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REVIEW ARTICLE

Impacts on prenatal development of the human cerebellum: a systematic review

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Abstract

Purpose: The cerebellum is essential for normal neurodevelopment and is particularly susceptible for intra-uterine disruptions. Although some causal prenatal exposures have been identified, the origin of neurodevelopmental disorders remains mostly unclear. Therefore, a systematic literature search was conducted to provide an overview of parental environmental exposures and intrinsic factors influencing prenatal cerebellar growth and development in humans.

Materials and methods: The literature search was limited to human studies in the English language and was conducted in Embase, Medline, Cochrane, Web of Science, Pubmed and GoogleScholar. Eligible studies were selected by three independent reviewers and study quality was scored by two independent reviewers.

Results: The search yielded 3872 articles. We found 15 eligible studies reporting associations between cerebellar development and maternal smoking (4), use of alcohol (3), *in vitro* fertilization mediums (1), mercury (1), mifepristone (2), aminopropionitriles (1), ethnicity (2) and cortisol levels (1). No studies reported on paternal factors.

Conclusions: Current literature on associations between parental environmental exposures, intrinsic factors and human cerebellar development is scarce. Yet, this systematic review provided an essential overview of human studies demonstrating the vulnerability of the cerebellum to the intra-uterine environment.

Keywords

Systematic review, cerebellum, growth and development, prenatal, human

History

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Introduction

One in six children in industrialized countries are affected by neurodevelopmental problems, including cognitive defects, motor disabilities and psychiatric diseases [1]. Most of these aberrations cause lifelong problems with severe societal and economic impact [2]. Harmful prenatal environmental exposures can alter epigenetic programming and structural development, potentially inducing neurodevelopmental shortcomings [3–5]. The exact contribution of environmental exposures to neurodevelopmental problems is poorly understood. Since individual brain regions develop asynchronously, the exact alterations are not only determined by the type or severity of harmful exposure but also the critical time windows [6,7].

Of the rapidly developing brain regions, the cerebellum precedes most brain structures and shows very early connectivity. It also shows a steep growth curve during fetal life, increasing up to 500% in cerebellar volume between 24 and 40 weeks of gestation [8–10]. Harmful environmental exposures during pregnancy may therefore pose a risk to disrupt prenatal cerebellar development [11]. Postnatally, the cerebellum is involved in a wide variety of sensorimotor tasks as well as cognitive, emotional and language behavior [12–14]. This may explain why an altered prenatal cerebellar development or injury may be associated with an increased risk for neurodevelopmental impairment and mental health issues [11,12,15–17].

Overwhelming evidence from animal studies have established the impact of an adverse intra-uterine environment compromised by toxic agents, environmental exposures, infection, inflammation, hypoxia, imbalances in vitamin or

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hormonal status on cerebellar development [7,11,18]. Human studies on this issue are scarce, predominantly focusing on postnatal cerebellar functions disregarding prenatal deviances in growth and development.

We believe that studying the impact of the intra-uterine environment on human prenatal cerebellar growth and development may provide more insight for better understanding consequences for neurodevelopmental functioning. Therefore, we provide an overview of the literature on parental environmental exposures and intrinsic factors influencing prenatal growth and development of the human cerebellum. The ultimate aim is to identify risk factors for impaired prenatal cerebellar growth and development with potential consequences for neurodevelopmental outcome.

Materials and methods

Search strategy and selection criteria

A literature search according to a predefined protocol was generated by an experienced medical information specialist from the Medical Library of the Erasmus MC University Medical Center. All relevant literature up to 4 September 2015 was searched in Embase, Medline, Cochrane central, WebofScience, Pubmed and GoogleScholar. The complete search strategy (Supplementary Appendix A) combined controlled vocabulary terms (in Medline and Embase) and free text words in title and/or abstract related to the exposure (e.g. alcohol, nutrition, ethnicity), the outcome (prenatal cerebellum in context of growth, development and abnormalities), and the studied population (e.g. pregnancy, pregnant women, maternal, paternal). The search was limited to human studies in the English language.

All randomized controlled trials, intervention studies, cohort studies, case-control studies and case reports were eligible for inclusion when they reported the human cerebellum as prenatal outcome measure, in terms of size, histology, morphology or any other measurement of the cerebellum during pregnancy. Eligible studies should report on any environmental or intrinsic factor as exposure, including maternal conditions or characteristics, environmental toxicities, occupational and lifestyle exposures. Exclusion criteria were (1) no or irrelevant exposure defined as an exposure that is not environmental or intrinsic; (2) postnatal cerebellar outcome only; (3) results obtained from animal or *in vitro* studies; (4) articles with no full text available; (5) book chapters and reviews lacking unique data analysis.

Working in pairs, three independent reviewers (IVK, MJT, GMEG) screened the titles and abstracts on the selection criteria. All differences in the study selection were resolved through discussion with the first reviewer (IVK) who read all abstracts. For all selected articles, full text was retrieved and evaluated to decide whether the study met the inclusion criteria. Reference lists of all included studies were checked for potential eligible articles.

Quality assessment

Two reviewers (IVK, MJT) independently scored the quality of the included studies according to a predefined quality score (Supplementary Appendix B) based on five items namely the study design, population size, exposure and outcome measurements and confounder handling. Each item could score zero, one or two points, resulting in a maximum of 10 points representing the highest quality. Case reports were not assessed on quality. Discrepancies in assigned quality scores were discussed until the reviewers agreed. As the quality score was not used as an exclusion criterion we did not define a cutoff score.

Results

The literature search resulted in 3872 unique articles. During title and abstract screening we excluded 3817 articles. Full texts of 55 studies were reviewed for relevance. We excluded studies because of irrelevant outcome (7), irrelevant study population (10), no or irrelevant exposure (9), irrelevant study type or no available full text (7), animal or *in vitro* models (6), duplicate data (1) or the manuscript was not written in the English language (1). Additionally, we included one study through hand search of reference lists of the included studies. In total, 15 studies were included in this systematic review.

Study characteristics

Table 1 presents details of the included articles and quality scores. In the selected literature, we found eligible case reports, cross-sectional, intervention and cohort studies on maternal smoking (4), maternal use of alcohol (3), endemic mercury exposure (1), the influence of *in vitro* fertilization (IVF) mediums (1), mifepristone (1) ethnicity (2) and maternal cortisol levels (1). Two case reports described fetuses with cerebellar anomalies after exposure to mifepristone and aminopropionitriles. No studies reported on paternal exposures or factors influencing cerebellar development. We identified environmental exposures defined as environmental toxicities, occupational and lifestyle exposures and intrinsic factors defined as factors that characterize the origin of a person including ethnicity and stress levels (Figure 1). Findings are presented per documented exposure.

Environmental exposures and intrinsic factors

Maternal smoking

Four studies evaluated the association between maternal smoking and fetal cerebellar development [19–22]. A prospective cohort described a significantly smaller fetal transcerebellar diameter (TCD) in addition to smaller head parameters in fetuses of mothers who continued smoking throughout pregnancy compared to nonsmoking mothers (-0.08 mm, 95%CI$= -0.15$; -0.00) when adjusting for known confounders [22]. Cerebellar growth did not differ significantly [22]. In addition, morphological associations between tobacco and cerebellar development have been studied by Lavezzi et al., suggesting defective maturation and migration of Purkinje cells in histology specimen of fetuses with sudden intra-uterine death [20]. In 91% of these cases at least one developmental alteration was shown, suggesting a strong correlation between tobacco exposure and prenatal cerebellar insults. Moreover, in a similar study, 92% of fetuses had bio-pathological alterations in the cerebellar cortex ($p < 0.05$) [21]. A fourth study showed that maternal smoking during pregnancy, compared to nonsmoking,

Table 1. Study selection, characteristics, quality score and main effects.

Ref.	First author	Year	Study design	Quality score	*n*	Method	GA at outcome assessment	Exposure window	Exposure	Main results
[22]	Roza	2007	pC	8	7042	US	25–40	Preconceptional and prenatal	Smoking	TCD: Smoking < Nonsmoking
[20]	Lavezzi	2013	CS	5	30	H	25–40	Preconceptional and prenatal	Smoking	Abnormal number and morphology of Purkinje cells in SIUDS, mostly smoking mothers
[21]	Lavezzi	2007	CS	4	21	H	20	Preconceptional and prenatal	Smoking	Smoking versus nonsmoking: Abnormal cytology and increased cell death
[19]	Falk	2005	CS	3	12	H	5-12	Prenatal	Smoking	Smoking versus nonsmoking: Increased expression of nicotinic and muscarinic receptors
[25]	Wass	2001	pC	6	167	US	18–42	Prenatal	Alcohol	TCD: Alcohol = no alcohol
[23]	Handmaker	2006	pC	5	255	US	17–40	Preconceptional and prenatal	Alcohol	TCD: Heavy < no alcohol and early abstainers
[24]	Kfir	2009	pC	4	166	US	13–38	Prenatal	Alcohol	TCD: Alcohol = no alcohol
[31]	Nelissen	2013	I	7	294	US	17–40	Preconceptional	IVF medium	TCD: Vitrolife > Cook medium
[30]	Lapham	1995	CS	7	40	H	NR	Preconceptional and prenatal	Mercury	Endemic versus non-endemic mercury exposure: Elevated levels in cerebellar white matter and cortex, no pathologic abnormalities
[32]	Sitruk-Ware	1998	rC	3	71	M	6–9	First trimester	Mifepristone and prostaglandin	One case of cerebellar atrophy
[28]	Afadapa	2006	CR	NA	1	M	17	First trimester	Mifepristone and prostaglandin	Right sided cerebellar agenesis
[29]	Dembinski	1997	CR	NA	1	M	32	Preconceptional and prenatal	Aminopionitriles	Cerebellar hypoplasia
[33]	Li	2012	pC	7	432	US	17–39	Third trimester	Cortisol	TCD: Inverse relation with cortisol levels
[35]	Jacqemyn	2000	CS	6	549	US	20–32	NA	Ethnicity	TCD: Moroccan > Turkish and Belgian
[34]	Araujo Junior	2007	pC	5	52	US	12–42	NA	Ethnicity	Cerebellar volume: Brazilian > Taiwanese

The study selection and study characteristics per included study are identified by name of the first author and year of publication. Ref: reference number. Study type categorized as: CR: case report; CC: case control study; C: cohort study; p: prospective; r: retrospective. Methods: H: histology; US: ultrasound; *n*: number of participants; GA at assessment: gestational age in weeks; NR: not reported; NA: not applicable; TCD: transcerebellar diameter; SIUDS: sudden intra-uterine death syndrome.

significantly increased the expression of nicotinic and muscarinic acetylcholine receptors in human cerebellum, pons and medulla oblongata tissue of fetuses between 5 and 12 weeks gestation obtained after routine abortion procedures [19].

Maternal use of alcohol

Three studies evaluating the association between maternal alcohol consumption and fetal cerebellar growth measured by TCD, showed inconsistent results [23–25]. The study with the highest quality investigated the influence of maternal alcohol consumption measured in average ounces of absolute alcohol consumption per day and fetal brain measurements in 167 women. Maternal alcohol consumption was reported to be associated with a reduction of the frontal cortex and not to cerebellar size (Pearson=–0.040, $p \geq 0.10$) [25]. This finding is supported by a prospective cohort which compared mothers using alcohol with mother not using alcohol in the second (mean difference TCD = 0.7 mm, $p > 0.05$) and third trimester (mean difference TCD = 0.2 mm, $p > 0.05$) [24]. In this study, alcohol consumption was recorded by validated self-administered questionnaires [26,27]. In contrast, using the same questionnaires another study reported smaller cerebellar size ($p = 0.087$) and significantly decreased cerebellar growth ($p = 0.008$) in heavy drinking women who continued drinking compared to early abstainers and nondrinkers [23].

Environmental toxicities

Five studies reported on the impact of maternal exposure to environmental toxicities on prenatal cerebellar development [28–32]. An intervention study reported differences in fetal TCD (mean difference = 0.4 mm, $p = 0.008$) in fetuses exposed as an embryo to different commercially available culture media (Vitrolife G1.3, Göteborg, Sweden versus Cook K-SICM, Brisbane, Australia), establishing the culture medium as a direct environment for the growing embryo outside of the uterus [31]. In fetal brain tissue from the Seychelles endemically exposed to mercury demonstrated a correlation of dietary mercury exposure and levels in the brain. These levels were highest in posterior fossa structures and subcortical nuclei [30]. Although this study

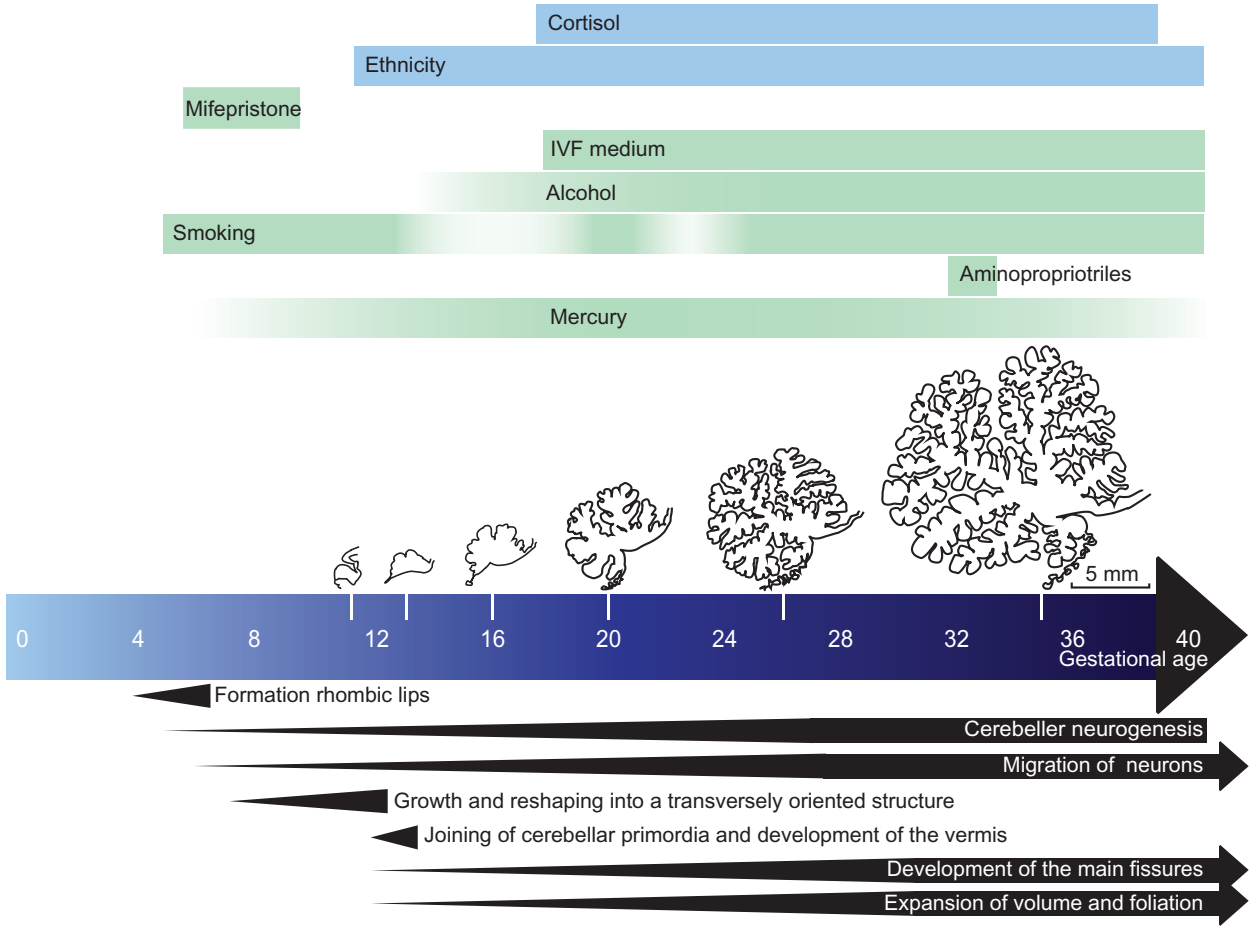

Figure 1. Impact of maternal environmental exposures and intrinsic factors on prenatal development of the human cerebellum. A schematic display of the evidence found in this systematic review of the impact of maternal factors, divided in environmental exposures (green/light grey) and intrinsic factors (blue/dark grey) on prenatal development of the human cerebellum with respect to gestational age and the most essential developmental stages of the cerebellum. Adjusted from Rakic and Sidman [66].

identified no structural pathological alterations, histological alterations were found in cerebellar white matter of which clinical significance remains unclear [30]. Two cases of cerebellar anomalies after failed induction of abortion with mifepristone and prostaglandins have been reported, including cerebellar atrophy and half-sided cerebellar agenesis [28,32]. Teratogenic effects of aminopropionitriles have been suggested in a case report of an exposed fetus with multiple congenital anomalies including cerebellar malformations [29].

Intrinsic maternal factors

Li et al. conducted a cross-sectional study in relatively low risk singleton pregnancies to evaluate associations of maternal stress levels measured by serum cortisol before delivery and fetal growth measures. A negative correlation between maternal serum cortisol and mid-gestation TCD ($R^2 = 0.76$, $p = 0.014$) not late TCD was demonstrated, adjusting for maternal body mass index, age and body weight at delivery, moment of the ultrasound, infant gender, moment of cortisol measurement and maternal uterine contraction states [33]. Two studies reported ethnicity in relation to cerebellar size [34,35]. TCD measurements were dependent of ethnicity when comparing measurements from Moroccan, Turkish and Belgian fetuses [35]. Additionally, cerebellar volume of Taiwanese fetuses compared to Brazilian fetuses showed a significantly increased cerebellar growth curve (mean difference = 0.366 mm, $p < 0.001$) [34].

Discussion

This review provides a complete overview of the current published literature of the effects of parental environmental exposures and intrinsic factors on prenatal human cerebellar growth and development. Notable, we did not find any evidence of paternal factors affecting cerebellar development. Although the available data were collected from heterogenic study populations with various outcomes, they provide ample evidence to support the particular susceptibility of the human cerebellum to maternal environmental exposures and intrinsic factors [12]. We found associations between maternal smoking, use of alcohol, type of IVF culture medium, mercury, mifepristone, aminopropionitriles, ethnicity, maternal cortisol levels and cerebellar growth or development. We discuss these findings in detail and aim to guide future studies investigating impacts on prenatal development on the human cerebellum.

Maternal smoking

We found evidence in histological and ultrasound studies that maternal smoking has a harmful effect on prenatal cerebellar development, complementing previously documented reduced cerebellar volumes in prematurely born infants of smoking mothers [36]. So far, direct influences of maternal smoking have only been demonstrated in animal studies reporting alterations in various receptors and cellular processes [37,38]. Human studies have only reported indirect evidence for harmful influences of nicotine on behavioral and cognitive outcome in the offspring [39]. Previous imaging studies also showed that maternal smoking was associated with reduced head growth and total brain volume measured in the second half of pregnancy [22,40,41]. However, whether the relationship between maternal smoking and neurodevelopmental outcome is mediated by derangements in brain development needs to be elucidated. However as the brain overall is affected, one could reason that the cerebellum as a separate entity is not spared. In addition, reduced cerebellar growth might be a secondary network injury effect due to lack of innervation. Toxicity of tobacco may alter epigenetic mechanisms and vascular processes which in turn may directly and/or indirectly influence cerebellar growth and maturation [40].

Maternal use of alcohol

Although previous studies reported that cerebellar neurons are particularly susceptible to alcohol-induced developmental disruptions [42–44], ultrasound studies did not demonstrate consistent associations between alcohol exposure and cerebellar size. One study provided evidence for reduced prenatal cerebellar growth in relation to heavy alcohol exposure compared to non-alcohol exposure or early-abstainers [23]. These findings may support the possible benefit of early abstinence for fetal growth measures including cerebellar growth. Although there is no comparable animal data available, decreased cerebellar weight and cerebellar neuronal loss was recorded due to ethanol induced neurotoxicity [45]. Alcohol-induced cerebellar alterations may result from underlying mechanisms, such as excitotoxicity, nutritional deficiencies, growth factor alterations, glial abnormalities, apoptosis, oxidative stress and compromised energy production [46]. However, adverse effects of maternal alcohol exposure on cerebellar growth were not detected in the other studies [24,25]. This may be due to the relatively small effect sizes and considerable variability in study populations, quality and methodology. In addition, reliance of self-reported alcohol consumption is limited. We speculate that the impact of maternal alcohol intake on the developing cerebellum may be revealed in larger ultrasound cohorts using more precise measures for alcohol consumption in contrast to the relatively crude measures for maternal alcohol intake at conception used previously [25]. However, to date prenatal ultrasound evaluation of fetal brain development in women using alcohol during pregnancy receives little attention.

Environmental toxicities

Environmental toxicities including IVF-mediums, mercury, mifepristone and aminopropionitriles were associated with a variety of cerebellar anomalies and altered development [28–32]. However, quality of the evidence was relatively low, based on two case-reports and studies with quality scores between 3 and 7. One study reported the interesting finding that IVF culture mediums could influence cerebellar growth during the second trimester of pregnancy [31]. This suggests that already during *in vitro* stages, embryonic growth can be influenced, which also affects the cerebellum and connecting brain structures. This may indicate that the embryo's own epigenetic programming and early neurogenesis by modulation of neurotrophic factors can be directly influenced by its environment, being a culture medium or the womb [3,4].

Only one study reported on the neurotoxic effects of mercury *in utero* on the human cerebellum showing elevated levels of mercury in the brains of endemically exposed fetuses, in the absence of clear pathologic developmental alterations [30]. Although the evidence from this small sample is rather scarce, animal models provide clear evidence for neurotoxic effects of mercury including dose-related cerebellar damage, anomalous cerebellar development and altered Purkinje cell migration [47–51]. In addition, mercury levels in the cerebellum among other posterior fossa structures were reported higher than in the cerebral cortex. This finding is consistent with a rat model showing the highest mercury concentrations in the cerebellum and hippocampus after *in utero* exposure [49]. Potentially this indicates greater susceptibility of these structures to destructive neurotoxic effects of mercury [30]. Although the results of this prenatal study remained inconclusive, previously significantly reduced neonatal cerebellar measurements were reported after antenatal mercury exposure [52].

Considering that only two studies reflected on the potential teratogenic effects of mifepristone, this finding seemed of little significance as failed termination of pregnancy was reported in fewer than 0.02% of cases [28]. In addition, causal relation between occupational aminopropionitriles exposure and cerebellar development cannot be concluded from one fetus diagnosed with Cantrell-sequence. Although the evidence of a neurotoxic impact of aminopropionitriles on cerebellar morphology seems limited, effects on a finer scale or on cerebellar connectivity cannot be excluded.

Intrinsic maternal factors

Two studies demonstrated that cerebellar size measured with TCD and cerebellar volume varied among different ethnicities. Ethnical differences in transcerebellar size are highly interesting, as this may impact obstetrical care and management, seeing that the TCD measurement is part of routine ultrasound examinations and used for second trimester estimation of gestational age [53]. Therefore, universal reference curves disregarding ethnical differences of cerebellar size may not be accurate for pregnancy dating in later pregnancy. However, to investigate a spectrum of ethnical backgrounds in association with fetal cerebellar growth warrants larger longitudinal cohorts.

Although large-scale studies have provided evidence on the impact of maternal stress on prenatal brain development and neurodevelopmental outcomes [54–57], the evidence for a detrimental impact on cerebellar development was limited to one study. Although Li et al. demonstrated a negative association between pre-labor cortisol levels and TCD [33], we note that the cortisol level was only determined once in this cross-sectional study. Previously this was demonstrated to be an unreliable recording of maternal stress because of its daily and pregnancy-related fluctuations [58–60]. Therefore, adjustment for these fluctuations in the statistical analyses, which was performed in this study, seemed insufficient. Animal studies provided more evidence for the neurotoxic effects of prenatal stress on Purkinje cell morphology but show no effects on cerebellar growth measurements [61,62]. To crystallize this issue in humans, prospective studies with repeatedly measured stress hormone levels could provide more robust conclusions.

Based on our review, we conclude that cerebellar growth and development showed signs of susceptibility to maternal environmental exposures and intrinsic factors. For each factor that influenced the developing cerebellum, the level of impact may vary with the timing, severity and type of insult [12]. Potentially, effects may also differ among specific cerebellar regions [6,7]. Subsequent derangements in cerebellar development potentially affect downstream connectivity and development of other brain structures.

Despite our extensive literature search, we stress that the amount of evidence and its quality was relatively low. From the current literature no conclusions on causal relations can be drawn. Our search yielded the whole spectrum of developmental deformations and abnormal growth of the cerebellum. However we did not specifically include Arnold Chiari malformations often co-occurring with myelomeningocele. Although these malformations are often considered as cerebellar anomalies, they typically result from mechanical forces, without which the cerebellum otherwise would have developed normally. Furthermore, only a minority of the studies adjusted for confounding factors. Therefore, residual confounding may have influenced the reported associations. Due to the numerous potential confounders in human research, findings from animal studies may contribute to a great extent to the understanding of environmental effects on cerebellar development [11]. Nevertheless, human research is indispensable as the human cerebellum is significantly different from animals, engaging in a more extensive and complex set of tasks and functions and neuro-embryology follows different timelines. Caution is needed when translating animal experimental results to the human setting. Therefore, we did not incorporate animal data in this systematic literature search.

Currently, most human evidence concerns cerebellar development during the second half of pregnancy. However, new evidence indicates that embryonic growth can predict fetal growth with consequences for health and disease in later life [63,64]. Therefore, research needs to incorporate these earlier developmental stages to study causes of derangements in cerebellar development which may originate early in the embryonic period. More precise and reliable measures of cerebellar growth, as well as maternal environmental exposures and intrinsic factors are warranted to investigate the small cerebellar effects of these impacts. This kind of epidemiological evidence may be provided by large prospective cohort studies using three-dimensional ultrasound, biomarkers and epigenetic patterns [64,65].

Declaration of interest

The authors report no conflicts of interest. This study was funded by the Department of Obstetrics and Gynecology, Erasmus MC University Medical Center, Rotterdam, the Netherlands. IVK was supported by the Sophia Foundation for Medical Research, Rotterdam, The Netherlands (SSWO grant number 644). Additionally, MJT worked at ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd.) and Metagenics Inc. Moreover, FEH is supported by NWO-ALW (VIDI 864.11.016) and ZON-MW (TOP-GO.L.10.066) grants. None of the funders had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review or approval of the manuscript.

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