled out and socio-demographic characteristics(parental age, family income, parental ethnic background, parental educational level, marital status, and parity) in the antenatal models and additionally adjusted for mode of delivery, child sex, and child's birth characteristics (birth weight and gestational age) in the postnatal models..

CHAPTER 5

# Behavioral outcomes of picky eating in childhood: a prospective study in the general population

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# Abstract

## Background

Picky eaters in the general population form a heterogeneous group. It is important to differentiate between children with transient picky eating (PE) and persistent PE behavior when adverse outcomes are studied. We analyzed four PE trajectories to determine the associations with child mental health prospectively.

## Methods

From a population-based cohort, 3,748 participants were assessed for PE at 1.5, 3 and 6 years of age using maternal reports. Four trajectories were defined; 1) persistent; PE at all ages, 2) remitting; PE before 6 years only, 3) late-onset; PE at 6 years only, and 4) never; no PE at any assessment. Child's problem behaviors were assessed with the Teacher's Report Form at 7 years of age. We examined associations between picky eating trajectories and emotional problems, behavioral problems and pervasive developmental problems using logistic regressions. Analyses were adjusted for child, parental, and socioeconomic confounders. We also adjusted for maternal-reported baseline problem behavior at age 1.5 years; the never picky eating group was used as reference.

## Results

Persisting PE predicted pervasive developmental problems at age 7 years (OR = 2.00, 95% CI 1.10 - 3.63). The association remained when adjusted for baseline pervasive developmental problems at 1.5 years (OR = 1.96, 95% CI 1.10 - 3.51). Persistent PE was not associated with behavioral (OR = 0.92, 95% CI 0.53 - 1.60) or emotional problems (OR = 1.24, 95% CI 0.74 - 2.07). Other PE trajectories were not related to child behavioral or emotional problems.

## Conclusions

Persistent PE may be a symptom or sign of pervasive developmental problems, but is not predictive of other behavioral problems. Remitting PE was not associated with adverse mental health outcomes, which further indicates that it may be part of normal development.

## Key points

### *What is already known*

- Picky eating is a major concern for many parents, although picky eating problems between 1 and 4 years generally remit. Child outcome studies are needed to evaluate the prognosis of persistent and remitting picky eaters.
- Previous studies associated picky eating with more behavioral, emotional and pervasive developmental problems in childhood, and characterized it as a symptom for general psychopathology.

### *What this study adds*

- In this study, persistent picky eating, but not late-onset or remitting picky eating, was an early sign for pervasive developmental problems.
- Remitting picky eating was not associated with child behavior problems, suggesting that remitting picky eating is part of normal development.

# Introduction

Picky eating is a frequent eating problem in early childhood, characterized by food refusal, eating a limited variety of food, an unwillingness to try new food (food neophobia) [1] and aberrant eating behaviors, such as low enjoyment of food, slowness in eating and higher satiety responsiveness [2]. The prevalence of picky eating is highest (14% - 50%) in preschool children [1–4], and declines (7% - 27%) in later childhood [4–5]. Incidence also declines after preschool age [4]. The high prevalence and incidence are an indication that picky eating in the preschool age is often part of normal development [4]. Indeed many health professionals tend to regard picky eating as a normal phase which eventually passes [6]. However, this is in contrast to how many parents experience picky eating, i.e., as a major cause of concern [4, 7–9]. Parents often seek medical help for their child's picky eating [9], and express frustration with physicians for dismissing their concerns [10]. Our previous report within the Generation R Study on picky eating trajectories, confirmed that the majority of children's picky eating problems in the preschool age remitted before the age of 6 years [11]. However, we also found a small group of children with persisting picky eating problems who had a lower birth weight, were more often male and from a non-Dutch and low socioeconomic background, compared with non-picky eaters [11].

In previous studies, picky eating was associated with higher levels of behavioral, emotional and pervasive developmental problems in childhood [5-6, 12] and was suggested to be a precursor for anorexia nervosa [13]. The most recent studies concluded that picky eating in children of school age must be seen as a risk factor or marker for general psychopathology, rather than a precursor of eating disorders [5, 12]. However, picky eating problems are also specifically associated with pervasive developmental disorders [14]. The prevalence of picky eating in children with autism was found to be as high as 90% [15] and often present from early age onwards [16]. In addition, feeding problems and eating disorders are associated with anxiety problems [17-18], and distorted child-parent interactions are suggested to play an important role in feeding problems [19].

However, most picky eating studies have some important limitations. First, most studies were limited by their cross-sectional design. Second, they did not differentiate between different trajectories, clustering remitting and persistent picky eaters. Third, a lack of correction for baseline differences makes temporal inferences difficult. Also, most studies did not adjust or only poorly adjusted for confounders. Only a few studies included child, parental, and socioeconomic characteristics [11–12, 20]. Gender, weight at birth, parental income, maternal ethnicity and age, birth order, higher levels of child emotionality and maternal negative affectivity were found to predict picky eating at later age [11, 20]. Lastly, the majority of studies in the field of eating disorders research rely on one informant to report both the

determinant and outcome. However, this practice of using a single informant can lead to spurious associations, i.e. information bias (shared method variance) [21]. Typically, mothers' reports are used to assess picky eating as well as emotional and behavioral problems, possibly introducing this type of bias.

It is important to study the course and outcome of picky eating in the general population to determine which children are at high risk for adverse mental health outcomes. Furthermore, this should be evaluated in the context of the child's age. First, we hypothesize that remitting picky eating problems in the preschool age (0 - 4 years) are part of normal development and are not associated with an increased risk of any adverse mental health problems. Second, we hypothesize that children with persisting picky eating problems have a higher risk for adverse mental health outcomes. In particular, we expect that persistent picky eating is associated with more pervasive developmental problems and anxiety problems. Third, we will test whether late-onset picky eating is associated with emotional or behavioral problems; however, there are insufficient studies to date to formulate a specific hypothesis for this item.



# Methods

## Study design and population

This study was embedded within the Generation R Study [22]. The Generation R Study is a prospective population-based cohort in Rotterdam (the Netherlands), that aims to identify environmental and genetic causes of normal and abnormal growth, development and health from fetal life onwards. Pregnant women residing in Rotterdam with an expected delivery date between April 2002 and January 2006 were invited to participate. Written informed consent was obtained from all participants. The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, approved the study. Information about child and family characteristics was obtained by postal questionnaires filled out by parents, and from the medical records of hospitals, midwives and community Child Health Centers.

Picky eating was assessed by parental report questionnaires when children were 1.5, 3, and 6 years old. Children who were not assessed for picky eating at any of these time points, or with an inconsistent picky eating pattern, were excluded from the study. Behavioral outcomes were determined using the Teacher Report Form (TRF) when the child was 7 years old (mean 6.7, SD 1.3 years; N = 4,696). A total of 3,748 (78.8%) children were included in the present study.

## Measures

### *Trajectories of picky eating*

Picky eating was assessed with two questions of the Child Behavioral Checklist (CBCL) at age 1.5, 3, and 6 years. The detailed methodology is described elsewhere [11]. In short: at each assessment wave, mothers indicated whether their child "did not eat well" and "refused to eat" on a 3-point Likert scale. Based on the sum score of these two items (sum range 2 - 6) children with a score of sometimes and/or often (score of ≥ 4) were identified as a picky eater. This method approximates the concept of picky eating as defined by Dovey and colleagues [1], with reduced caloric intake, lower variety of foods, higher food fussiness, less enjoyment of food, higher satiety response and slowness in eating [11]. It is important to note that our method aims to determine picky eating problems in the general population, including (but not limited to) clinically significant 'picky eating disorders'. Four main picky eating trajectory groups were created, i.e. 1) never picky eaters: those who were never identified as picky eaters, 2) remitting picky eaters: those who were picky eaters at 1.5 and/or 3 years, but not at 6 years of age, 3) late-onset picky eaters: those who were picky eaters at 6 years of age only, 4) persistent picky eaters: those who were picky eaters during all assessment waves (1.5, 3, and 6 years). The remaining 242 children with an inconsistent pattern (i.e. children assessed as picky eaters at 1.5 years and 6 years, but not at 3 years, and children that were picky eaters at 3 and 6 years, but not at 1.5 years) were excluded from further analysis for two main reasons: 1) the accurate categorization would depend strongly on future follow-up of picky eating status, with the possibility that these children would then be categorized into remitting, late-onset or persistent picky eaters, 2) analyses of this group revealed a different pattern compared to the other trajectories and did not differ from the never picky eaters (results not shown).

### *Child's problem behavior*

To determine children's problem behavior the Dutch translation of the TRF [23] was used. The TRF is the teacher version of the CBCL, comprising 120 problem items that can be scored on a 3-point Likert scale (i.e. not true, sometimes true, or often true). The TRF has the following six DSM-Oriented Scales: affective problems, anxiety problems, pervasive developmental problems, attention deficit/hyperactivity problems, oppositional defiant problems, and conduct problems. The DSM-Oriented Scale problems were defined using the established borderline clinical cut-offs [24]; however, linear regression analyses with continuously modeled outcomes are also presented to demonstrate that our findings do not depend on choice of cut-off (see Supplementary Table S5.1). Three main groups of problems were formed in line with

Micali and colleagues [5]; 1) 'emotional problems' consisting of the summed anxiety and affective problems, 2) 'behavioral problems' consisting of attention/hyperactivity and oppositional defiant problems and 3) pervasive developmental problems. Conduct problems were excluded from the behavioral problem group since, at a young age, the diagnosis of conduct disorder has a low prevalence [25]. The Dutch TRF has good reliability and validity [23].

Baseline problem level was assessed by the mother using the CBCL / 1.5 - 5 when the child was 1.5 years of age. The CBCL [26] is a 99-item parent report questionnaire that assesses child emotional and behavioral problems in a manner similar to the TRF. The Dutch CBCL is reported to have good reliability and validity [26]. Three main problem groups (as described above) were formed. However, in contrast to the TRF, the CBCL scale scores were used continuously with a higher score indicating more problems. One of the items used to assess picky eating was also present in the emotional problems scale. To avoid bias, this item was excluded from the emotional problems scale score.



*Child, parental, and sociodemographic information*

Based on previous studies [11, 20, 27 - 28], we defined several child, family, and socioeconomic characteristics as confounders. Information about child gender, birth weight, and gestational age at birth was obtained from midwife and hospital registries. Maternal ethnicity, family income, and child's birth order were assessed by postal questionnaire. Maternal educational level was coded as high (some college or university education), middle (secondary education), or low (primary education or none). Family income per month was coded as high or middle (above median income >2200 euro), low (1200 - 2200 euro), or very low (<1200 euro). Birth order was defined as firstborn or later born. Maternal ethnicity was coded as Dutch, Moroccan, Turkish, a combined code (Sur/Ant/Cape) for mothers with a Surinamese, Dutch Antillean or Cape Verdian ethnicity, other Western, and other non-Western. Birth weight is given in grams, gestational age at birth in weeks, and BMI in bodyweight/height$^2$ (kg/m$^2$).

Maternal psychiatric symptoms were assessed with the Brief Symptom Inventory (BSI) during pregnancy. The BSI is a validated self-report questionnaire [29-30] that consists of 53 items scored on a 5-point Likert scale. It assesses a spectrum of psychiatric problems such as anxiety, depression, somatization, and hostility problems. The global severity index is the mean of all subscales and is an appropriate measure of general psychopathology [30-31]; that overall mean score was used as a continuous measure, with higher scores indicating more problems.

Table 5.1 | Population characteristics

| | | N=3,748 |
|---|---|---|
| **Child characteristic** | | |
| Gender | Boy, % | 50.6 |
| | Girl, % | 49.4 |
| Birth weight | Normal weight, % | 88.6 |
| | Underweight, % | 4.3 |
| | Overweight, % | 7.2 |
| Gestational age at birth | Aterm, % | 87.5 |
| | Preterm, % | 4.9 |
| | Postterm, % | 7.6 |
| **Parental characteristic** | | |
| Age mother [a], in years | Mean (SD) | 30.9 (5.0) |
| Age father [a], in years | Mean (SD) | 33.7 (5.7) |
| Maternal ethnicity | Dutch, % | 57.9 |
| | Moroccan, % | 5.5 |
| | Turkish, % | 8.5 |
| | Sur/Ant/Cape [b], % | 12.3 |
| | Other Western, % | 8.1 |
| | Other non-Western, % | 7.7 |
| Maternal educational level [c] | High [d], % | 56.5 |
| | Middle, % | 38.8 |
| | Low, % | 4.7 |
| Family income | High or middle, % | 59.6 |
| | Low, % | 15.3 |
| | Very low, % | 25.1 |
| Birth order | Firstborn, % | 55.15 |
| | Later born, % | 44.85 |
| Smoking during pregnancy | No, % | 75.7 |
| | Stopped at pregnancy, % | 8.8 |
| | Yes, % | 15.5 |
| Picky eating trajectories [e] | Never | 1,926 |
| | Remitting | 1,197 |
| | Late-onset | 177 |
| | Persistent | 206 |

[a] At intake.

[b] Suriname / Antillean / Cape Verdean.

[c] Highest followed.

[d] Low = none or primary, middle = secondary school, high = higher vocational education/ university.

[e] N is based on imputed trajectory groups. The inconsistent group (n=242) was excluded.

## Statistical analysis

To examine the relationship between picky eating and child's behavioral problems separate logistic regressions were carried out with emotional problems, behavioral problems, and pervasive developmental problems as outcome, and the trajectories of picky eating as the independent variable. The never picky eating group was used as the reference group. First (Model 1), a univariate logistic regression was performed. In the second analysis (Model 2) many of the confounder variables found to predict picky eating [11, 20] were added. These included gender, weight at birth, maternal ethnicity and income, birth order and maternal psychopathology. Because maternal age did not predict picky eating in our earlier study [11], it was not included as a confounder in the present study. Finally (Model 3), to address the temporal sequence of the relation, we corrected for baseline child behavioral problems. For this, we also adjusted for maternal-reported child behavioral problem using the CBCL at age 1.5 years. In addition, we re-ran all analyses using maternal-reported emotional, behavioral and pervasive developmental outcomes using the CBCL at 6 years of age, to enable comparison with other studies. These additional analyses are presented in Supplementary Table S5.2 and are contrasted with analyses using teacher reports in the same sample and also highlight possible informant bias. Except for the dependent variables, missing values were estimated using multiple imputation techniques. As the CBCL data included some missing values (<30% per assessment wave), proportions of trajectories of picky eating were based on multiple imputation if one or more scores were obtained. The pervasive developmental problems group was the only dependent variable (outcome) with missing data (N = 3734, missings n=14). The presented results are based on pooled estimates of five imputed datasets. Analyses were performed using STATA/SE 12.0.

# Results

## Study population

General child and family characteristics of the study population are presented in Table 5.1. The amount of boys and girls was almost equal. The majority of the mothers were of Dutch ethnicity (57.9%), and from a higher socioeconomic status (56.5% higher education). The majority of the children never had picky eating problems (51.4%; n = 1926). Approximately 5.5% (n = 206) were persistent picky eaters, while 31.9% (n = 1197) were remitting picky eaters. These numbers are best estimates (variation < 4% of sample) as they are based on imputed data.

Table 5.2 | Longitudinal association[a] between trajectories of picky eaters and borderline behavioral problems

| | | Behavioral problems | |
|---|---|---|---|
| Picky eating trajectories | N[b] | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
| Never | 1,926 | reference | reference |
| Remitting | 1,197 | 1.07 (0.74 – 1.55) | 1.03 (0.66 – 1.61) |
| Late-onset | 177 | 1.42 (0.64 – 3.13) | 1.05 (0.42 – 2.61) |
| Persistent | 206 | 0.92 (0.53 – 1.60) | 0.66 (0.38 – 1.15) |

Behavioral problems; attention deficit hyperactivity and oppositional defiant problems.

Model 2: adjusted gender, weight at birth, gestational age at birth, maternal ethnicity, household income, birth order and maternal psychopathology.

[a] Logistic regression.

[b] N is based on imputed trajectory groups. The inconsistent group (n=242) was excluded.

Table 5.3 | Longitudinal association[a] between trajectories of picky eaters and borderline emotional problems

| | | Emotional problems | |
|---|---|---|---|
| Picky eating trajectories | N[b] | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
| Never | 1,926 | reference | reference |
| Remitting | 1,197 | **1.54* (1.01 – 2.36)** | 1.47 (0.92 – 2.33) |
| Late-onset | 177 | 1.53 (0.67 – 3.51) | 1.21 (0.56 – 2.64) |
| Persistent | 206 | **1.71* (1.01 – 2.91)** | 1.24 (0.74 – 2.07) |

Emotional problems; anxiety and affective problems.

Model 2: adjusted gender, weight at birth, gestational age at birth, maternal ethnicity, household income, birth order and maternal psychopathology.

The **bold values** are given to accentuate that these values are significant findings.

[a] Logistic regression.

[b] N is based on imputed trajectory groups. The inconsistent group (n=242) was excluded.

* $p < .05$.

## Picky eating trajectories and associations with child behavioral problems

No associations were found between remitting, late-onset, persistent picky eaters and never picky eaters, and behavioral problems (Table 5.2).

In the unadjusted analyses (Model 1), remitting and persistent picky eaters showed more emotional problems than the reference group (Table 5.3). No difference in emotional problems was found between late-onset picky eaters and never picky eaters. After adjusting for child, family and sociodemographic variables (Model 2), no differences in emotional problems were found.

Persistent picky eating was associated with more pervasive developmental problems, unadjusted (Model 1; OR = 2.41, 95% CI 1.37 - 4.22), and after adjusting for confounders (Model 2; adjusted OR = 2.00, 95% CI 1.10 - 3.63) (Table 5.4). After additionally adjusting for baseline pervasive developmental problems at 1.5 years, persistent picky eating remained associated with a higher risk of pervasive developmental problems (Model 3; adjusted OR = 1.96, 95% CI 1.10 - 3.51; data not in table). None of the other picky eating trajectories were associated with pervasive developmental problems.



Table 5.4 | Longitudinal association[a] between trajectories of picky eaters and borderline pervasive developmental problems

| | | Pervasive developmental problems | |
|---|---|---|---|
| Picky eating trajectories | N[b] | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
| Never | 1,920 | reference | reference |
| Remitting | 1,192 | 1.02 (0.64 – 1.61) | 0.97 (0.59 – 1.59) |
| Late-onset | 176 | 0.70 (0.21 – 2.24) | 0.57 (0.16 – 2.05) |
| Persistent | 205 | **2.41**(1.37 – 4.22)** | **2.00* (1.10 – 3.63)** |

Model 2: adjusted gender, weight at birth, gestational age at birth, maternal ethnicity, household income, birth order and maternal psychopathology.

The **bold values** are given to accentuate that these values are significant findings.

[a] Logistic regression.

[b] N is based on imputed trajectory groups. The inconsistent group (n=242) was excluded.

* p < .05; ** p < .01.

# Discussion

In this population-based study, we found that persistent picky eating was longitudinally associated with pervasive developmental problems at age 7 years as reported by teachers, even after adjustment of baseline pervasive developmental problems at 1.5 years. Remitting and late-onset picky eating were not associated with adverse mental health outcomes.

In line with our first hypothesis, the present study demonstrates that remitting picky eating was not prospectively associated with adverse mental health outcomes. This suggests that remitting picky eating in pre-school children can be seen as part of normal development in the general population [6]; a behavior that might be considered as age-appropriate and will eventually remit without behavioral or emotional consequences. This is further strengthened by the fact that our findings are based on a longitudinal design. However, in the present study we did not include somatic health measures and other adverse outcomes cannot be ruled out [9, 32].

Second, we hypothesized that persistent picky eating would be prospectively associated with pervasive developmental problems. In line with clinical studies reporting more picky eating problems among children with autism spectrum disorders (ASD) [14], our study suggests that persistent picky eating is also more common in children from the general population with elevated pervasive developmental problems. Importantly, when we corrected for baseline pervasive developmental problems, persistent picky eating remained related to pervasive developmental problems at age 7 years. Thus, the finding cannot be explained by developmental problems early in life. This assessment was based on maternal reports, as parents usually recognize signs of autism in an early stage [33]. Potentially, picky eating can help to detect pervasive developmental problems earlier, as picky eating in young children is easily noticed by parents. In the study of Emond et al. [16], parents reported that difficulty in eating is often present in children with autism from infancy (6 months) onwards and persists throughout early childhood; our finding that persistent picky eating can be an early symptom or sign for pervasive developmental problems extends this observation and suggests that in the general population picky eating can precede other pervasive developmental problems symptoms.

However, the median age of the first ASD diagnosis remains older than age 4 years [34-35]. Persistent picky eating trajectories in our study are based on assessments from 1,5 to 6 years of age, thus a majority of children with ASD would already be diagnosed before persistent picky eating can be defined. However, as the age at which ASD is diagnosed is inversely associated with the number of symptoms observed [35], persisting picky eating can be used to detect ASD only in a minority of children in those with less severe or clear symptoms. Future studies are needed to evaluate if a persistent picky eating trajectory can be delineated earlier, that is at age 4 - 5 years. Since

parents often seek medical help for their child's eating behavior [9], clinicians should pay attention to children who persist in having picky eating behavior, as these children are at higher risk of pervasive developmental disorders. However, autism spectrum disorders are usually diagnosed around 4 years of age, and thus some caution is warranted as the CBCL assesses pervasive developmental problems and is not a diagnostic instrument; however, several studies have demonstrated that the CBCL pervasive developmental problem scale can be used to screen for ASD, but has a particularly high specificity in the assessment of pervasive developmental disorders [36-38].

We did not confirm our hypothesis that persistent picky eating was also prospectively associated with anxiety problems. Rather, persistent picky eating was not associated with problems other than pervasive developmental problems. This is in contrast with an earlier report of the ALSPAC study that found strong associations of picky eating with behavioral and emotional problems [28]. In our study, the existing association between persistent picky eating and emotional problems disappeared when confounders were controlled for. Also, the present study found lower odds ratios compared with Micali et al. in the UK [28]. The differences between the two studies might be explained by the design of our study (cross-sectional vs. longitudinal and repeated measures design) and, most importantly by a different informant (a teacher report vs. a mother report) as a measure for outcome. An earlier study showed that, when maternal reports are used for both the determinant and the outcome measure, the associations were strongly inflated [21]. Thus, when mothers report both picky eating and problem behavior of the child, any observed association of picky eating with behavior and emotional problems is prone to reporter bias. Furthermore, mothers who are over-concerned about their child's wellbeing might rate their child's behavior as problematic in general. Our results suggest that the associations of picky eating with emotional and behavior problems may be inflated when mothers' reports of emotional and behavior problems are used (see Supplementary Table S5.2). However, others may argue that teachers underreport (which would probably reduce precision) or more often incorrectly report, which would reduce the estimated effect of the associations.

Some caution is required when interpreting these results. First, because the concept of picky eating has not been fully operationalized [1] and the boundaries between picky eating, food neophobia and eating disorders are not yet well defined. Also, in the present study, we defined trajectories of picky eating to differentiate subgroups across time that might have distinct outcomes. Although we found no association between picky eating and emotional problems, picky eating persisting from early to late childhood might predict eating disorders in adolescence [13] or might be a risk factor for other severe psychopathology. However, this was beyond the scope of the present study and more research is required on this topic.

Our results emphasize the importance of differentiating between trajectories of picky eaters, as picky eating comprises distinct groups with different symptom clusters ranging from mild symptoms to clinical disorders such as Avoidant/Restrictive Food

Intake Disorder (ARFID). ARFID can be considered an extreme form of picky eating and is associated with more pervasive developmental disorders compared with other eating disorders in a clinical setting [39]. Therefore, we cautiously speculate that persistent picky eaters are at a higher risk for the development of ARFID.

Finally, we tested whether late-onset picky eating was associated with emotional or behavioral problems. Although late-onset picky eating was not longitudinally associated with any adverse mental health outcome, a study by Micali and colleagues [5] found more emotional, behavioral and pervasive problems, as described above. It is possible that our study was underpowered to detect minor differences, given the relatively small group of late-onset picky eating to find differences when comparing them to children without picky eating problems. In the present study, late-onset picky eaters tended to have more emotional and behavioral problems, but only in the unadjusted models; after correcting for confounders the odds ratios were strongly attenuated. This implies that the observed effect of picky eating behavior in early childhood is partially explained by socioeconomic differences between groups.

## Strengths and limitations

This study had several strengths including the large sample size, its population-based longitudinal design and inclusion of a large amount of confounders. Additional strengths are the use of the teacher report (as an independent measurement for child psychopathology) and correction for baseline problems.

Some limitations should also be discussed. First, the TRF reports on the DSM-Oriented Scales and is not equivalent to a DSM diagnosis. Thus some caution is necessary interpreting these results, more so as the borderline clinical cut-off was used. Second, we had no measurements at 4 and 5 years of age in order to better determine picky eaters with a persistent pattern or late-onset. Also, parents might have adjusted eating regimes to compensate for their child's pickiness [40], resulting in a misclassification of the remitting group. However, maternal reports for the assessment of picky eating have been validated [41]. We used "my child refuses to eat" and "my child doesn't eat well" to assess picky eating status. However, previous analyses [11] found that this method correlates well with measures of picky eating, including a lower variety of food, lower caloric intake, more food fussiness, slowness in eating and lower enjoyment of food. This indicates that our definition is a valid approximation of the concept. Lastly, a small group of picky eaters was excluded from further analysis due to having an inconsistent picky eating pattern. Follow-up of this group is needed to determine whether children in this group should be classified as remitting or persistent picky eaters, and whether picky eating is associated with adverse mental health outcomes.

## Clinical implications

Persistent picky eating was found to be an early symptom for pervasive developmental problems, whereas remitting picky eating was not associated with adverse mental health outcomes. We cautiously propose to regard remitting picky eating as part of normal development and, in line with consensus-based professional health guidelines, suggest a watchful waiting approach to picky eating problems in preschool age. However, health professionals should be aware of the possible mental health implications of persisting picky eating and, if necessary, perform additional testing.

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SUPPLEMENT 5.1

S5.1 | Associations between trajectories of picky eaters and continuously modeled child's behavioral problems

| Picky eating trajectories | Total N = 3,748 [a] | Emotional problems B ( 95% CI) | Behavioral problems B (95% CI) | Pervasive problems [b] B (95% CI) |
|---|---|---|---|---|
| Never | 1,926 | ref | ref | ref |
| Remitting | 1,197 | 0.18 (-0.16 – 0.52) | 0.06 (-0.49 – 0.61) | 0.02 (-0.11 – 0.15) |
| Late-onset | 177 | 0.06 (-0.36 – 0.48) | -0.24 (-1.41 – 0.93) | -0.05 (-0.35 – 0.25) |
| Persistent | 206 | 0.08 (-0.55 – 0.72) | -0.70 (-1.88 – 0.47) | 0.28* (0.01 – 0.55) |

*p < .05.

Estimates are derived from a multivariable linear regression.

Emotional problems consisting of anxiety and affective problems,

Behavioral consisting of attention deficit hyperactivity and oppositional defiant problems, Pervasive consists of pervasive developmental problems.

Adjusted for gender, weight at birth, gestational age at birth, maternal ethnicity, household income, birth order and maternal psychopathology.

[a] N is based on imputed trajectory groups. The inconsistent group (n=242) was excluded.

[b] Pervasive problems: N= 3744 due to missings.

SUPPLEMENT 5.2

S5.2 | Possible informant bias in the association between trajectories of picky eating and problem behavior: Using teacher vs. mother reported outcome

| | | Emotional problems | | Behavioral problems | | Pervasive developmental problems [b] | |
|---|---|---|---|---|---|---|---|
| Picky eating trajectories | Total N= 2,942 [a] % | Teacher report B ( 95% CI) | Maternal report B ( 95% CI) | Teacher report B (95% CI) | Maternal report B (95% CI) | Teacher report B (95% CI) | Maternal report B (95% CI) |
| Never | 51.8 | ref | ref | ref | ref | ref | ref |
| Remitting | 32.4 | 0.07 (-0.06 – 0.20) | 0.11* (0.00 – 0.22) | 0.00 (-0.10 – 0.10) | 0.11 (-0.01 – 0.22) | 0.02 (-0.13 – 0.16) | 0.16 (-0.14 – 0.45) |
| Late-onset | 4.4 | 0.05 (-0.15 – 0.24) | 0.41***(0.18 – 0.65) | -0.03 (-0.23 – 0.18) | 0.28***(0.08 – 0.49) | -0.05 (-0.33 – 0.23) | 0.65***(-0.19 – 1.11) |
| Persistent | 5.3 | 0.01 (-0.28 – 0.31) | 0.56***(0.33 – 0.79) | -0.12 (-0.31 – 0.07) | 0.36***(0.16 – 0.55) | 0.26* (0.05 – 0.48) | 0.94***(0.54 – 1.35) |

*p < .05; **p < .01; ***p < .001.

Overlapping sample used to facilitate comparison.

The continuous scale scores are standardized in standard deviation (SD) scores.

Emotional problems consisting of anxiety and affective problems,

Behavioral consisting of attention deficit hyperactivity and oppositional defiant problems, Pervasive consists of pervasive developmental problems.

Adjusted for gender, weight at birth, gestational age at birth, maternal ethnicity, household income, birth order and maternal psychopathology.

[a] N is based on imputed trajectory groups. The inconsistent group (6.1%) was excluded.

[b] Pervasive problems: N= 2929 due to missings.

CHAPTER 6

# Role of ghrelin in the pathophysiology of eating disorders

## Implications for pharmacotherapy

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# Abstract

Ghrelin is the only known circulating orexigenic hormone. It increases food intake by interacting with hypothalamic and brainstem circuits involved in energy balance, as well as reward-related brain areas. A heightened gut-brain ghrelin axis is an emerging feature of certain eating disorders such as anorexia nervosa and Prader-Willi syndrome. In common obesity, ghrelin levels are lowered, whereas post-meal ghrelin levels remain higher than in lean individuals. Agents that interfere with ghrelin signalling have therapeutic potential for eating disorders, including obesity. However, most of these drugs are only in the preclinical phase of development. Data obtained so far suggest that ghrelin agonists may have potential in the treatment of anorexia nervosa, while ghrelin antagonists seem promising for other eating disorders such as obesity and Prader-Willi syndrome. However, large clinical trials are needed to evaluate the efficacy and safety of these drugs.

# Introduction

Since its discovery in 1999 [1], ghrelin has emerged as an important gut-brain signal for appetite control and energy balance. It is a 28-amino acid peptide and the only known peripherally produced and centrally active orexigenic hormone. Ghrelin has been implicated in the pathophysiology of several diseases, including eating disorders and obesity. Thus, ghrelin agonists or antagonists may have therapeutic potential. In this review we focus on evidence indicating a role for ghrelin in the pathophysiology of eating disorders and obesity and evaluate existing pharmacological evidence to determine the therapeutic potential of new ghrelin-related drugs.

## A brief history of ghrelin



The discovery of ghrelin follows a rather unusual history, initiating in 1977 with the identification of the first member of a series of synthetic peptides (and later, non-peptides) that were derived from met-enkephalin and had potent growth hormone (GH)-releasing activity – the so-called 'growth hormone secretagogues' (GHS). The hexapeptide, GHRP-6 [2], now recognized as a ghrelin mimetic, received considerable attention due to its potent GH-releasing effects. Another GHS with improved biological availability after oral administration, named MK-0677 [3], was used in clinical trials for different purposes, such as the treatment of GH-deficient adults [4], hip fractures [5,6], sleep problems [7] and obesity [8], and for counteracting the effects of aging [9,10]. By 1993, it was already known that GHS activate hypothalamic arcuate nucleus cells [11], later shown to include not only those involved in GH regulation but also an orexigenic cell group, the neuropeptide Y (NPY) cells [12]. A specific GHS receptor (GHS-R1a) was identified and a limited expression analysis reported in 1996 [13]. The first indication that GHS stimulation increased food intake was provided in 1995 [14], although the potential importance of this finding only emerged after the discovery of ghrelin, the first endogenous ligand for the GHS-R1a, in 1999 [1].

## The biosynthesis of ghrelin

Preproghrelin messenger RNA (mRNA) is mainly expressed in X/A cells in the oxyntic mucosa of the gastric fundus [15], but lesser amounts are also produced elsewhere in the gastrointestinal tract and in other peripheral organs [16]. Preproghrelin is processed by cleavage of the signal peptide, which results in proghrelin and obestatin [17]. Proghrelin is further cleaved into desacylated ghrelin by the endoprotease prohormone convertase 13 in (rat) stomach [18]. In order to bind to its receptor, ghrelin needs to be acylated [1]. However, only a minority of circulating ghrelin is acylated [19-21]. Active, acylated

ghrelin consists of 28 amino acids, of which the serine-3 residue is n-octanoylated [1], a reaction catalysed by ghrelin-O-acyl transferase (GOAT) [22-24].

### The ghrelin receptor

Two different variants of the GHS-R have been found, GHS-R1a and GHS-R1b, of which GHS-R1a is the fully functional $G_q$-protein coupled receptor that binds acylated ghrelin [16]. The GHS-R1b is physiologically inactive. In the brain, GHS-R1a is abundantly expressed in hypothalamic and brainstem areas linked to energy balance but also in mesolimbic and limbic areas involved in reward and emotion/cognition [16,25-28]. The extent to which activation of this receptor is only dependent on the afferent gut-brain signal provided by ghrelin remains to be determined as this receptor appears to have constitutive activity [29,30] and potentially heterodimerizes with other receptors such as the dopamine receptor 1 [31].

## The neurobiological effects of ghrelin

Physiological role of ghrelin in the regulation of appetite and food intake

In humans and rodents plasma levels of ghrelin rise preprandially and fall postprandially, suggesting a role for ghrelin in meal initiation or meal anticipation [32-40]. This is also reflected by the finding that plasma ghrelin levels correlate with hunger scores [34,41-43]. Acute ghrelin injection stimulates food intake in rats [44,45] and in humans. [46,47] In addition, chronic administration of ghrelin leads to increased body weight gain [42,45,48] and adiposity [42,49] in rodents. Both the feeding and adipogenic effects appear to be dependent on GHS-R1a as evidenced from studies using ghrelin antagonists [50]. Mice with knockout of ghrelin or its receptor have normal food intake when fed chow, and reductions as well as no alterations in body weight have been reported [51-56]. When fed a high-fat diet, both female and male GHS-R null mice eat less food and show some protection from diet-induced obesity from an early age [55,56]. In addition, GHS-R1a knockout mice have a failure in anticipating food [57,58].

Interestingly, the adipogenic effects of ghrelin may reflect effects on fat utilization rather than food intake alone. Acute and chronic administration of ghrelin has been reported to increase respiratory quotient [42,59], indicating a metabolic switch from the utilization of fat to carbohydrates, while it does not appear to affect energy expenditure [42,45]. Consistent with this, ghrelin knockout -/- mice decrease respiratory quotient when exposed to a high-fat diet [54]. Importantly, these effects on fat utilization were demonstrated after central ghrelin administration and are therefore likely to be centrally mediated [59]. Collectively these data suggest that the GHS-R1a is a relevant therapeutic target for the control of food intake and body weight regulation.

## The neurobiology of the orexigenic effects of ghrelin

The hypothalamus, a key area for the homeostatic regulation of appetite and food intake, is a well established target for ghrelin, reflected not only by the abundance of GHS-R1a in discrete cell groups [27,28], but also by the clear targeted Fos response to ghrelin injection in the arcuate nucleus, reflecting neuronal activation [12,38,45,60-63]. However, mesolimbic areas involved in reward may be especially important for the effects of ghrelin on food intake by stimulating goal-directed behaviour for food.

Within the hypothalamus, one major target neuronal population for ghrelin is the orexigenic NPY neurons that co-express another orexigenic peptide, agouti-related protein (AgRP). These neurons are activated by ghrelin as shown by stimulation of Fos expression [12,64,65], by electrophysiological studies [66,67], and by increased NPY and AgRP mRNA expression [45,48,68,69]. The feeding effects of ghrelin appear to require normal NPY/AgRP signalling as they are abolished in mice with deletions of both NPY and AgRP [68], in mice with ablations of AgRP neurons [70] and in rodents treated with NPY receptor antagonists [45]. Downstream targets include the anorexigenic pro-opiomelanocortin (POMC) system that becomes inhibited as ghrelin increases GABAergic signalling, from NPY/AgRP to POMC neurons [66]. Consistent with this, ghrelin-induced food intake can be blocked by α-melanocyte-stimulating hormone (α-MSH, a product of the POMC gene) [71,72]. Moreover, mice with deletions of melanocortin 3 receptor and melanocortin 4 receptor, the target brain receptors for α-MSH, do not show an orexigenic response to ghrelin [68].

Although most research on the orexigenic effects of ghrelin focuses on the hypothalamus, ghrelin signalling via the caudal brainstem plays a role as well. GHS-R1a is expressed in the area postrema (AP) [28] and roughly 40% of AP neurons respond to ghrelin [73]. Peripheral administration of ghrelin activates the AP directly, and the dorsal motor nucleus of the vagus and nucleus of the solitary tract indirectly [74]. Ghrelin injections of the caudal brainstem elicited feeding [75] and lesions of the AP attenuated ghrelin-induced feeding, without affecting its body weight increasing effects [76]. Furthermore, disruption of the connections between the hypothalamus and nucleus of the solitary tract prevented the orexigenic effect of ghrelin after peripheral administration, but not following central administration [77].

## Reward-related effects of ghrelin

Ghrelin exerts its effects on food intake and food-oriented behaviours through multiple brain mechanisms and not only, as initially believed, through hypothalamic energy balance circuits (for a review of this emerging field see Skibicka and Dickson [78]). In humans, ghrelin administration elicits an increased neural response to food images in brain areas involved in encoding reward-value to food [79].

GHS-R1a is expressed in several nodes of the mesolimbic system [27,28,80] including the ventral tegmental area (VTA) and nucleus accumbens (NAc) [81]. Ghrelin action at these sites has been suggested to increase reward-related food intake. However, the VTA and other non-circumventricular organs are less accessible than the Arc to circulating peptides and hormones, as they are protected by the blood-brain barrier. Activation of GHS-R1a in the VTA could be achieved by either circulating ghrelin that crosses the blood-brain barrier [82,83] or by centrally produced ghrelin [67,84,85]. Ghrelin administration directly in either the VTA or the NAc was found to have an orexigenic effect [80,86]. Furthermore, ghrelin specifically enhances the intake of palatable food [87], which is dependent on VTA ghrelin signalling [88]. Multiple studies reveal that ghrelin can increase the rewarding value of palatable food as measured by classic tests of reward (conditioned place preference) [88,89] and food motivation (progressive ratio operant responding) [89-92]. These effects are at least partly mediated by the VTA, while the NAc seems not to play a role in the effects of ghrelin on motivated behaviour [91].

Dopamine is the main neurotransmitter involved in reward-related behaviours. More than 50% of dopaminergic VTA neurons co-express GHS-R1a. In addition, GABAergic VTA neurons that regulate activity of the dopaminergic neurons also express GHS-R1a [80]. Thus, ghrelin might augment afferent reward signals via increased dopaminergic transmission from the VTA to the NAc [81]. In line with this idea, ghrelin administration resulted in increased dopamine levels in the NAc [80,93-95], which requires GHS-R1a in the VTA. In addition to the effect of ghrelin on dopaminergic neurons in the VTA, ghrelin may be able to modulate dopaminergic transmission at synaptic terminals both presynaptically [67] and postsynaptically via heterodimerization of GHS-R1a with dopamine receptor 1 [31], although this needs to be confirmed in vivo. Interestingly, ghrelin can also amplify the effects of other reinforcing behaviours, such as drug- and alcohol-induced behaviours [96-103]. Therapeutic avenues that exploit GHS-R1a signalling may therefore span disease areas like substance use disorders and eating disorders, including those that lead to obesity.

# The role of ghrelin in eating disorders

The regulation of appetite and energy balance is complex. Peripheral signals from adipose tissue, pancreas and the gastrointestinal tract influence central circuits in the hypothalamus, brain stem and limbic system to modulate food intake and energy balance. Most peripheral signals are anorexigenic. Leptin and adiponectin are hormones produced by adipose tissue implicated in long-term satiety, while gut hormones such as peptide YY, glucagon-like peptide-1 and cholecystokinin regulate shorter-term appetite control. Ghrelin is the only known gut-brain hormone that is

Table 6.1 | Ghrelin and other peripheral peptides in eating disorders

| Hormone | Eating disorder | | | | | |
|---|---|---|---|---|---|---|
| | Obesity | PWS[a,b] | AN[c] | BN[c] | BED[a] | NES |
| Orexigenic hormones | | | | | | |
| Ghrelin levels | ↓ | ↑ | ↑[d] | =[d] | =/↓ | ↓ |
| Postprandial response | Blunted | Blunted/normal | Blunted/normal | Blunted | Blunted/normal | ? |
| Ghrelin levels after weight normalization | = | ? | = | NA | = | NA |
| Anorexigenic hormones | | | | | | |
| Leptin levels | ↑ | = | ↓ | =/↑/↓ | =/↑ | ↓[e]/= |
| Adiponectin levels | ↓ | ↑ | =/↑/↓ | =/↑/↓ | ↓[f] | ? |
| Cholecystokinin levels | = | ↑ | =/↑ | =/↓ | = | ? |
| Postprandial response | Normal | Blunted/normal | Augmented/normal | Blunted | Augmented/normal | ? |
| Glucagon-like peptide 1 levels | ↓ | = | =/↓ | =/↓ | = | ? |
| Postprandial response | Blunted | ? | Blunted | Blunted/normal | Normal | ? |
| Insulin levels | ↑ | ↓ | =/↑/↓ | =/↓ | = | =/↑ |
| Peptide YY levels | ↓ | =/↓ | =/ ↑/ ↓ | = | = | ? |
| Postprandial response | Blunted | Blunted/normal | ↑ | ↑/↓ | Augmented/normal | ? |
| References | [104-111] | [112-122] | [106,123,124] | [123,125,126] | [127-132] | [133] |

[a] BMI-matched controls.[b] Results from children and adults with PWS.

[c] Adapted from Monteleone.[123]

[d] Result found in the majority of studies.

[e] Diurnal rise.

[f] Compared with healthy controls.

orexigenic. By modifying food intake and altering the incentive value of food, ghrelin plays an important role in eating behaviour and body weight control. A dysfunctional ghrelin axis is therefore implicated in eating behaviour disorders and obesity. Ghrelin agonists or antagonists may provide diagnostic clinical tools and/or new treatment options for these disease areas. A brief overview of important hormones and their changes in different eating disorders are presented in Table 6.1 [104-133]. This review will only focus on the specific role of ghrelin in eating disorders.

## Obesity

Obesity has a multifactorial aetiology involving genetic, metabolic, cultural and psychosocial factors and changes in lifestyle, which result in increased food intake and reduced energy expenditure. Despite extensive research, the prevalence of obesity is still increasing. In recent years it has become a major health problem [134-136]. Currently, the only effective obesity therapy involves bariatric surgery, which carries its own health risks and adverse consequences [137].

In obese individuals total and acylated ghrelin levels are low and negatively correlated to body mass index (BMI) [138-140] and increase during weight loss (see Table 6.1) [141]. While the mechanism behind the reduced ghrelin levels in obese patients is unclear, one potential explanation is that this suppression is secondary to hyperinsulinemia (a consequence of obesity). This is supported by data indicating that hyperinsulinemia inhibits ghrelin secretion [142]. Furthermore, obesity-prone rats showed decreased ghrelin levels prior to increased adiposity as compared with obesity-resistant rats [143]. Given that ghrelin is able to induce feeding responses in obese subjects [144], it seems that obesity is not associated with ghrelin resistance in humans.

In addition to the difference in baseline levels of plasma ghrelin, obese patients may also have altered postprandial ghrelin dynamics. The postprandial decrease in plasma ghrelin seems to be blunted compared with lean subjects [145-147], possibly due to the already lower baseline fasting ghrelin. However, other studies reported a complete absence of postprandial ghrelin suppression in obese subjects [138,148]. Importantly, an absence or a blunted postprandial decrease may lengthen the time an obese individual feels hungry, leading to further weight gain [138,145-148].

Maintaining weight loss is difficult and the reasons for weight regain are complex and not completely understood. Ghrelin might be one of the contributing factors to dietary failure; i.e. after diet-induced weight loss, ghrelin levels increase [141,149] and appear to remain elevated even at 1 year of weight loss [150]. This could be expected to promote increased food intake, possibly leading to renewed weight gain. New treatment options that aim to decrease ghrelin signalling through ghrelin antagonists or ghrelin antibodies might be viable for obesity.

Table 6.2 | Clinical trials with ghrelin-based drugs

| Disorder | Study | Subjects | Drug | Dose, route | Duration of treatment | Effects | Adverse effects | Reference |
|---|---|---|---|---|---|---|---|---|
| Obesity | Double-blind, placebo-controlled | 87 obese subjects | Ghrelin-antagonist vaccine CYT009-GhrQb | 300 µg s.c. injections at 0, 4, 8, 16 weeks | 6 months | Median weight loss of 3.6 kg in both control and vaccinated group | None mentioned: safe and well tolerated | [151] |
| AN | Acute interventional | 9 women with restrictive AN, 7 healthy controls | Acylated ghrelin | 1 µg/kg i.v. | One bolus | [a] Hunger in 6 of 9 AN patients and 5 of 7 controls | No serious adverse effects | [152] |
| | Acute interventional | 9 acute AN patients (4 purging, 5 restrictive), 6 recovered AN, 10 consti-tutionally thin women | Human ghrelin | 5 pmol/kg.min i.v. | 300 min | No significant effect on appetite | Increased sleepiness | [153] |
| | Pilot | 5 female restrictive AN | Acylated human ghrelin | 3 µg/kg i.v. | 14 days twice daily before breakfast and dinner | Increased hunger and daily energy intake by 12–36%, which remained high in post-treatment period. Decreased gastro-intestinal symptoms | Loose stool and mild sweating, but no serious adverse effects or somnolence reported | [154] |

[a] the primary outcome was the endocrine response; hunger was mentioned as a side effect.

AN = anorexia nervosa; s.c. = subcutaneously; i.v. = intravenously.

It can be concluded that therapeutic interventions aiming to suppress the ghrelin axis remain a viable therapeutic approach to treat obesity. Despite this, ghrelin antagonists have yet to enter clinical testing. Unfortunately, one phase I/IIa, double-blind, placebo-controlled, clinical trial with a first-generation anti-ghrelin vaccine, CYT009-GhrQb, was discontinued due to lack of weight loss [151], likely reflecting the production of neutralizing antibodies (see Table 6.2) [152-154].

## Prader-Willi Syndrome

Prader-Willi Syndrome (PWS) is a congenital disorder characterized by obesity, reduced muscle tone, mental ability and hormone deficiencies. It is caused by a defect on chromosome 15q11-q13 [155], although the underlying mechanism that causes obesity remains unknown. Children with PWS have hyperphagia resulting in morbid obesity. In contrast to obese people, children with PWS have high ghrelin levels despite their high BMI (see Table 6.1) [115,156-158]. Ghrelin levels are also positively correlated with feelings of hunger [157], which indicates that the hyperphagia could be ghrelin driven [115,157].

The postprandial decrease of ghrelin is present in PWS children [158-160], as well as in PWS adults [115], albeit possibly blunted [114]. The latter is in contrast to earlier findings of an absent postprandial decrease of ghrelin levels in adults [157]. Compared with lean subjects, ghrelin levels remain elevated postprandially [114,115,157]. High ghrelin could override the satiety response after a meal. Indeed, PWS patients did not experience a suppression of hunger after a large meal [115].

Overall, ghrelin seems to play a primary role in the pathophysiology of PWS by promoting hyperphagia, which results in morbid obesity. Therefore, inhibition of ghrelin signalling could provide a treatment option for patients with PWS.

In fact an indirect manner to suppress circulating ghrelin levels with somatostatin and somatostatin analogues, such as the long-acting somatostatin analogue octreotide, [161,162] have already been tested in PWS patients. Unfortunately, while ghrelin levels were suppressed during the trials, the hyperphagia and elevated body weight did not change [162,163]. Although the lack of effect in this study might be explained by the small sample size or poor efficacy of the somatostatin analogues on ghrelin signalling, it is also possible that satiety in PWS adults may be independent of ghrelin levels, in contrast to children with PWS [157,159]. However, treatment with octreotide caused known serious side effects, i.e. impaired glucose tolerance and gallstones [162]. Treatments directly acting on the ghrelin system remain unexplored (see Table 6.3) [164-171,173-177].

Table 6.3 | Different pathways of ghrelin-based drugs

| Mechanism of action | Development | Drug | Function | Effects | References |
|---|---|---|---|---|---|
| Agonist | Phase III | Human ghrelin<br>Ghrelin analogues | Activates GHS-R1a | Increases FI and lean body mass. No significant adverse effects in cachexia studies. Adverse effects in AN: sleepiness, loose stool and mild sweating | [152-154,164-166] |
| Antagonist | Preclinical | Differs, see[164] | Blocks activation of GHS-R1a | Improves glucose tolerance. Reduces FI and weight loss (selective loss of fat mass) | [164,167,168] |
| Inverse agonist | Preclinical | Differs, see[164] | Reduces high constitutive activity of GHS-R1a | Reduces FI and body weight in mice | [164,168] |
| Immunization | Phase III/preclinical | CYT009-GhrQb<br>Immunoconjugates<br>Acyl-ghrelin specific antibody | Immune response specific to acylated ghrelin | Reduces body weight gain without affecting FI. In humans no significant body weight reduction. No serious adverse effects | [151,168-170] |
| GOAT inhibitor | Preclinical | GO-CoA-Tat<br>Small molecule antagonist of GOAT | Blocks acylated ghrelin production through antagonism of GOAT | Prevents weight gain with lower fat mass, but not lean mass relative to controls. No effect on FI. Blunts insulin response. No toxicity reported | [168,171,172] |
| RNA-Spiegelmer | Preclinical | Nox-B11 | Specific binding for acylated form of ghrelin; blocks biological effect peripherally (does not cross the blood-brain-barrier) | Long-lasting peptide neutralization blocks ghrelin-induced feeding, but does not stimulate FI. Promotes weight loss in diet-induced obese mice. Suppresses GH-release | [168,173-176] |

## Anorexia Nervosa

Anorexia nervosa (AN) is a psychiatric disorder of unknown aetiology, characterized by the refusal to maintain body weight above a minimum, fear of weight gain and a disturbed body image.

Elevated acylated/desacylated ghrelin levels have been reported in acute-stage fasted AN patients [178-189]. This increase seems to normalize after weight recovery [185,188-190]. Some reports indicate a significant lower ghrelin level during treatment compared with control subjects [180,184]. This could partially explain the decrease in drive among recovering AN patients to eat sufficient amount of food for continuing recovery.

In AN, ghrelin antagonists could be used in the treatment of hyperactivity, which is present in up to 80% of all AN patients. Hyperactivity has been regarded as a conscious attempt to lose body weight, but it may also be an expression of foraging behaviour in AN [58]. It has been found to impact treatment outcome [191], lead to longer hospitalization [192] and is associated with a higher relapse rate [193]. Ghrelin antagonists were found to reduce locomotor activity in animals in an AN model, without affecting food intake [58]. Reducing hyperactivity remains an important treatment goal in AN. However, the use of ghrelin antagonists to reduce hyperactivity in AN patients is controversial due to the potential reduction in food intake.

When differentiating between subtypes of AN, higher ghrelin levels have been found for binging/purging AN compared with restrictive AN [186,188], which could imply a role for ghrelin in binging/purging behaviour. The link between ghrelin and binging/purging AN is further supported by the finding that single nucleotide polymorphisms in the ghrelin gene are specifically associated with binging/purging AN [194]. However, this association with binging/purging behaviour was not replicated by other studies [195,196]. Contrasting reports also exist that indicate lower acylated and total ghrelin levels in binging/purging AN [179]. Findings on ghrelin dynamics in AN are also mixed. However, most reports found intact postprandial ghrelin responses [190,197-200]. A few studies indicated an almost absent postprandial decrease [182] or delayed nadir [187] after food intake. The contrasting result of these studies may be (partially) due to difference in study populations (restrictive vs binging/purging), in measured stages of the disorder, in experimental conditions (different test meals) and even in assays used to determine ghrelin plasma levels.

Taken together, these findings indicate the complexity of the role of ghrelin in the pathophysiology of AN. As a new therapeutic treatment option, administration of ghrelin agonists could increase food intake and hunger in restrictive AN patients and thus promote weight gain.

To date, only three studies have measured the effect of ghrelin injections on patients with AN (see Table 6.2). In the first study hunger, food intake and body weight were not measured as primary outcomes, but hunger was mentioned as an adverse

event [152]. A recent pilot study again reported increased hunger sensation, and more importantly an increase in food intake after ghrelin administration to patients with restrictive AN [154]. This was not found in an earlier study [153], perhaps reflecting differences in population, treatment duration and dose. More research is needed to determine whether ghrelin indeed has a role in binging/purging behaviour. On the other hand, ghrelin agonists do seem to be beneficial in increasing food intake in restrictive AN patients. Larger clinical trials are needed to confirm this finding.

## Bulimia Nervosa

Bulimia nervosa (BN) is characterized by binging episodes (the consumption of large amounts of food in a short amount of time) with the feeling of loss of control during the binges and concomitant compensatory behaviours afterwards, typically consisting of purging (self-induced vomiting), misuse of laxatives and excessive exercise. In BN, fasting ghrelin levels were found to be elevated [196,201,202] specifically in patients with binging/purging behaviour in contrast to non-purging patients [196]. However, in subsequent studies, no difference was found in fasting ghrelin levels between BN patients and healthy matched control subjects, and between binging/purging and non-purging patients [140,181,203-206]. In contrast, lower fasting levels of ghrelin have also been reported in one study [179].

The postprandial decrease in ghrelin levels has been reported to be blunted in BN [205,207], possibly indicating a reduced satiety response, which in turn could explain binges. This is further strengthened by the finding that sham feeding resulted in elevated ghrelin levels compared with control subjects during the cephalic phase, which correlated positively with ghrelin levels [208]. Elevated ghrelin levels during the cephalic phase could potentially induce binging/purging behaviour independent from hunger sensation [208]. These data suggest that ghrelin dynamics may have an important role in BN pathology. Further research is needed to determine whether ghrelin antagonists could reduce binging/purging behaviour.

## Binge Eating Disorders

Binge eating disorders (BED) are characterized by binges in which the individual experiences loss of control over eating behaviour, with no compensatory behaviour afterwards. This increases the risk for obesity [209]. Ghrelin levels were found to be significantly lower preprandially, postprandially and during fasting, while ghrelin decreased less postprandially with a longer time to nadir compared with obese subjects without BED [129,130], although not by all [128]. The altered ghrelin dynamics could contribute to longer and larger meals as seen during binge episodes. However,

fasting ghrelin levels do not seem to correlate with the frequency and severity of binging/purging behaviour in BED [140]. A negative relationship between ghrelin levels and binge/purging behaviour has been found, but this most likely reflects nutritional status rather than eating pathology [204]. This is along the lines of lower fasted ghrelin levels found in non-obese BED patients, which is probably secondary to the positive energy balance due to binges [140].

A link between ghrelin and BED is suggested by association of a polymorphism of the ghrelin gene with BED [210]. Whether there is a role of ghrelin in BED eating pathology remains to be elucidated.

### Night Eating Syndrome

Night eating syndrome (NES) is a disorder characterized by hyperphagia or binge episodes in the evening/night, sometimes with waking up to consume food. It is currently proposed as a new disorder for the DSM-5, though at present there are no official diagnostic criteria [211].

Two recent studies [212,213] have reported significantly lower nocturnal ghrelin levels in NES patients compared with control subjects. Whether this is due to altered hormonal patterns or secondary to altered food intake could not be determined [213]. However, ghrelin had a lack of phase coherence with other circadian rhythms, which, according to Goel and colleagues [213], may represent an important mechanism in NES.

These lower ghrelin levels are in contrast to a (case) report that reported elevated mean nocturnal ghrelin levels [214]. The latter suggests a clear primary role of ghrelin in the pathophysiology of NES, i.e. higher ghrelin level throughout the night result in waking up for food intake in the evening/night. Despite mixed results these limited data do suggest an important role for ghrelin in the pathophysiology of the disorder.

## Clinical development

It is beyond the scope of this paper to discuss structure, affinity and pharmacological profile of the different drugs in development. For this purpose we refer to an excellent review by Chollet and colleagues [164]. There are several drugs in development that target the ghrelin system. These drugs can be subdivided into ghrelin agonists (GHS included) [164], antagonists and inverse agonists [164], antibodies [151,169,170], and RNA-spiegelmers [173-175] (see Table 6.3). They also include inhibitors of GOAT [172], the enzyme responsible for the unique n-acyl modification of ghrelin that is required to enable binding to GHS-R1a.

For treatment of obesity the lack of effect of the anti-ghrelin antibody therapy

has been disappointing [151,170]. This could be an effective treatment in children with PWS, since appetite and obesity in PWS children seem to be induced by high ghrelin levels. GOAT inhibitors and ghrelin antagonists/inverse agonists remain a plausible option for the treatment of PWS but require continuous pharmacotherapy because the chronic elevated ghrelin levels are inherent to the disorder. Ghrelin antagonists or GOAT inhibitors could be more beneficial for the treatment of obesity and relapse prevention where the (long-term) reduction of preprandial ghrelin signalling, and normalization of postprandial decrease of ghrelin are therapeutic aims. This, however, would most likely be add-on therapy to dieting.

Ghrelin agonists and GHS are being tested in phase I/II and phase III trials in cachexia, a process of reduced food intake and weight loss in chronically ill patients [165,215]. The overall effect of ghrelin administration in cachexia patients with reduced food intake due to a somatic disorder is promising and results in increased food intake and body weight. Little to no adverse effects were reported [165]. The advances already made with ghrelin agonists along with the potential beneficial effect on food intake and weight encourage future clinical trials for AN patients [183]. For the treatment of BN and BED more research is needed to determine whether eating pathology is related to altered ghrelin dynamics.



# Summary

Ghrelin levels and dynamics are altered in eating disorders. Ghrelin has a variety of functions, which can potentially be utilized for different diagnostic and treatment purposes [216]. In eating disorders, ghrelin has been proposed as a diagnostic marker in order to differentiate between (sub)types [179].

For (restrictive) AN, ghrelin agonists are likely to have beneficial effects by increasing food intake and lean body mass and thus remains a very promising new drug for the treatment of AN. The pathological eating behaviour in BN, BED and NES seems to be related to altered ghrelin dynamics. However, more research is needed to determine whether ghrelin antagonists or even ghrelin agonists could be used as a treatment option or diagnostic tool in these disorders.

In obesity several different potential drugs are in development. Ghrelin antagonists combined with dieting seem to remain the most promising. In PWS, lowering of ghrelin levels through immunization is an interesting option. Large clinical trials are needed to evaluate the efficacy and safety of these drugs. Unfortunately, at this moment there are no commercialized ghrelin-based drugs available.

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CHAPTER 7

# General discussion

The aim of this thesis was to elucidate the early life determinants, and the prognosis of picky eating. Four main aspects were addressed.

1. Further conceptualization of the construct of picky eating
2. The prevalence of picky eating
3. Risk factors associated with different trajectories of picky eating
4. Adverse mental health outcomes associated with different trajectories of picky eating

This chapter will summarize the main findings, followed by an interpretation and general discussion of these findings. Lastly, methodological considerations and implications for further (clinical) research are discussed.

# Summary and interpretation of findings

## Conceptualization of the construct of picky eating

The term picky eating is relatively new in scientific literature. Although food-neophobia is sometimes used interchangeably with picky eating, Dovey poses that they are two different constructs [1]: food-neophobia is limited to an unwillingness to try new foods, while picky eating is a broader construct and indicates "children who consume an inadequate variety of foods through rejection of foods that are familiar and unfamiliar". This can lead to a reduced caloric intake. Research is hampered by a lack of clear definitions or accepted classifications for picky eating [1]. No gold standard for the measurement of picky eating exists, assessment typically relies on parent report, and different assessment methods are in use, varying between single questions to complete questionnaires [2].

In this thesis picky eating was operationally defined by the sum of mother's response to two items of the Child Behavior checklist (CBCL), a symptom checklist commonly used for children; "my child does not eat well" and "my child refuses to eat". The items are rated on a 3-point Likert scale ranging from 1 (never) to 3 (always). In line with other studies, the group responding with '2 - somewhat' or '3 - always' were defined as the picky eating group (sum score 4 or higher). On the one hand one could argue that picky eating status should be limited to the "always" group (sum score 6) only, as these children most likely have the highest risk for adverse health outcomes, such as weight loss or nutritional deficiencies. On the other hand there are several arguments to adopt a wider definition of picky eating status: first, even moderate picky eating behavior correlates with psychopathological symptoms both cross-sectionally and longitudinally [3]. Second, not the severity but the perseverance

of the picky eating may be central to the picky eating status. Picky eating in young children is most likely a phase of normal development [4], and it is expected that -regardless of the severity- remitting picky eating will not have (long-term) adverse health outcomes. Furthermore, picky eating in general (not only the most severe form) is described by parents as a feeding problem that is difficult to deal with, which is an often heard problem in primary care [5]. Health care professionals should be aware that picky eating in a broad sense can lead to problems in the parent-child interaction, and thus may require professional attention and counseling. Lastly, although some of the children with picky eating problems may develop an Avoidant/ Restrictive Food Intake Disorder (ARFID), it is not known whether picky eating in the general population is a precursor for ARFID, and if the at risk group consists solely of children with the highest picky eating score. Thus we adopted a broad definition of a picky eater and included the 'somewhat' responders.

The current methods of assessing picky eating, although diverse, seem to approximate a common concept of picky eating: an eating behavior in the general population defined by parents as problematic [6]. No further indication of adverse (long-term) health outcomes is part of the definition, but to a selective eating pattern.



There have been several attempts to validate the construct of picky eating [6-8], although additional characteristics beyond the selective eating pattern remain elusive. A central theme in the construct of picky eating is, as Jacobi implied [6], a child with a pattern of inhibited eating. The focus in chapter 2 & 3 was on the further conceptualization of this construct of picky eating. The picky eating behavior was found to be associated with other problematic feeding behaviors as assessed by the child eating behavioral questionnaire (CEBQ). The CEBQ eating scales pertain to the most often mentioned characteristics of the picky eating construct. Comparing picky eating defined by the CBCL with the CEBQ scales provides information whether picky eating assessed with the CBCL relates to this "picky eating construct". As described in chapter 3, an association was found between picky eating and food-neophobia (as part of the fussy eating style scale), higher food satiety and slowness in eating, emotional under-eating, and less enjoyment of food. Chapter 2 reviews the scientific literature and shows that a more consistent picture emerges: the picky eating construct is a behavioral tendency which encompasses food selective and neophobic behaviors (possibly) leading to a reduced caloric intake, with related characteristics being less enjoyment of food, higher food satiety and slowness in eating. Because these characteristics are mostly child inherent [9], parents – although they try their best to give their child an adequate food intake – accept picky eating as a part of their child's identity instead of continuing to struggle over mealtime problems [10].

## Prevalence of picky eating

In chapter 2 and 3 the prevalence of picky eating was discussed. Important to note is that, depending on the assessment method and cut-off used, prevalence estimates will vary. In the general population of Rotterdam, the Netherlands, (chapter 3) prevalence estimates of picky eating were found to be 26.5% (CI 95% 25.1 - 29.7) and 27.6% (26.1 - 29.1) at respectively 1,5 and 3 years of age, and decreased to 13.2% (12.2 - 14.3) at 6 years of age. In preschool children in other western countries similarly high prevalence rates with wide ranges were found; i.e. 10 - 29% in the USA [11 dubois, 12] (with a high peak prevalence rate of 50% noted in one study in two years old in the USA [13]), 8 - 11% in the UK [2, 5], 14 - 17% in Canada [14], 20% in Italy [15], 22 - 35% in Norway [16], and 34.1% in Australia [17]. Using another computational method (latent class analysis) lower prevalence rates have been found in children 4 years of age, e.g. 5.6% in the same cohort as in chapter 3 [18] and 7.3% in Denmark [19]. Picky eating rates in preschool children in Non-western countries are comparable with Western prevalence rates, with a range from 12.7 to 38.7% [2, 20–23]. Taylor and colleagues [2] therefore conclude that prevalence rates of picky eating seem comparable, regardless of country, age, or assessment method. In later childhood (after preschool age) few prevalence studies have been conducted and varying age ranges hamper comparability [11, 23–24].

In chapter 3 we evaluated picky eating behavior from a developmental perspective. A “picky eating phase” is considered by many health professionals as a normal phase in the child’s development which eventually will pass [4]. Children usually readily accept food offered when complementary feedings starts around the 6$^{th}$ month of age. Around the age of 1 picky eating problems emerge in some children and [25], as commonly agreed, remit after the age of 4 for the majority of these children. The different trajectories of picky eating in our study were defined taking this developmental phase into account. Our analysis of predictors and outcome of predefined trajectories is quite novel within picky eating research, and is an attempt to differentiate several subtypes of picky eating behavior and to establish clinical relevance for the different trajectories. Between 1 and 6 years of age approximately 45% of the children in our general population study were described by parents as being a picky eater in at least one assessment wave (1, 3 and 6 years). About 4% had picky eating problems from preschool (age 1 and 3) up to the age of 6 years (the persisting picky eaters). Another 4% were found to have picky eating problems at the age of 6 only (the late-onset picky eaters). 32% were children with picky eating problems in preschool (1 and/or 3 years) only; their picky eating problems had remitted before the age of 6 years (the remitting picky eaters). A remaining 5% had an inconsistent pattern of picky eating over time.

Feeding difficulties in general are worth clinical attention as they can negatively impact parent-child interactions [11, 23]. A comparative assessment is needed to

determine whether splitting into different subtypes helps understand underlying causes of a behavior and may inform prognosis or therapeutic options. In order to achieve this, advances are needed in establishing distinct constructs with clear boundaries. In chapter 5 we found that only the persisting picky eating group (and not the group of remitting picky eaters) was at risk for adverse mental health outcomes; the implications of this are discussed below. Thus, the use of picky eating trajectories differentiates between clinical relevant picky eating groups.

## Risk factors of picky eating

Several risk factors for picky eating are known [2, 6, 16]. Most of these risk factors are indicators of low socio-economic status (SES) and general parental psychopathology. In addition, duration of breastfeeding, introduction of complementary food, and other child characteristics such as gender and birth weight have been associated with picky eating [6, 16]. For example, breastfeeding could expose the child to different tastes during early childhood, reducing the chance of picky eating [16]. In chapter 3 & 4 many potential risk factors were examined. In particular, we studied if risk factors of picky eating differed between children with different trajectories of picky eating. We hypothesized that few if any risk factor predicted membership in the remitting picky eating group as remitting picky eating is considered a variant of normal development. When looking specifically at the difference in risk factor profiles between trajectories, remitting and never picky eaters indeed hardly differed. This fits well with the hypothesis that remitting picky eating is part of normal development. The only risk factor that differed between the remitting and never picky eating trajectories was birth order. Being first born was predictive for remitting picky eating. Birth order was neither predictive nor protective in the other trajectories. In contrast children with persisting or late-onset trajectories had a different risk factor profile compared to never picky eaters. Risk factors associated with both trajectories were predominantly indicative of lower SES (maternal ethnicity and household income). Only the persisting picky eaters had child related risk factors (low birth weight and male gender). The latter strengthens the hypothesis that the persistent picky eating trajectory resembles a feeding disorder, as males are more often diagnosed with ARFID [26]. In the ALSPAC study [2] more risk factors for picky eating were found than those reported in chapter 3, such as maternal age, maternal education, BMI before pregnancy and smoking status. In our study (chapter 3) those same risk factors were taken into account and in the preliminary analyses were indeed found these to be associated with picky eating. However, in the multinomial logistic regression this effect disappeared. It is possible that our study was underpowered to find an association. However, it is more likely that the risk factors found in the ALSPAC study were confounded by other factors. Our study (chapter 3 and 4) did not include breastfeeding and introduction

of complementary foods as possible risk factors of picky eating. More research is needed to assess the influence of these factors in the development of picky eating.

In chapter 4, parental psychopathology was measured before child birth to disentangle the potentially bi-directional relation between picky eating behavior of the child and anxiety and depressive symptoms of the parents. Our results demonstrate that antenatal parental psychopathology was predictive for picky eating at 4 years of age, independent of postnatal internalizing symptoms. Parental psychopathology can influence eating behavior in different ways. For example, a genetic explanation could be that anxiety is heritable [27], which in turn is reflected in picky eating by the child. On a behavioral level, parents who are more anxious could be more cautious in the introduction of complementary foods for the fear of their child choking. And parents with anxious and depressive symptoms could respond less adequately to the child's feeding behavior and/or feeding needs. Those factors could lead to late (after 10 months of age) introduction of solids foods or to insufficient encouragement of children to eat a greater variety of foods, increasing the possibility of developing picky eating problems. This "maternal catastrophizing" and reduced engagement with the child has been demonstrated in observational studies [28 - 30].

It is important to find out how factors such as breastfeeding, introduction of complementary foods, parenting factors and peer influences determine the trajectories of picky eating, as studies show that these factors can have a long lasting effect on the eating behavior of the child [31].

## Adverse mental health outcome measurements of picky eating

Extreme picky eating that meets diagnostic criteria for ARFID is inherently linked to adverse health outcomes, as part of the classification criteria. However, there is debate whether moderate to severe picky eating behavior in the general population is associated with adverse health outcomes (see Zucker et al., 2015) [3]. Picky eating has been associated with lower weight, functional constipation, some nutritional deficiencies and problematic child-parent interactions [13, 23, 32 - 34], anxiety, depressive symptoms and pervasive developmental disorders [19], and even anorexia nervosa [24].

In chapter 5 our results demonstrate that remitting picky eating had no adverse mental health outcomes. Regardless of the underlying mechanism, if remitting picky eating is not predictive for adverse mental health outcomes in our study, this strengthens the theory that it is a normal developmental variation. Persisting picky eating may be associated with pervasive developmental problems as children with autism spectrum disorders have a high prevalence of picky eating problems [35]. Late-onset picky eating could reflect problematic parent-child interactions, but there are insufficient data to formulate a specific theory. In our study even the persisting picky eating trajectory was only associated with pervasive developmental problems.

This complements the finding that up to 80% of the children with autism spectrum disorders have feeding difficulties [35]. As the persisting picky eating trajectory may be of clinical relevance, research should focus on this trajectory to elucidate prognosis and outcomes.

In contrast to earlier studies, in our study no association was found between anxiety and depressive symptoms in any of the picky eating trajectories. This may be the effect of adjustment for (multiple) confounding which other studies lack; we found an association between emotional (anxiety and depressive symptoms) in remitting as well as in persisting picky eaters, but the effect disappeared when controlling for other risk factors.

There may be a reversed relation between picky eating and internalizing problems. I hypothesize that children with internalizing problems could be at risk for developing picky eating problems, as anxiety in childhood predicts eating problems at later age [36]. In contrast, children with less anxiety and more externalizing problems could be protected against the development of picky eating problems. Some nuance is in place if these results from the general population are generalized to a clinical setting as comorbid behavioral problems were high in children with feeding problems in an inpatient clinic [37]. Conversely eating problems have been found to be predictive for depressive and anxiety disorders in adolescence [38], demonstrating the complex interaction between feeding and adverse mental health.



Chapter 5 addressed adverse mental health outcomes. However, to determine whether remitting picky eating is part of normal development, somatic adverse health outcomes should also be taken into account. A recent study of de Barse and colleagues [39] demonstrated that persistent picky eaters only (not those with remitting or late-onset picky eating) were at risk to be underweight at 6 years of age.

Our persisting picky eating group was formed by children who were picky eaters from 1 year of age onwards. Possibly if picky eating emerges at 3 years of age and persist throughout childhood, the same adverse health outcomes may be expected. This would indicate that the essence is not the age at which picky eating emerges but whether it persist. However, a persisting aberrant eating pattern does not per se lead to adverse somatic health outcomes. For example, a recent review demonstrated that food neophobia did not affect child weight status [40], and picky eaters with normal weight were not at risk of becoming underweight at follow-up [41].

Summarizing, remitting picky eating has a risk profile comparable to that of the never picky eaters, and is not predictive for mental and somatic adverse health outcomes. Thus we cautiously propose that it should be treated as being part of normal development. In contrast, health care professionals should be aware that the persisting picky eating trajectory is more often associated with adverse health outcomes and may require additional testing and treatment. It is unclear if persisting picky eating or other picky eating trajectories develop into feeding disorders (diagnosed by pediatricians) or ARFID (diagnosed by psychiatrists). As picky eating

is proposed to be seen as a continuum between normal eaters at one end, and ARFID at the other (chapter 2), it is important to determine which factors contribute to the development of ARFID, and when these developments take place. Objective measurements regarding food intake [42], underlying somatic pathology, distress, and family interactions are needed to further differentiate between ARFID and picky eating. This is discussed in the methodological considerations.

# Methodological considerations

## Taxonomy and dimensionality in selective eating problems

Diagnosing mental health disorders in early childhood and research on this subject is challenging due to several reasons as Egger & Angold summarized [43]; it is difficult to decide which diagnostic criteria should be used, in particular since early childhood is a period of rapid developmental change and it is unclear what the differences between normative, temperamental and clinical variation are. The DSM IV (and subsequently the DSM-5) do not take these developmental changes into account. During early childhood it is essential to study the parent-child dyad, as this may also be a cause of the child's mental health problems.

When narrowing in on feeding problems, the term "Failure To Thrive" (FTT) has often been used by pediatricians. FTT was described as an umbrella diagnosis, referring to a plethora of problems that caused the child to fall significantly below a certain weight or inability to gain weight appropriately [44]. FTT was subdivided into organic FTT and nonorganic FTT (involving parent-child interaction problems, environmental factors and/or child's psychopathology) [44]. However, the concept of FTT had its limitations in clinical use as the two forms (organic and nonorganic) overlapped, and most children with feeding disorders had no growth problems [44]. In recent years FTT is seen as the result of an interaction between a child's health, environment and behavior [45]. In an attempt to better categorize feeding problems the American Psychiatric Association (1994) introduced the category of "Feeding Disorder of Infancy and Early Childhood". This disorder was defined by a persistent failure to eat adequately resulting in significant failure to gain weight or significant loss of weight over at least one month, without an association with a gastrointestinal or other general medical condition or mental disorder. The onset was postulated to be before the age of 6 years. Other classifications systems have been proposed, the most commonly known is from Chatoor [46] and distinguishes 6 subtypes of feeding disorders. However, these classification systems have not become universally accepted as they leave large groups of children unclassified [47]. In an attempt to cover this heterogeneous population, the diagnostic category ARFID has been proposed and included in DSM-5, replacing the Feeding disorder of infancy and childhood [48].

ARFID is a diagnostic category described as a feeding disturbance leading to weight loss, nutritional deficiency, dependence on enteral feeding or marked interference with psychosocial functioning [48]. In line with the general direction of DSM-5, ARFID can also be present in adolescents and adults and the onset criterion of 6 years has been dropped. As ARFID is a new diagnostic category future research is needed to distinguish between normal behavioral variation in feeding and eating, ARFID, and other feeding and eating disorders. This is especially difficult in the case of ARFID as there is a wide variation of parent reported problematic eating behaviors in children, picky eating being one of them. In contrast to "Failure To Thrive" and "Feeding Disorder of Infancy and Early Childhood", ARFID may be comorbid with medical conditions and other disorders. ARFID can be diagnosed if the severity of the eating disturbance exceeds what is expected of the medical condition or disorder. Thus the DSM-5 has continued the categorical taxonomy of psychiatric disorders, but a "dimensional approach" [49] was introduced in the form of a severity index [50].

This thesis had several "dimensional vs. categorical approach" aspects. For example in chapter 5 the teacher report form score was dichotomized to have a categorical outcome measure. Instead of using clinical cut-off levels, lower cut-offs that indicate a subclinical problem level were used to increase statistical power. However, continuously modeled outcomes were also presented to demonstrate that the findings were not dependent on cut-off choice. In chapter 4, picky eating was assessed using a cut-off of ≥ 4 (sum range: 2 - 6) with a total agreement between mothers and fathers of 76.7%. A dimensional approach can more easily integrate the different sources of information, than a categorical approach [49]. A possibility would be to categorize picky eating behavior on a continuum or into three broad categories: the normal picky eating variant; picky eating at high risk for adverse health outcomes; and ARFID. However, clinicians still need to make categorical decisions whether to treat or not [49]. Differentiating between subtypes of picky eating problems is valid if it has clinical relevance and is predictive for outcome. This may be the case as we demonstrated that it is possible to distinguish a normal picky eating phase - containing the majority of picky eaters with no expected adverse health outcomes – from a non-normal picky eating trajectory – containing a minority of picky eaters who are at risk for adverse health outcomes. Future research is needed to distinguish between ARFID and the persistent picky eating group [2].



## Picky eating assessment

No gold standard exists for the assessment of picky eating. In chapter 3 and 5 maternal reports were used to assess picky eating status to establish the prevalence of picky eating behavior in the general population. Studies have demonstrated that measures of picky eating as perceived by mothers are correlated with assessments of standardized meals and nutrient intake, and that maternal ratings are an acceptable measure of picky

eating status in children [1]. Our aim was to achieve an assessment across the total range of picky eating by capturing all children with picky eating problems - ranging from mild picky eating behavior, which may be part of normal development, to the most extreme form of picky eating which, could be classified as ARFID.

It is evident that this method results in a heterogeneous picky eating population. To further narrow down picky eating problems, additional testing would be required on dietary pattern and underlying pathology in order to exclude (picky) eating due to somatic disorders, familial-environmental factors or ARFID. However, such specific additional testing is not feasible in a large cohort study such as our Generation R Study. More feasible would be an approach with two or more stages to identify children at high risk. In this thesis a first step was done by differentiating between picky eating trajectories and establishing which of these trajectories were associated with a higher risk for adverse health outcomes. As a next step (video home) observations of picky eating behavior could be considered after which evaluation by an expert who can differentiate between ARFID and picky eating could follow. Home mealtime observations have several advantages over maternal reports of picky eating: first, since the child is in its natural environment it behaves more naturally and a more accurate assessment of mealtime behavior is to be expected [51]. More importantly, the parent-child dyad can be observed, including the severity of mealtime behavioral problems, feeding styles, and problematic parent-child interactions; most video mealtime observations [52 - 54] evaluate appropriate (i.e. asking for food and interacting with parents) as well as disruptive (i.e. food refusal and oppositional behavior) feeding behaviors, and aversive (i.e. coaxing) and non-aversive (i.e. encouragement) parental behavior. Observations could be less biased than parental or teacher reports [55]. However, video observations methods also have several limitations [56]; the most important relate to validity questions regarding the “camera-in-situ” effect on the observation, and whether the recordings of what is observed approximates the reality; other studies have demonstrated that observational studies can lead to bias by observers and those being observed [56]. Other issues regard the coding and additional training required to rate or summarize the data. The rating is time consuming and a special focus on inter-rater reliability is necessary [56]. Observational methods are more expensive and more burdensome for the participants [57]. Video home meals can be combined with mealtime records [52, 58] to assess the amount of food offered and consumed by the child. Finally, the food offered by parents during the recorded meals must be considered: families could serve their usual meals or standardized meals can be offered [59]. Parents tend to adjust the diets of their picky eating child by offering more accepted food types [60]. To address this, a more standardized meal with a variety of foods offered can assess the current food and texture preferences of a child [59]. All in all, a multiple informant approach is needed to further assess picky eating and whether to diagnose ARFID; observational tests are an essential part of this [61-62].

## Ghrelin: The use of Animal models in anorexia research

In chapter 6 the role of ghrelin agonists as well as antagonists were discussed as a new potential drug for the treatment of anorexia nervosa (AN). Ghrelin is one of the hormones that regulate appetite. Ghrelin plasma levels rise before meals, and fall postprandially. In rodents[63-64] and in healthy human volunteers [65-66] ghrelin was found to increase food intake; therefore it makes sense that ghrelin was proposed as a new potential treatment drug for AN (chapter 6). However, as studies are often cross-sectional it remains unclear whether the high ghrelin level found in AN patients is an adaptation to their malnourished state (in order to promote food intake), or whether ghrelin has a role in the pathophysiology of AN as it also is involved in food reward (chapter 6). Animal studies are often used to explore underlying neurobiological and pathophysiological mechanism, as well as to evaluate (adverse) effects of new medicines.

For psychiatric disorders there are relatively few animal models that can be used. One of the most important limitations is that psychiatric disorders often have cognitive and/or emotional elements, which are difficult to translate or measure in animal models [67-68]. A rodent cannot describe whether it does not eat out of fear of gaining weight or if it has a disturbed body image. Rather than trying to mimic anorexia nervosa in animal models, animal models are mostly used to highlight a specific aspect of the disorder. Different animal models have pointed to potential underlying neurobiological mechanisms regarding the role of ghrelin in eating, food reward, and AN (chapter 6). One of specific interest is the "activity-based anorexia" model (ABA-model). This model mimics the starvation and hyperactivity found in anorexia nervosa patients. Hyperactivity is present in up to 40 - 80% of the AN patients [69, 70]. There are several explanations for the hyperactivity behavior in AN [69, 70]. It could be a top-down regulated behavior to increase loss of body weight. From an evolutionary perspective, hyperactivity can be seen as food anticipatory activity (foraging behavior) to find more food during food scarce periods. Hyperactivity is an important aspect of AN as it hampers weight recovery [69], and is often described as involuntary activity by patients with AN. The ABA-model achieves hyperactivity by restricting food intake to one hour feeding a day with free access to a running wheel [68, 70]. The hyperactivity and reduced food intake cause a rapid decrease in body weight, leading to death in several days [68, 70]. Surprisingly the rodents in this model eat less food during the one hour feeding than control rodents in inactive conditions. Face validity is further increased as especially young female rodents are susceptible to the ABA model [68]. There are several methodological considerations in using animal models, mostly regarding the validity of animal models. There is a scientific debate what is measured with the ABA-model (construct validity). For example, giving hydrated food negates the hyperactivity and weight loss [68]. Thus the reduced food intake is possibly caused by a dehydrated animal not willing to eat dry chow, and not

from an underlying neurobiological foraging behavior. Also, increasing temperature using a warm plate or increasing ambient temperature reduces hyperactivity and weight loss [71-72], but this could point to a mechanism to reduce hypothermia as a side-effect of weight loss [69]. The uncertainties regarding the underlying neurobiological mechanisms hamper the translational effects of the findings in animal studies. For example, heat vests were used in the treatment of anorexia nervosa patients, but no increase in weight gain from warming was found [73]. The same holds true for the pharmacological validity of animal models. Pharmacological validity relates to whether drugs have the same effect in animal models as in patients during treatment [67]. For example, ghrelin injections are known to increase food intake in rodents and in humans [74]. It is possible that ghrelin can also increase food intake in AN patients. Indeed, Hotta and colleagues [75] demonstrated that in 5 AN patients ghrelin injections increased hunger and food intake. They did however note that these patients were motivated to gain weight, but were unable to do so due to gastric symptoms [75]. This motivation could explain why in an earlier study no increase in weight gain was found after ghrelin injections, as the AN patients refused to eat [76]. This further emphasizes the difficulty of translational research; having an animal model with face and construct validity does not necessarily imply that the effect will also be measurable in patients, as patients are more capable of top-down control. Nevertheless, animal models are important in establishing the underlying neurobiological mechanism of eating, reward, and eating disorders.

# Clinical relevance and recommendations for future research

This thesis aimed to further conceptualize the construct of picky eating, elaborating on prevalence rates, risk factors and adverse mental health outcomes of different trajectories of picky eating. We found that the “picky eating trait” encompasses more than a selective variety of foods consumed, food neophobia and a reduced caloric intake, but also includes slowness in eating, higher satiety responsiveness and less enjoyment of food (chapter 2). This thesis also confirms the consensus-based view of a normal developmental phase of picky eating; that is, a substantial group of children will develop picky eating problems in early childhood but these problems typically remit before the age of 6 years (chapter 3). More importantly, these remitting picky eaters will most likely not be at risk for adverse health outcomes compared to never picky eaters (chapter 5). Thus we propose to regard remitting picky eating as part of normal development. We also found that the prevalence rates of picky eating problems seem to decline after 4 years of age (chapter 3). Therefore, health professional may take a watchful waiting approach, reassuring the parents that this phase will most likely pass. Health professionals can advise parents regarding

proper mealtime behaviors and frequency of food exposure needed to increase food variability (chapter 2). However, around 4% of the children in the general population have persisting picky eating problems throughout early childhood. These persistent picky eaters are at slightly higher risk for being underweight [39] and adverse mental health outcomes (chapter 5), more specifically pervasive developmental problems. Clinicians should be aware of the risk factor profiles predicting persisting picky eating and the possible adverse health outcomes involved if picky eating persist to 6 years of age (chapter 3 and 4), and whether additional testing is required.

Future research is needed to see if there are predictive risk factors that can identify a persisting picky eating trajectory at an earlier age. Also more research is needed to follow up the late-onset picky eating trajectory to see how it develops over time. Lastly, this thesis was an attempt to further conceptualize the picky eating behavior. Defining trajectories of picky eating was a novel method to distinguish between transient picky eating behavior with little risk for adverse health outcomes and picky eating at higher risk for adverse health outcomes. A next step would be to study the relation between picky eating and ARFID, notably whether picky eating is a precursor for ARFID, and which factors play a role in the development of ARFID, as at this moment very little is known about the etiology, course and outcome of ARFID [48]. In the long term is important to study whether picky eating is associated or is predictive for other eating disorders [24].

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CHAPTER 8

# Summary
# Samenvatting

# Summary

Picky eating is one of the most common development problems in early childhood. Parents reported that around a quarter of the preschoolers have picky eating problems. Although this behavior has a high prevalence and is of major concern for parents, little is known about the etiology, course and outcome of picky eating. At present picky eating is considered to be a normal rite of passage which usually remits. However, picky eating can also lead to a poor nutritional status, faltering weight gain and growth, and is associated with unfavorable mental health outcomes. Thus picky eating embodies two (possibly distinct) trajectories, which are diametrically opposed in their clinical relevance; one group of children who remit and experience little to no clinical consequences and one group that may develop health problems.

The aim of this thesis is to extend the existing knowledge on picky eating by identifying determinants that differentiate between picky eating as part of normal development, and picky eating at risk for adverse (mental) health outcomes. The core of this thesis addresses picky eating in the general population, and aims to establish a better working concept by differentiating between normal and problematic trajectories of picky eating. The majority of the studies were embedded within the Generation R Study, a large prospective population-based cohort study from fetal life onwards (N = 7,295 for the preschool phase) in Rotterdam, the Netherlands. The aims of this thesis were to study 1) the further conceptualization of the construct of picky eating, 2) the prevalence of picky eating, 3) risk factors associated with different trajectories of picky eating, and 4) adverse mental health outcomes associated with different trajectories of picky eating.

Chapter 2 gives an overview of the current body of literature regarding picky eating. It focuses on the conceptualization, factors involved in the development, and the management of picky eating. The findings suggest that the etiology of picky eating is multifactorial. Children with picky eating problems more often have food neophobia, consumption of a limited variety of food, less enjoyment of food, slowness in eating, and a higher satiety responsiveness compared to non-picky eaters. Parental anxiety, stress, and feeding styles probably have a bi-directional association with picky eating. Management of this behavior focuses on reducing parental anxiety and reducing picky eating using food exposure interventions.

In chapter 3 the prevalence, trajectories and prognostic factors of picky eating in early childhood are described. We demonstrated that parents reported picky eating problems at some point in early childhood for nearly half of the children. Prevalence of picky eating was 26.5% at 1.5 years of age and 27.6% at the age of 3 years; at 6 years of age it had declined to 13.2%. Thus, in the majority of children these problems remitted before the age of 6. Only a small portion of children (4%) had persistent picky eating problems in early childhood. These persistent picky eaters were more likely to be male, underweight at birth, and from a social disadvantaged background.

The child characteristics could be an indication of a biological predisposition that promotes picky eating.

The role of parental psychopathology in the development of picky eating is discussed in chapter 4. It is unclear whether parental psychopathology is a risk factor for the development of picky eating, or whether a child with picky eating problems causes parental stress leading tot parental psychopathology. Our results demonstrated that maternal and paternal anxiety and depressive symptoms (even at non-clinical level) predicted picky eating at 4 years of age. More importantly antenatal maternal anxiety problems predicted picky eating, independent of mothers' symptoms at 3 years. These results emphasize the importance of parent-child interactions in child feeding practices.

The association between picky eating and child mental health is discussed in chapter 5. Children with a trajectory of persisting picky eating problems were compared with children with a trajectory of remitting picky eating problems and with persistently non-picky eaters. We demonstrated that in the general population persisting picky eating from 1.5 years to 6 years predicted pervasive developmental problems at 7 years of age. This association remained even after adjusting for baseline pervasive developmental problems at 1.5 years of age.

In other studies picky eating has been associated more broadly with behavioral and emotional problems in childhood. However most of these studies did not control well for potential confounders. There was no prospective association of remitting picky eating problems with adverse mental health outcomes in children. This suggests that remitting picky eating in pre-school children can be seen as part of normal development

Chapter 6 gives an overview of the ghrelin hormone and the potential role the gut-brain ghrelin axis plays in certain eating disorders. The role of ghrelin agonists and antagonists are discussed for their therapeutic potential. However, most of these drugs are in their preclinical phase of development.

In the final part of this thesis, chapter 7, the main findings of the studies in this thesis are summarized and major methodological considerations, as well as implications for clinical practice and future research, are discussed. The main findings of this thesis confirms the consensus-based view of a normal developmental phase of picky eating; that is, a substantial group of children will develop picky eating problems in early childhood but these problems typically remit before the age of 6 years. These remitting picky eaters are not at risk for adverse health outcomes. Thus we propose to regard remitting picky eating as part of normal development. Health professional may take a watchful waiting approach, reassuring the parents that this phase will most likely pass. Only a small group of children (4%) in the general population have persisting picky eating problems throughout early childhood. These persistent picky eaters are at slightly higher risk for pervasive developmental problems. Clinicians should be aware of the risk factor profiles predicting persisting picky eating, and

whether additional testing is required.

Future research is needed to see if there are predictive risk factors that can identify a persisting picky eating trajectory at an earlier age. Also more research is needed to follow up the late-onset picky eating trajectory to see how these children develop over time.

# Samenvatting

Dit proefschrift gaat over picky eating en picky eaters - ofwel Moeilijke eters in de terminologie van het Centrum voor Jeugd en Gezin. Picky eating is een veel voorkomend probleem in de ontwikkeling van het kind tijdens de vroege jeugd. Een kwart van de ouders rapporteert dat hun peuter picky eating problemen heeft. Ondanks dat picky eating dus vaak voorkomt en voor ouders vaak een reden is van grote zorg, is er weinig bekend over de etiologie, beloop en gevolgen van dit gedrag. Op dit moment wordt picky eating beschouwd als een "rite de passage" die meestal vanzelf overgaat. Picky eating kan echter ook leiden tot een verslechterde voedingstoestand en een vertraging in lengtegroei en gewichtstoename. Verder is picky eating ook geassocieerd met latere psychische problemen. Picky eating omvat dus twee verschillende ontwikkelingstrajecten die haaks op elkaar staan wat betreft hun klinische relevantie: een groep met kinderen die weinig problemen ervaren en waarvan het picky eating gedrag vanzelf over gaat en een groep die gezondheidsklachten kan ontwikkelen.

Het doel van deze dissertatie is om determinanten te identificeren die picky eating - als onderdeel van de normale ontwikkeling - onderscheiden van picky eating gedrag met een risico op latere gezondheidsproblemen. De focus van deze dissertatie ligt op picky eating in de algemene bevolking en is er op gericht een helderder concept te krijgen door onderscheid te maken tussen normale en problematische picky eating. De meeste studies waren ingebed in de Generation R Study, een groot prospectief bevolkingscohort (N = 7.295 op peuterleeftijd) in Rotterdam, met data verzameling vanaf de foetale leeftijd.

Deze dissertatie bespreekt onderzoek naar 1) een helderder concept voor picky eating, 2) de prevalentie van picky eating, 3) de risicofactoren die geassocieerd zijn met verschillende trajecten van picky eating en 4) psychische klachten geassocieerd met verschillende trajecten van picky eating.

Hoofdstuk 2 geeft een overzicht van de huidige picky eating literatuur. De focus ligt op de conceptualisatie, factoren betrokken bij de ontwikkeling, en methodes voor het omgaan met het picky eating gedrag. De bevindingen suggereren dat de etiologie van picky eating multifactorieel is. Kinderen met picky eating problemen hebben vaker angst voor nieuwe voedingsmiddelen (food neophobia), eten een beperkte variatie aan soorten voedingsmiddelen, en hebben minder plezier in het eten, trager eetgedrag en een sneller voedselverzadigingsgevoel dan kinderen zonder picky eating problemen. Angstklachten, stress en voedingsstijlen bij de ouders hebben waarschijnlijk een wederkerig verband met picky eating. Het hanteren van dit gedrag is voornamelijk gericht op het verlagen van de angstklachten bij ouders middels psychoeducatie en het verminderen van het picky eating gedrag door middel van exposure aan voeding.

In hoofstuk 3 worden de prevalentie, verschillende trajecten en risicofactoren van picky eating in de vroege jeugd beschreven. We vonden dat ouders bij bijna de helft van de kinderen op een gegeven moment in de vroege jeugd picky eating

problemen rapporteerden. De prevalentie van picky eating was 26.5% op 1,5 jaar, 27,6% op 3 jaar en op 6 jaar gedaald naar 13,2%. Het merendeel van de kinderen met picky eating problemen had hier op de leeftijd van 6 jaar dus geen last meer van. Een klein percentage van kinderen (4%) had in de vroege jeugd persisterende picky eating problemen. Deze kinderen waren vaker jongens met een ondergewicht bij de geboorte en met een lagere sociaal-economische status. Deze kind kenmerken geven een indicatie voor een mogelijke biologische predispositie voor picky eating.

Het aandeel van psychopathologie bij de ouders in de ontwikkeling van picky eating wordt beschreven in hoofdstuk 4. Het is onduidelijk of psychopathologie van de ouders een risicofactor is voor het ontwikkelen van picky eating problemen, of dat omgekeerd een kind met picky eating problemen stress bij de ouders veroorzaakt, wat leidt tot psychische klachten bij ouders. Onze resultaten laten zien dat angstklachten en depressieve klachten (zelfs op niet-klinisch niveau) van zowel moeder als vader picky eating op vierjarige leeftijd voorspellen. Angstklachten bij de moeder tijdens de zwangerschap, voorspelden picky eating problemen bij het kind, onafhankelijk van eventuele symptomen van de moeder, als haar kind 3 jaar oud is. Deze bevindingen benadrukken het belang van de ouder-kind interacties in de voedingspraktijk.

De associatie tussen picky eating en psychische problemen bij het kind wordt beschreven in hoofdstuk 5. Hierin werden kinderen met persisterende picky eating problemen vergeleken met kinderen waarvan de picky eating problemen vanzelf overgingen of niet aanwezig waren. We hebben aangetoond dat in de algemene bevolking persisterende picky eating problemen van 1,5 tot 6 jarige leeftijd voorspellend waren voor op 7 jarige leeftijd aanwezige pervasieve ontwikkelingsproblemen, vastgesteld door de leerkracht. Deze associatie bleef ook bij correctie voor pervasieve ontwikkelingsproblemen op 1,5 jarige leeftijd in stand.

In andere studies is picky eating geassocieerd met bredere gedrags- en emotionele problemen. De meeste van deze onderzoeken corrigeerden echter onvoldoende voor mogelijke confounders. Bij picky eating problemen die vanzelf overgingen werd bij kinderen geen prospectief verband gevonden met latere psychische klachten. Deze resultaten versterken de theorie dat deze vorm van picky eating gedrag in peuters als een normale fase in de ontwikkeling van het kind gezien kan worden.

Hoofdstuk 6 geeft een overzicht van het ghreline hormoon en de mogelijke rol die de hersenen-darm ghreline-as speelt in sommige eetstoornissen. De rol van de ghreline-agonisten en antagonisten als therapeutische interventies wordt beschreven. De meeste van deze medicijnen zitten echter nog in de pre-klinische fase van ontwikkeling.

In het laatste gedeelte van deze dissertatie, hoofdstuk 7, worden de belangrijke bevindingen van de onderzoeken in deze dissertatie samengevat en worden methodologische overwegingen, als ook de implicaties voor de klinische praktijk en toekomstig onderzoek bediscussieerd.

De belangrijkste bevindingen van deze dissertatie bevestigen de op consensus

gebaseerde gedachte dat picky eating een normale fase in de ontwikkeling is. Beter gezegd: een substantieel deel van de kinderen zal in de vroege jeugd picky eating problemen ontwikkelen, maar deze problemen zullen vanzelf overgaan vóór het zesde jaar. Deze kinderen hebben geen verhoogde kans op gezondheidsklachten. Daarom stellen we voor dit type picky eating te beschouwen als zijnde onderdeel van de normale ontwikkeling van het kind. Zorgprofessionals kunnen een afwachtend vinger-aan-de-pols beleid voeren, waarbij ouders gerustgesteld kunnen worden dat deze fase waarschijnlijk vanzelf overgaat. Alleen een kleine groep kinderen (4%) in de algemene bevolking heeft persisterende picky eating problemen in de vroege jeugd. De kinderen met persisterende picky eating problemen hebben een iets verhoogde kans op pervasieve ontwikkelingsproblemen. Clinici moeten op de hoogte zijn van de risicofactor-profielen die persisterende picky eating problemen voorspellen en of aanvullend onderzoek nodig is.

Toekomstig onderzoek is nodig om te zien of op jongere leeftijd risicofactoren geïdentificeerd kunnen worden die persistentie van picky eating problemen voorspellen. Ook is meer follow-up onderzoek nodig om te zien hoe kinderen met persisterend picky eating op 6-jarige leeftijd zich verder ontwikkelen.

CHAPTER 9

# Abreviations
# Author affiliations
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# Abbreviations

| | |
|---|---|
| α-MSH | α-Melanocyte-Stimulating Hormone |
| ABA | Activity-Based Anorexia |
| AgRP | Agouti-Related Protein |
| ALSPAC | Avon Longitudinal Study of Parents and Children |
| AN | Anorexia Nervosa |
| AP | Area Postrema |
| ARFID | Avoidant/Restrictive Food Intake Disorders |
| ASD | Autism Spectrum Disorder |
| BED | Binge Eating Disorders |
| BMI | Body Mass Index |
| BN | Bulimia Nervosa |
| BSI | Brief Symptom Inventory |
| CBCL | Child Behavior Checklist |
| CEBQ | Child Eating Behavior Questionnaire |
| CFQ | Child Feeding Questionnaire |
| CI | Confidence Interval |
| DSM-5 | Diagnostic and Statistical Manual |
| FFQ | Food Frequency Questionnaire |
| FI | Food Intake |
| FTT | Failure To Thrive |
| GH | Growth Hormone |
| GHS | Growth Hormone Secretagogues |
| GOAT | Ghrelin-0-Acyl Transferase |
| ICD | International Classification of Diseases |
| mRNA | messenger RNA |
| NAc | Nucleus Accumbens |
| NES | Night Eating Syndrome |
| NPY | Neuropeptide Y |
| OR | Odds Ratio |
| PE | Picky Eating |
| POMC | Pro-opiomelanocortin |
| PWS | Prader-Willi Syndrome |
| RRR | Relative Risk Ratio |
| SES | Socio-Economic Status |
| TRF | Teacher Report Form |
| VTA | Ventral Tegmental Area |

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# About the author

Sebastian Cardona Cano was born on the 16th of October 1982 in Santa Barbara, Colombia. At the age of 6 he immigrated to the Netherlands were he has lived since.

He studied Medicine at Erasmus University, Rotterdam, in 2001, where he also enrolled in the Master of Neuroscience programme. Sebastian always had a special interest in translational neurobiology and psychiatry in order to "unravel the mysteries of the brain". In 2007 he received his degree in Neuroscience and in 2009 he graduated from medical school. He worked as a medical doctor at Altrecht Eating Disorders Rintveld, Zeist, while continuing with research at the Brain Center Rudolf Magnus, UMC Utrecht, focusing on translational research in eating disorders under supervision of Prof. R. Adan and Prof. A. van Elburg.

In 2010 he started his psychiatric residency at Parnassia Psychiatric Institute. He combined this with his PhD studies, first at the Utrecht Research Group for Eating disorders in Utrecht, and later within the Generation R Study Group at Erasmus MC.

In 2014, after finishing his psychiatric fellowship, he started working as a psychiatrist in two community psychiatric teams of Lucertis, the child and adolescent department of Parnassia Psychiatric Institute. During this period he finalized his thesis. As of 2016 he is also the clinical manager of the Fjord, a centre for orthopsychiatry, and project manager for a national (TOP-GGZ) eating disorder project. He hopes to combine clinical practice and research in psychiatry.

# Portfolio

## Summary of PhD training and teaching

| | |
|---|---|
| Name PhD student: | Sebastian Cardona Cano |
| Erasmus MC Department: | Child and Adolescent Psychiatry, Generation R |
| PhD period: | January 2007-2017 |
| Promotors: | Prof.dr. H.W Tiemeier and Prof.dr. H.W. Hoek |
| Co-promotor: | Dr. D. van Hoeken |

| Training | Year | ECTS |
|---|---|---|
| Master of Neuroscience, Erasmus MC | | |
| Performance during the research phase | 2007 | 20 |
| Presentation of research project | 2007 | 10 |
| Master Thesis | 2007 | 30 |
| Erasmus Summer Programme | | |
| Methods of Clinical Research | 2011 | 0.7 |
| Cohort Studies | 2011 | 0.7 |
| Introduction to Data-analysis | 2012 | 0.7 |
| Regression Analysis | 2012 | 1.4 |
| Logistic Regression | 2012 | 1.4 |
| Attended seminars and workshops | | |
| Workshop ARFID, R. Bryant-Waugh | 2016 | 0.5 |
| International Feeding disorder conference<br>UCL Institute of child health, London | 2016 | 1.0 |
| Nederlandse Academie voor Eetstoornissen congres<br>Eetproblemen bij (jonge) kinderen - SCEM | 2016 | 0.5 |
| Nederlandse Academie voor Eetstoornissen congres | 2014 | 0.5 |
| Nederlandse Academie voor Eetstoornissen congres | 2012 | 0.5 |
| INTACT symposium 8th international conference<br>on eating disorders and obesity – Prague | 2011 | 1.0 |

| Conference presentations and teaching | |
|---|---|
| Anxious mothers vs picky eaters; the chicken or the egg<br>International Feeding conference,<br>UCL Institute of Child Health, London | 2016 |
| Voedingsstoornissen – verpleegkundig referaat<br>Parnassia Groep | 2016 |
| Picky eating; a problem in development<br>PsyQ Eetstoornissen, Rotterdam, Parnassia Groep | 2016 |
| Moeilijke eters en Autisme – Sarr centrum voor autisme,<br>Rotterdam, Parnassia Groep | 2016 |
| Conference presentations and teaching (continued) | |
| Voedingsstoornissen in de DSM-5 – Wetenschappelijk<br>Middagprogramma Haaglanden, Parnassia Groep | 2016 |
| Risk factors and trajectories of picky eating<br>Eindreferaat Psychiatrie, Consortium Psychiatrie ZHN | 2014 |

| Poster presentations | |
|---|---|
| “The Prevalence of Picky Eating in a Prospective<br>Population-Based Cohort of Young Children”<br>Eating Disorders Research Society | 2012 |
| “Prevalentie en incidentie van picky eating<br>bij jonge kinderen”<br>Nederlandse Academie voor Eetstoornissen | 2012 |

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