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Do prenatal factors shape the risk for dementia?

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Shaping the risk for late-life neurodegenerative disease: A systematic review on prenatal risk factors for Alzheimer's disease-related volumetric brain biomarkers

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Abstract

Environmental exposures including toxins and nutrition may hamper the developing brain in utero, limiting the brain's reserve capacity and increasing the risk for Alzheimer's disease (AD). The purpose of this systematic review is to summarize all currently available evidence for the association between prenatal exposures and AD-related volumetric brain biomarkers. We systematically searched MEDLINE and Embase for studies in humans reporting on associations between prenatal exposure(s) and AD-related volumetric brain biomarkers, including whole brain volume (WBV), hippocampal volume (HV) and/or temporal lobe volume (TLV) measured with structural magnetic resonance imaging (PROSPERO; CRD42020169317). Risk of bias was assessed using the Newcastle Ottawa Scale. We identified 79 eligible studies (search date: August 30th, 2020; Ntotal=24,784; median age 10.7 years) reporting on WBV (N=38), HV (N=63) and/or TLV (N=5) in exposure categories alcohol (N=30), smoking (N=7), illicit drugs (N=14), mental health problems (N=7), diet (N=8), disease, treatment and physiology (N=10), infections (N=6) and environmental exposures (N=3). Overall risk of bias was low. Prenatal exposure to alcohol, opioids, cocaine, nutrient shortage, placental dysfunction and maternal anemia was associated with smaller brain volumes. We conclude that the prenatal environment is important in shaping the risk for late-life neurodegenerative disease.

Keywords 3-12

Brain reserve; Alzheimer's disease; MRI; developmental programming; systematic review

1 Introduction

The fetal brain grows and develops at a remarkable speed. At three weeks post-conception, primitive cerebral hemispheres have already developed. By mid-gestation, the fetal brain has largely achieved the adult neuronal number (Dobbing and Sands, 1973; Prayer et al., 2006). As a result of this exceptional growth rate, the prenatal period is a critical period during which the developing brain is especially vulnerable to adverse exposures (Whalley et al., 2006).

Adverse exposures during prenatal development may impact the brain, hampering developmental processes and preventing it from developing to its full potential. For instance, prenatal exposure to alcohol or tobacco restricts fetal brain growth, mostly observed as reduced whole brain and regional brain volumes (e.g. Banderali et al., 2015; Caputo et al., 2016; Ekblad et al., 2015; Popova et al., 2021). Exposure to adverse prenatal circumstances is also negatively associated with cognitive functioning in (early) childhood. For example, maternal cannabis, cocaine or alcohol use during pregnancy has been associated with deficits in cognitive functioning and increased risk for psychopathology or substance use disorders in childhood (Grant et al., 2018; Paul et al., 2021; Singer et al., 2018).

There is some evidence that these harmful effects of prenatal exposures on brain structure and functioning last throughout life. Exposure to prenatal undernutrition was associated with poorer cognitive performance at the age of 58 (de Rooij et al., 2010). In addition, sex-specific effects of undernutrition during early gestation on brain volumes at the age of 68 were reported, demonstrating smaller volumes in exposed men (de Rooij et al., 2016). Thus, the impact of the prenatal environment on brain structure and cognitive functioning appears to be present in early childhood and may potentially last throughout life, although the number of

studies on long-term brain-related outcomes of adverse prenatal exposures measured in late-life is limited.

Adverse prenatal circumstances may also be associated with an increased risk of dementia in late life (Borenstein et al., 2006; Seifan et al., 2015). Among numerous potential pathways, the increased risk of dementia could result from hampered development of the fetal brain following a suboptimal prenatal environment, limiting the reserve capacity of the adult brain. Brain reserve capacity can be defined as a buffer determined by neural factors such as brain size and the number of neurons and synapses (Borenstein et al., 2006). As the brain ages, neurodegeneration and vascular damage can accumulate, which may be part of normal ageing, or pathological, such as observed in Alzheimer's disease (AD). As neurodegeneration progresses, the brain reserve may determine whether an individual experiences symptoms of cognitive decline. At the same level of neurodegeneration, an individual with a large brain reserve may continue to function normally whereas someone with a limited brain reserve may reach the threshold of cognitive dysfunction earlier. Thereby, acting as a structural buffer, brain reserve can compensate for some of the neurodegeneration associated with AD in late life, alleviating the effects of initial neurodegeneration on cognitive functioning (Borenstein et al., 2006; de Rooij, 2022; Stern, 2012). Thus, through a limited development of brain reserve, adverse prenatal exposures may result in an increased risk of developing AD in late life.

AD is a neurodegenerative disease marked by amyloid-beta plaques, tau tangles and a general pattern of brain atrophy (Ausó et al., 2020). Magnetic resonance imaging (MRI) studies can provide markers of AD-related neurodegeneration (Pini et al., 2016). Generally, MRI studies of AD report reduced

whole brain volume (WBV), temporal lobe volume (TLV) and hippocampal volume (HV) as established neurodegenerative volumetric biomarkers for AD (Franke et al., 2010; Frisoni et al., 2010; Hane et al., 2017; Pini et al., 2016; Wardlaw et al., 2013). Reduced HV is seen early in the neurodegenerative process (Pini et al., 2016), as is temporal lobe atrophy. Further progression of AD neurodegeneration is associated with widespread cortical atrophy across the brain (Pini et al., 2016). Both hippocampal and whole-brain atrophy rates are used as markers for neurodegenerative progression of AD (Frisoni et al., 2010). Hampered development of the HV, TLV and WBV as a result of adverse prenatal circumstances may lead to a reduced brain reserve to buffer AD-related neurodegeneration in late-life (Borenstein et al., 2006).

All in all, the prenatal environment may play an essential role in determining the risk for developing AD by impacting brain reserve. There is, however, no overview of the available body of evidence on prenatal exposures and their impact on structural brain measures that have been associated with an increased risk for developing AD in late life. The purpose of this systematic review is to summarize all currently available evidence for the association between prenatal exposures (including prenatal illicit drug exposure, alcohol exposure, maternal stress and environmental exposures) and HV, TLV and WBV in humans. Thereby, we aim to address the following research question: 'Is there an association between prenatal risk factors and volumetric MRI neuroimaging biomarkers for AD?'. The present systematic review is essential to gain insight into the extent to which the prenatal environment may shape the risk for late-life neurodegenerative disease through brain reserve.

2 Methods

We registered the protocol for this systematic review at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020169317), and followed PRISMA reporting guidelines for systematic reviews (Page et al., 2021; Supplement).

2.1 Search strategy

An information specialist (JL) searched OVID Medline and EMBASE from inception to August 30th, 2020. MESH terms and text words for 1. general prenatal terms, including antenatal and fetus, or specific prenatal exposures were combined with 2. terms for structural MRI brain biomarkers. We excluded conference abstracts and reviews, but did not apply language or date restrictions. The full search strategy is available in supplement B. The bibliographic records were imported and deduplicated using EndNote. We cross-checked reference lists and citing articles of identified relevant papers in Web of Science and adapted the search in case of additional relevant studies.

2.2 Eligibility criteria

We included peer-reviewed and published human cohort, cross-sectional and case-control studies examining prenatal factors in association with predefined neuroimaging biomarkers related to sporadic late-onset AD. No restrictions were made for age at outcome measurement. We defined a prenatal factor as any exposure that occurs during pregnancy. All direct, specific exposures were of

interest, indirect measures of the prenatal environment such as birth weight or other birth characteristics were not included. Studies focusing on premature birth as the only factor of interest were excluded, since premature birth can be the result of a large variety of potential exposures throughout pregnancy. Studies investigating specific prenatal exposures that may result in premature birth were included. We defined our outcomes of interest as WBV, TLV and/or HV as measured by structural MRI scans (Franke et al., 2010; Frisoni et al., 2010; Hane et al., 2017; Pini et al., 2016; Wardlaw et al., 2013).

In the original review protocol, additional vascular variables were listed as outcomes of interest. However, these outcomes were rarely identified in relation to direct prenatal exposures. Therefore, we additionally excluded the studies reporting on these outcomes to reduce the heterogeneity of the included studies.

We excluded studies involving specific clinical populations including those with Familial early-onset AD, vascular dementia, Korsakoff syndrome and Down's syndrome. Studies focusing on a clinical population (e.g. patients with congenital heart disease) were included only if they studied the association between the exposure and outcome of interest separately in the group of healthy controls. In this case, the results from the healthy control group were extracted. We restricted on analysis methods by excluding voxel-based morphometry studies, since this analysis approach is significantly different from other analysis methods, which makes the comparison of results between these studies difficult.

2.3 Study selection and data extraction

All screening steps were performed by two authors independently, blinded for the other's decisions. AB and AMW independently screened the title and abstract of retrieved papers using Rayyan software (Ouzzani et al., 2016). Discrepancies were discussed and, if needed, resolved by a third reviewer (SdR). Two pairs of authors screened full texts (AB and YV, AMW and MvdH). The same pairs of authors performed data extraction, where the data was extracted by one reviewer and checked by the other. All discrepancies were discussed in pairs, and discussed with all four reviewers if needed. In case of considerable overlap in study samples, we included the study with the largest number of participants. We extracted the following data items: study aim, design, year of publication, cohort (if applicable), location, population, number of participants (per group), participant age at outcome assessment, exposure(s), timing of exposure (if applicable), control conditions, exposure assessment, relevant outcome(s), outcome volume, outcome assessment methods, scanner details, analysis details, confounders/covariates adjusted for in the analyses, the statistical relationship between exposure and outcome(s) (unadjusted and adjusted for confounders) and sub-group results. Template study selection and data extraction forms can be requested from the corresponding author.

2.4 Risk of bias assessment

The same author pairs performed risk of bias assessment using the Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized studies in duplicate, blinded to the other's decisions (Wells et al., 2000). Disagreements between the authors were discussed in pairs and resolved with all four reviewers if needed.

Prospective cohort studies were assessed using the NOS for cohorts, cross-sectional studies were assessed using the adapted NOS for cross-sectional studies (Alshabanat et al., 2015). When a cohort study had no prospective elements, we used the cross-sectional NOS as well since the items in this checklist were better suited for this study design. We removed the item "Demonstration that outcome of interest was not present at start of study" from the Cohort checklist since this question was not suitable for the studies included in our review given the nature of prenatal exposures. Thereby, both checklists had a maximum total score of 8.

2.5 Data synthesis

The results are presented in the form of a structured narrative synthesis, with the studies categorized on exposure and outcome. Outcome effect measures were reported as brain volumes, effect size (%difference) and statistical significance. In general, statistical significance was set at $p<0.05$. We did not perform meta-analyses given the large heterogeneity in study methodology and age at outcome assessment.

2.6 Protocol

The complete protocol can be accessed through PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020169317).

3 Results

Of 1696 unique studies, 84 were identified as eligible. Seven studies were subsequently excluded based on overlap in study participants (Acosta et al., 2020; Biffen et al., 2017; Coles et al., 2011; Fryer et al., 2012; Gross et al., 2018; Robey et al., 2014; Wu et al., 2020a). Two additional studies were identified through citation searching, resulting in 79 included studies in the final review (Figure 1). These studies had a total of 24,784 participants from 14 countries.

A large proportion of included studies investigated prenatal exposure to alcohol (N=30). Other exposures included illicit drugs (N=14), smoking (N=7), diet (N=8), environmental exposures (N=3), maternal disease, treatment and physiology (N=10) with the subcategories infections (N=6) and mental health problems (N=7). For numerous studies, there was an overlap between multiple exposures, mostly concerning exposures to alcohol, tobacco and illicit drugs. Prenatal illicit drug exposure studies often evaluated multi-drug exposures and mental health studies mostly evaluated a combination of prenatal stress, anxiety and depression exposure.

The majority of studies included WBV (N=38) and/or HV (N=63) as an outcome, with only a few (N=5) reporting TLV. Age at outcome assessment ranged between 22 weeks gestational age (GA) to 67 years postnatally, although most studies assessed the outcome in childhood (median age 10.7 years). An interactive bubble map of the evidence according to exposure category, outcome and direction of effect created using EPPI reviewer software is available as a supplementary file (Supplementary Figure 1; Thomas et al., 2020).

3.1 Risk of Bias assessment

An overview of risk of bias score per exposure category and study design is provided in Figure 2. Studies had a mean score of 5.8/8 on the NOS. With a maximum score of 8 on the NOS, 1 study had a score of 2/8 (1%), 3 studies were scored with a 3/8 (4%), 5 with a 4/8 (6%), 24 with a 5/8 (30%), 16 with a 6/8 (20%), 23 with a 7/8 (29%) and 7 with 8/8 (9%). Especially studies in the categories of environmental exposures, diet and illicit drugs had satisfactory scores on the NOS. In general, studies scored poorly on the description of response rate and characteristics of non-respondents, follow-up adequacy and sample size justification.

For specific exposure categories, studies in the infections category were often hampered by an inadequate representativeness of the study sample. Both infection and alcohol exposure studies had a notable risk of bias in selection of the unexposed cohort. Smoking and mental health studies scored poorly on the ascertainment of exposure. Mental health studies often did not report the assessment of outcome. Maternal disease, treatment and physiology studies and infection studies had poor comparability of the cohorts.

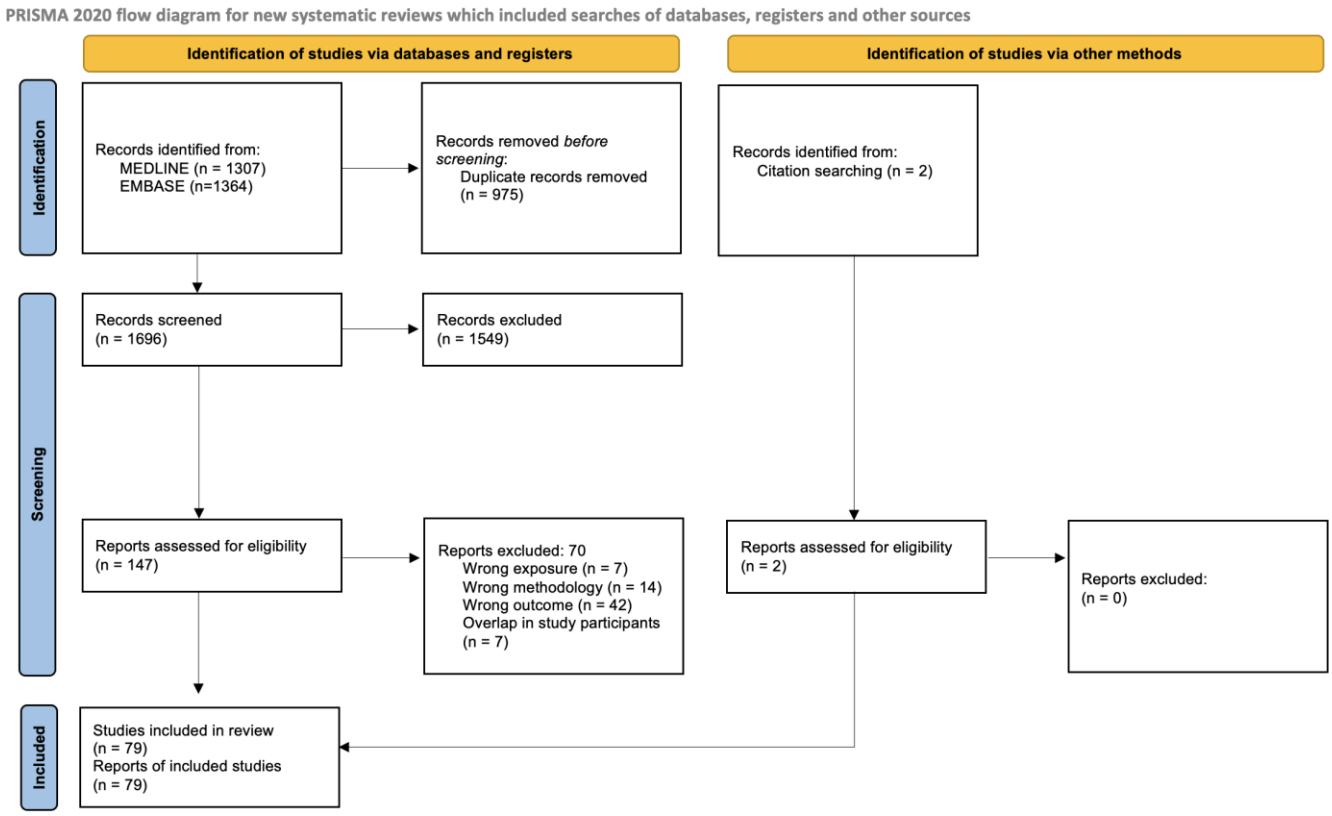
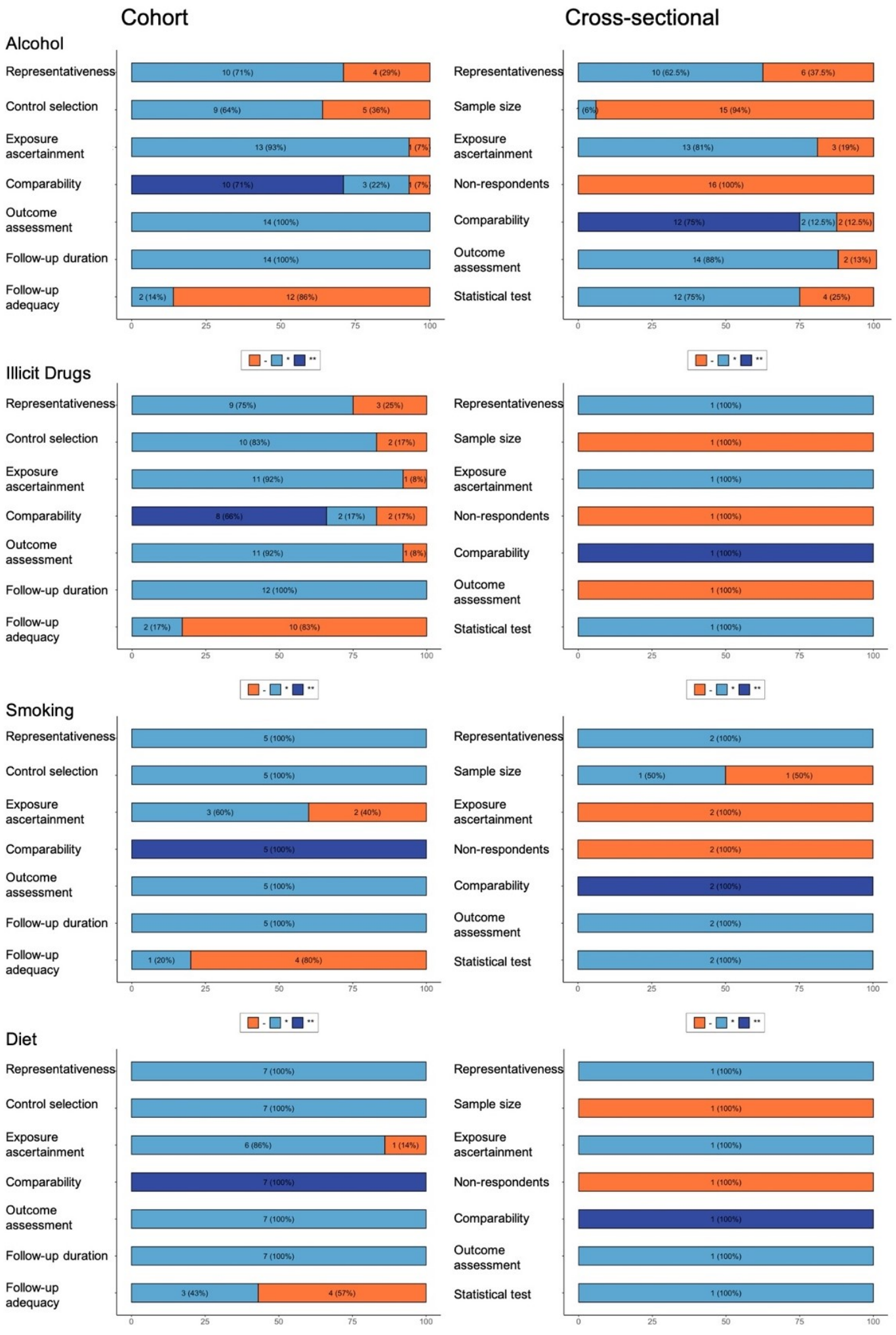
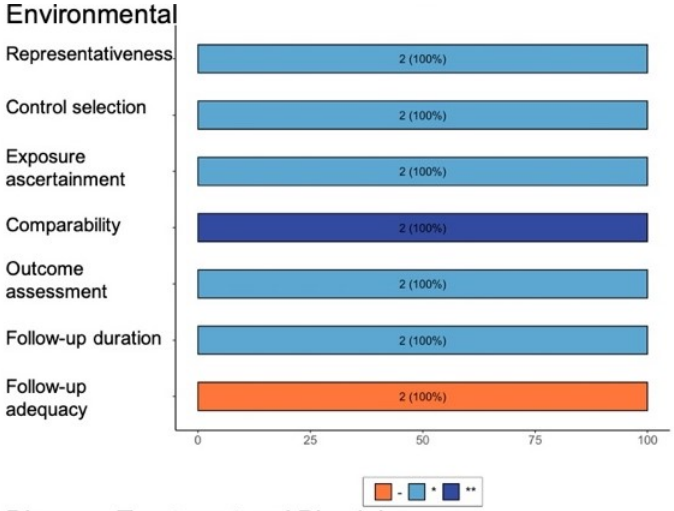
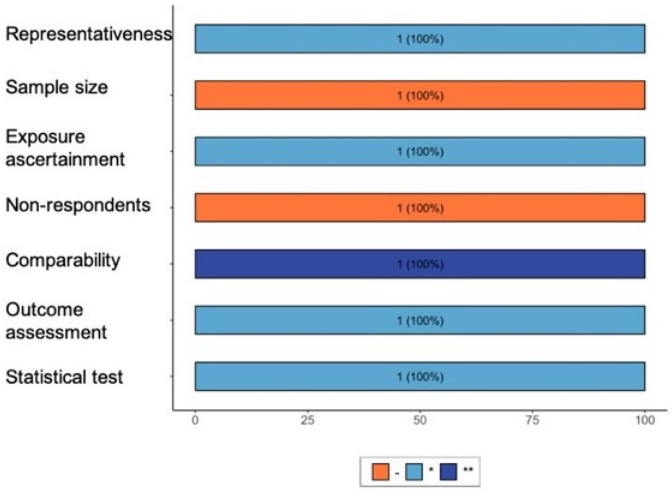


Figure 1. PRISMA 2020 flow diagram of study selection.

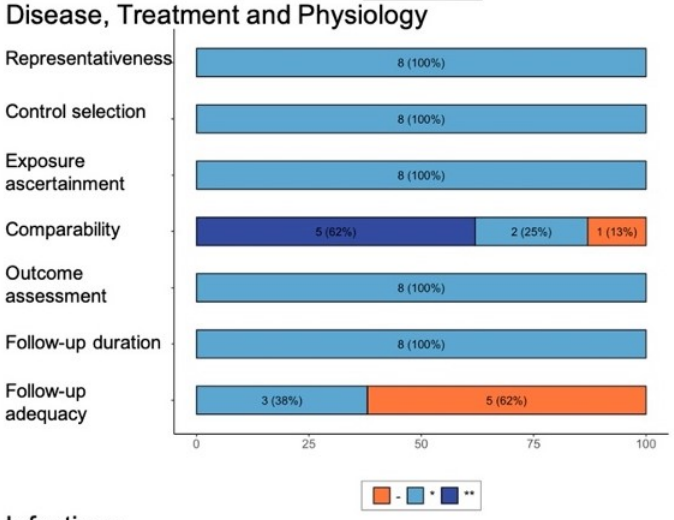

Cohort
Cross-sectional
Alcohol
Representativeness
Control selection
Exposure ascertainment
Comparability
Outcome assessment
Follow-up duration
Follow-up adequacy
10 (71%)
4 (29%)
9 (64%)
5 (36%)
13 (93%)
1 (7%)
10 (71%)
3 (22%)
1 (7%)
14 (100%)
14 (100%)
2 (14%)
12 (86%)
Representativeness
Sample size
Exposure ascertainment
Non-respondents
Comparability
Outcome assessment
Statistical test
10 (62.5%)
6 (37.5%)
1 (6%)
15 (94%)
13 (81%)
3 (19%)
16 (100%)
12 (75%)
2 (12.5%)
2 (12.5%)
14 (88%)
2 (13%)
12 (75%)
4 (25%)
0
25
50
75
100
- * **
Illicit Drugs
9 (75%)
3 (25%)
10 (83%)
2 (17%)
11 (92%)
1 (8%)
8 (66%)
2 (17%)
2 (17%)
11 (92%)
1 (8%)
12 (100%)
2 (17%)
10 (83%)
1 (100%)
Smoking
5 (100%)
3 (60%)
2 (40%)
1 (20%)
4 (80%)
2 (100%)
1 (50%)
Diet
7 (100%)
6 (86%)
1 (14%)
3 (43%)
4 (57%)

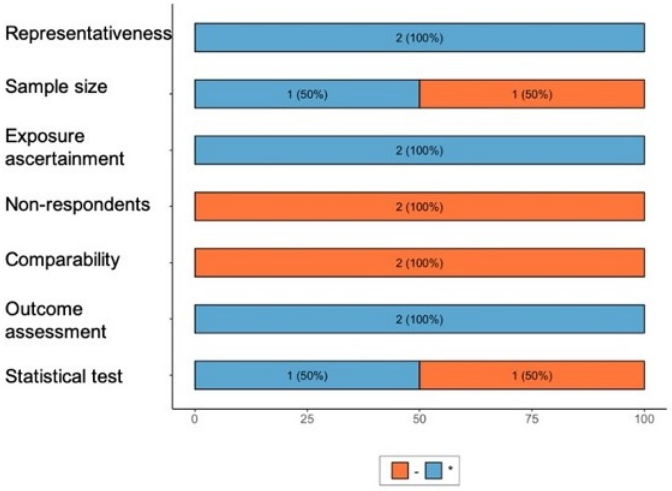
Environmental



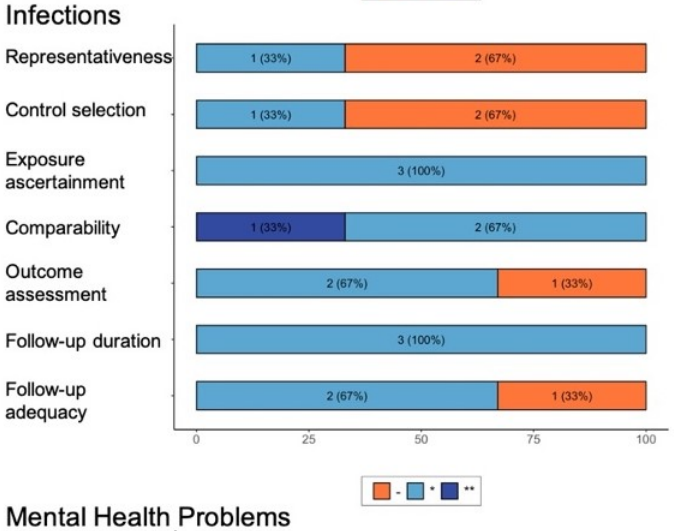


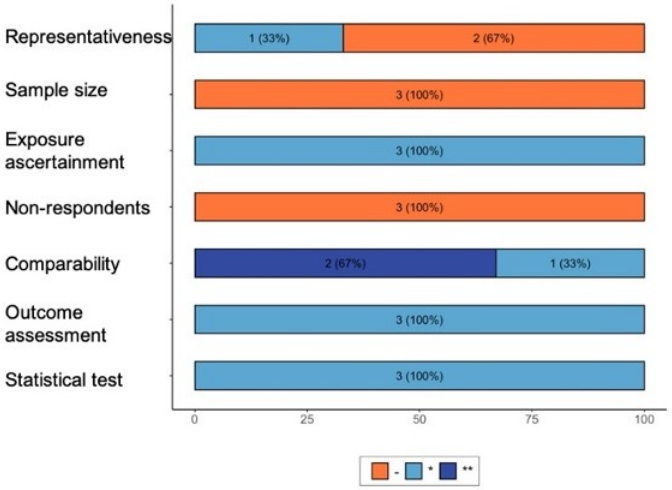
Disease, Treatment and Physiology





Infections





Mental Health Problems

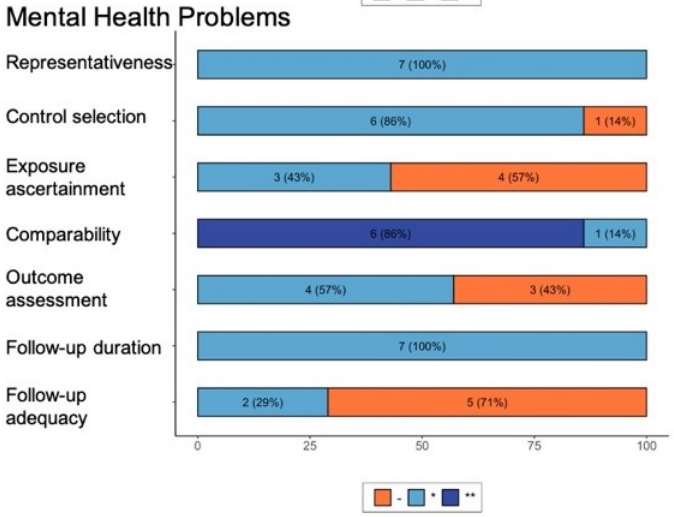


Figure 2. Newcastle Ottawa Scale risk of bias assessment score per exposure category and study design. Orange indicates no points (-), light blue indicates 1 point (*) and dark blue indicates 2 points (**), only applicable for the comparability category) on the NOS.

3.2 Alcohol

Thirty studies investigated the association between prenatal alcohol exposure and WBV (N=12), HV (N=20) and/or TLV (N=3). Many studies focused on severe prenatal alcohol exposure, often resulting in alcohol-related neurodevelopmental disorder (ARND) or fetal alcohol spectrum disorder (FASD). Several studies in this category had considerable overlap in their study participants. Nonetheless, they did contribute valuable information, for instance by studying different outcomes or a different age at outcome assessment (Chen et al., 2012; Coles et al., 2011; Lebel et al., 2008; Nardelli et al., 2011; Treit et al., 2017; Treit et al., 2013; Treit et al., 2016).

Most studies reported a significantly smaller WBV in exposed children compared to unexposed children, with effect sizes ranging from -26.1% to +2.0% (12 years, Astley et al., 2009; 22-24 years, Chen et al., 2012; 9-10 years, De Guio et al., 2014; 9-10 years, Lebel et al., 2008; 11 years, Rajaprakash et al., 2014; 12 years, Rivkin et al., 2008; 12 years, Spottiswoode et al., 2011; 11-12 years, Treit et al., 2013; 12-13 years, Zhou et al., 2018). The remaining studies investigating WBV reported no significant association, although they reported effect sizes ranging from -5.0% to +2.1% (9 years, de Zeeuw et al., 2012; 21 years, Willford et al., 2010). Lebel and colleagues performed a 2-year longitudinal study and reported no significant association with developmental trajectories (12-14 years, Lebel et al., 2012).

Individuals prenatally exposed to alcohol had a smaller HV, with effect sizes ranging from -26.1% to +2.0% (11-15 years, Archibald et al., 2001; 12 years, Astley et al., 2009; 11 years, Biffen et al., 2020; 22-24 years, Chen et al., 2012; 10-11 years, Dodge et al., 2020; 21-22 days, Donald et al., 2016; 12-13 years, Dudek et al., 2014; 12 years, Gautam et al., 2015; 12 years, Joseph et al., 2014; 12 years, Krueger et al., 2020; 12-13 years, McLachlan et al., 2020; 10 years, Meintjes et al., 2014; 11 years, Nardelli et al., 2011; 11 years, Riikonen et al., 2005; 13 years, Roussotte et al., 2012b; 13-14 years, Treit et al., 2017; 11-12 years, Treit et al., 2013; 12-14 years, Uban et al., 2020; 12 years, Willoughby et al., 2008; 12-13 years, Zhou et al., 2018). This effect was non-significant in the study by Joseph et al, although they did report a 9.1% smaller left HV and 1.7% smaller right HV in exposed children (Joseph et al., 2014). In addition, Willoughby et al. only reported a significantly smaller left HV, despite reporting 3.6% smaller HV in exposed children (Willoughby et al., 2008).

Prenatal exposure to alcohol had inconsistent associations with TLV, with exposed individuals having a 16.4% smaller TLV at age 13 (Sowell et al., 2002), but no statistically significant effect was observed at age 12 and 11-15 (No volumes reported; Archibald et al., 2001; Treit et al., 2016).

3.3 Illicit Drugs

We identified thirteen studies investigating the association between prenatal illicit drug exposure and WBV (N=8) and/or HV (N=10). No studies included TLV as an outcome.

Individuals prenatally exposed to opioids had a 3.0% to 16.0% smaller WBV compared to unexposed individuals at age 10-11, 12 and 19 (Nygaard et al., 2018;

Sirnes et al., 2017; Walhovd et al., 2007) or to the population mean (41 weeks, Yuan et al., 2014). This was statistically significant in three studies. Sirnes et al. reported no significant association, although exposed individuals had a 3.7% smaller WBV (Sirnes et al., 2017). Of note, there was overlap in the study samples of Walhovd et al. and Nygaard et al., although the outcome was assessed at different ages (Nygaard et al., 2018; Walhovd et al., 2007). Smaller WBV was reported after prenatal exposure to cocaine, which was statistically significant at age 12 (Rivkin et al., 2008) and not significant at age 15 (Roussotte et al., 2012a). No statistically significant associations between prenatal cannabis (7 years, El Marroun et al., 2016), marijuana (Rivkin et al., 2008) or methamphetamine (7 years, Chang et al., 2004) and WBV were reported, despite the 5.9% smaller WBV reported by Rivkin et al. and 3.1% smaller WBV reported by Chang et al. in exposed children.

Studies reported a 4.4% to 7.0% smaller HV in individuals prenatally exposed to opioids compared to unexposed individuals at age 10, 12 and 19 (Nygaard et al., 2018; Sirnes et al., 2017; Walhovd et al., 2007). None of these effects was statistically significant. Prenatal exposure to cocaine had uncertain results on HV at age 9, 13 and 15, with studies reporting mixed effects (effect size range -1.3% to +6.2%) with no statistically significant associations (Akyuz et al., 2014; Liu et al., 2013; Roussotte et al., 2012a). Of note, Akyuz et al. and Liu et al. included participants from the same cohort. Riggins et al. studied heroin and/or cocaine exposure, and reported a significantly larger left (+6.2%) and right (+5.3%) HV in exposed children (14 years, Riggins et al., 2012). Akyuz and colleagues additionally studied the growth of the HV between age 9 and 14 years, and reported a lower percent HV growth after prenatal cocaine exposure (1% vs 9% growth). Prenatal methamphetamine exposure had inconsistent results on HV, with a significantly smaller left (-20.5%) and right (-19.5%) HV at age 7, but no significant effects at 42

weeks GA and age 4 (Chang et al., 2004; Derauf et al., 2012; Warton et al., 2018). Warton et al. did report a larger HV after prenatal methamphetamine exposure (+2.5 and 3.3%), and Derauf et al. a smaller HV (-2.6%), although both effects were not statistically significant.

3.4 Smoking

We included seven studies investigating an association between maternal smoking and WBV (N=4) and/or HV (N=4). None of these studies included temporal lobe volume (TLV) as an outcome.

Individuals prenatally exposed to smoking had a smaller WBV compared to prenatally unexposed individuals. This was statistically significant in three studies (GA 24-35 weeks, Anblagan et al., 2013; 7 years, El Marroun et al., 2014; 12 years, Rivkin et al., 2008). For the fourth study performed by De Zeeuw and colleagues, the reported average WBV was smaller for exposed offspring compared to unexposed offspring, but the reporting on statistical significance was unclear (11 years, de Zeeuw et al., 2012). This study also had the highest risk of bias.

No studies reported a statistically significant association between maternal smoking and offspring HV. Of note, exposed children did have a smaller HV in the two studies that reported brain volumes and three studies corrected for ICV in their analysis, thereby potentially correcting for developmental effects (4 years, Derauf et al., 2012; 7 years, El Marroun et al., 2014; 14 years, Liu et al., 2013; 63 years, Salminen et al., 2019).

3.5 Diet

Seven cohort studies and one cross-sectional study investigated maternal diet in relation to WBV (N=6) and/or HV (N=6). No studies reported on the relationship between maternal diet and TLV.

Prenatal exposure to the Dutch famine had inconsistent results on WBV, with exposed individuals having a 6.7% larger WBV at age 51 (Hulshoff Pol et al., 2000), but a statistically significant smaller WBV (-2.4% to -7.3%) at age 67 (de Rooij et al., 2016). The smaller WBV at age 67 was mainly driven by a smaller WBV in exposed men. Of note, the effect reported by De Rooij et al. was only observed without correction for ICV, and Hulshoff Pol et al. reported results corrected for ICV. Therefore, it is unknown whether an ICV-dependent effect may have been present at age 51. Also, the number of participants in the analysis performed by Hulshoff Pol et al. was very small, limiting the power of this study to detect potentially smaller effect sizes. Studies reported no significant associations between maternal B12 or homocysteine levels (7 years, Ars et al., 2019) or prenatal LC-PUFA or 5-MTHF supplementation and WBV (10 years, Catena et al., 2019). Ars et al. did report a lower WBV in children exposed to low prenatal maternal folate levels compared to children exposed to normal prenatal maternal folate levels. Ogundipe and colleagues reported no statistically significant effect of essential brain-specific fatty acids supplementation across all participants (group difference range +1.9% to 3.1%). They did report a higher WBV in men after supplementation, pointing at a potentially differential sex sensitivity (0-4 weeks, Ogundipe et al., 2018). Lastly, Zou et al. reported a smaller WBV after exposure to continuous prenatal vitamin D insufficiency (10 years, Zou et al., 2020).

Alves et al. found a significant association between maternal prepregnancy BMI and HV, with a significant negative correlation between maternal prepregnancy BMI and HV in boys but not girls (8 years, Alves et al., 2020). Morton et al. reported a positive correlation between prenatal maternal omega-3 fatty acid intake reported by the mother and HV (27 days, Morton et al., 2020). This correlation was no longer significant after correcting for multiple testing and reporting of these results was limited. No statistically significant associations with HV were reported for low prenatal folate levels, B12 and homocysteine levels (7 years, Ars et al., 2019), prenatal LC-PUFA or 5-MTHF supplementation (10 years, Catena et al., 2019) or prenatal vitamin D levels (10 years, Zou et al., 2020). Furthermore, no significant effect of essential brain specific fatty acids supplementation was reported, although the supplementation group had a 1.9% larger HV (0-4 weeks, Ogundipe et al., 2018).

3.6 Environmental

Three studies investigated WBV (N=2) and/or HV (N=3) in relation to prenatal environmental exposures. No studies included TLV as an outcome.

Guxens et al. reported no association between multiple measures of prenatal air pollution and WBV in a large prospective cohort study (6-10 years, Guxens et al., 2018). HV was also mentioned as an outcome, but the results of this analysis were not reported. Van den Dries and colleagues investigated the association between prenatal exposure to organophosphate pesticides and offspring WBV and HV in the same cohort as Guxens et al. No statistically significant associations were reported (10 years, van den Dries et al., 2020). In the cross-sectional study performed by Janulewicz et al., no significant association was reported between prenatal tetrachloroethylene (PCE)-contaminated drinking water

exposure and offspring HV, although HV was 1.7% larger in exposed individuals (30 years, Janulewicz et al., 2013).

3.7 Disease, Treatment and Physiology

Ten studies investigated the association between a prenatal maternal disease, treatment and physiology exposure and WBV (N=5), HV (N=8) and/or TLV (N=1). Six additional studies on maternal infections and seven studies on maternal mental health problems are discussed in the subcategories below.

In their twin study on placental functioning, Luo and colleagues reported a negative association between WBV and placental-oxygen time to plateau (TTP) as a measure for placental oxygen transport (GA 29-34 weeks, Luo et al., 2017). Sammallahti et al. reported a negative association between WBV at age 10 years and the umbilical artery pulsatility index during the second trimester as a measure of placental vascular resistance, although this association did not survive correction for multiple testing (Sammallahti et al., 2020). No statistically significant associations with WBV were reported for maternal cancer and chemotherapy (GA 42 weeks, Passera et al., 2019) and maternal hypothyroxinemia (8 years, Ghassabian et al., 2014). Of note, the exposed infants in the study by Passera and colleagues did have a 6.8% smaller WBV. Korevaar et al. studied both increased and decreased maternal thyroid function in the same population as Ghassabian and colleagues. They did not observe a significant association between free thyroxine (FT4) and WBV, but did report a significant inverse U-shaped association between thyroid stimulating hormone (TSH) and WBV (8 years, Korevaar et al., 2016).

A significantly smaller HV was reported after prenatal exposure to maternal iron deficiency anemia at age 3-5 days (Basu et al., 2018). In addition, a significantly larger HV was reported after prenatal exposure to maternal-fetal Rhesus and ABO blood incompatibility at age 40 (Freedman et al., 2011). Willoughby et al. reported a significant negative association between maternal TSH levels in the second and third trimester and right HV (10 years, Willoughby et al., 2014). The five remaining studies investigating prenatal exposure to gestational diabetes (10 years, Jabes et al., 2015), maternal cancer and chemotherapy (GA 42 weeks, Passera et al., 2019), maternal pre-eclampsia (10 years, Ratsep et al., 2016), maternal hypothyroxinemia (8 years, Ghassabian et al., 2014) and FT4 or TSH (8 years, Korevaar et al., 2016) did not report a statistically significant association with HV. Of note, Ratsep et al. did report a larger HV in exposed children (left HV +9.5%, right HV +4.5%) and Ghassabian a smaller HV in exposed children (-1.9%). However, the statistical analyses were only performed with correction for ICV (Ratsep et al., 2016) or WBV (Ghassabian et al., 2014).

Individuals prenatally exposed to pre-eclampsia had a higher TLV compared to unexposed individuals at age 10 (Ratsep et al., 2016).

3.7.1 Infections

We included six studies investigating an association between prenatal maternal infections and HV (N=5) or TLV (N=1). None of these studies included WBV as an outcome.

Ellman and colleagues found no significant association between HV and maternal serum cytokine interleukin-8 levels, a measure of maternal infection (40 years, Ellman et al., 2010). Of note, this analysis had an unusually small sample size

458 of N=8 and may have been underpowered. Vertical HIV infection had inconsistent
459 effects on HV. Both Nwosu and Yadav and et al. reported smaller volumes of both
460 left and right HV in HIV-infected children at age 7 and 10 (Nwosu et al., 2018; Yadav
461 et al., 2017). However, this effect did not remain statistically significant after
462 correcting for multiple testing in the analysis performed by Nwosu and colleagues.
463 Paul et al. and Wade at al. have an overlap in their study participants, although the
464 extent of this overlap is unclear. Both studies reported no significant association
465 between HIV infection and HV at age 11, although the exposed children had 1%
466 larger HV in the study by Paul and colleagues. In addition, Wade et al. reported no
467 longitudinal changes (follow-up median 53 weeks) in HV associated with HIV
468 infection (Paul et al., 2018; Wade et al., 2019).

469 Hoffmann and colleagues observed a significantly smaller TLV in fetuses
470 exposed to a cytomegalovirus infection compared to unexposed fetuses, which was
471 independent of WBV (GA 33 weeks, Hoffmann et al., 2010).

472

473 ### 3.7.2 Mental Health Problems

474 Seven included studies investigated any measure of maternal mental health during
475 pregnancy in association with offspring HV. One of these studies additionally
476 included WBV as an outcome, none included TLV.

477 Wu et al. reported no significant association between maternal stress,
478 anxiety or depression and WBV (GA 28-36 weeks, Wu et al., 2020b).

479 The children exposed to maternal psychopathology in the study by
480 Björnebekk et al. had a 1.6% larger HV compared to unexposed children, but this
481 difference was not statistically significant (4.5 years, Björnebekk et al., 2015). In

addition, no significant associations between maternal depressive symptoms (26 days, Lehtola et al., 2020; GA 28-36 weeks, Wu et al., 2020b; 10 years, Zou et al., 2019), maternal stress (23 years, Mareckova et al., 2018; Wu et al., 2020b), maternal anxiety (Lehtola et al., 2020; 40-66 weeks post-conception, Qiu et al., 2013; Wu et al., 2020b) or maternal cortisol (7.5 years, Buss et al., 2012) and HV were reported. Wu et al. tested for associations between maternal depression, stress, state anxiety and trait anxiety and HV. Of these exposures, only maternal trait anxiety had a significant negative association with HV which remained after correction for multiple testing.

Qiu and colleagues did not identify an association between prenatal anxiety exposure and bilateral HV at birth or six months. They did report slower bilateral hippocampal growth between these time points after exposure to prenatal maternal anxiety. This effect was independent of postnatal maternal anxiety for the right hippocampus only.

4 Discussion

The 79 studies included in this systematic review provide evidence that prenatal exposures are associated with brain size, especially with WBV and HV; the evidence for an association with TLV is scarce (N=5 studies). The most substantial evidence was found for smaller WBV and/or HV after prenatal alcohol exposure, smoking, opioid or cocaine use, nutrient shortage and disease or placental/umbilical cord dysfunction. The outcomes were mostly assessed in childhood and effect sizes ranged between -40% and +19%, although many studies failed to report a measure of effect size. Limited evidence was found for other types of prenatal illicit drug exposure, mental health problems, dietary supplementation or physiological ranges, thyroid function, infections or environmental exposures being associated with the outcomes of interest, although evidence was scarce or inconclusive for numerous exposures. Overall risk of bias was low, although studies scored poorly on the description of response rate and characteristics of non-respondents, follow-up adequacy and sample size justification.

4.1 Conclusion per exposure

4.1.1 Alcohol

The overall body of evidence for a smaller WBV and HV after prenatal alcohol exposure is convincing. Given the large number of studies investigating this exposure (N=32), the overlap in study sample for some studies will not have significantly impacted the overall outcome. Notably, most studies have measured the outcome between 11 and 14 years of age, which leaves a large knowledge gap in brain development before and after this age range.

4.1.2 Illicit Drugs

The included studies provide evidence for a smaller WBV after prenatal opioid and cocaine exposure in neonates, children and teenagers. No studies investigated these associations in (late) adulthood. The smaller group difference in the study by Roussotte at age 15 versus Rivkin at age 12 (1.4% versus 6.9%) could potentially indicate a dilution of the effect of the prenatal exposure on neurodevelopment, although additional studies investigating these effects in late childhood and (late) adulthood are needed to determine these associations. No associations between prenatal exposure to cannabis, marijuana or methamphetamine and WBV were reported, but the evidence was limited. Evidence was provided for a smaller HV after prenatal opioid exposure. Associations between heroin, cocaine and methamphetamine and HV were heterogeneous and reported by a small number of studies.

4.1.3 Smoking

The included studies demonstrate that the negative association between maternal smoking and offspring WBV is present in the fetal brain and appears to continue into childhood. The evidence for an association between maternal smoking and HV was insufficient. No studies were performed in early and mid-adulthood and the single study that measured HV in late adulthood did not report on WBV, and only reported HV analyses corrected for ICV. It thus remains unclear whether an effect may be observed for WBV or ICV-dependent HV in (late) adulthood.

4.1.4 Diet

Although the included studies on the association between maternal prenatal diet and brain development investigated a large variety of nutrients, they report an overall pattern of smaller WBV after nutrient shortage. This pattern appears to be a general effect across the WBV, few specific effects were observed in the HV. In addition, the effects appear to have sex-specificity, with boys potentially being more vulnerable. The negative correlation of maternal prepregnancy BMI with HV in boys, and the positive correlation of prenatal maternal omega-3 fatty acid intake with HV do point at a potential vulnerability of the hippocampal development to maternal diet.

4.1.5 Environmental

No evidence of associations with prenatal environmental exposures was provided by the included studies. Nevertheless, only three studies were included in this category of which two were conducted in the same cohort, and all administered indirect and inaccurate measures of exposure. More studies investigating the impact of prenatal exposure to harmful environmental circumstances are needed to improve our understanding of the potential association with brain development.

4.1.6 Disease, Treatment and Physiology

Despite the large diversity in exposures, the included studies provide evidence that maternal medical conditions can impact fetal brain development. In particular, maternal TSH levels, iron deficiency anemia, maternal-fetal rhesus and ABO blood incompatibility and pre-eclampsia were associated with altered brain outcomes. Surprisingly, larger HVs were observed in individuals exposed to maternal-fetal

rhesus and ABO blood incompatibility at age 40 years (Freedman et al., 2011). Furthermore, larger TLVs were observed in individuals exposed to maternal pre-eclampsia (Ratsep et al., 2016). The authors suggest that this may be indicative of adaptive resilience in exposed individuals (Freedman et al., 2011).

4.1.6.1 Infections

The included studies provide some indication that prenatal infections may impact the development of the hippocampus and temporal lobe regions, although evidence is scarce. Most evidence for an association with smaller HV was found in the studies investigating vertically transferred HIV, although study results were inconsistent.

4.1.6.2 Mental Health Problems

No evidence for an association between mental health problems and WBV or HV was provided by the included studies. Nevertheless, most studies on HV only report their outcomes corrected for either ICV or WBV, so we cannot infer that HV developmental alterations are dependent on ICV or WBV. The large majority of studies was performed in infants and no studies assessed the outcome past 10 years. This limits the available information on developmental brain trajectories after prenatal exposure to maternal mental health problems. The reduced right hippocampal growth independent of postnatal mental health problems reported by Qiu and colleagues does indicate that some association may be present. Additional studies are needed to elucidate this potential association, especially since this study was performed in young children only.

4.2 General interpretation

Taken together, these studies provide a convincing body of evidence for an association between adverse prenatal exposures and smaller brain volumes in brain regions associated with AD. However, several nuances should be considered. First, the specific impact of any exposure depends on the type of exposure and the underlying mechanisms which drive the effect. Several prenatal exposures had a clear impact on brain volumes, whereas others showed no hint of an association. Furthermore, the effect size is likely dependent on the severity and timing of the exposure. Little attention is given to the timing of exposure in the majority of included studies. Moreover, many exposures may last throughout pregnancy and continue postnatally, providing challenges in determining the effect at specific points in pregnancy. For instance, by definition, populations of children vertically infected with HIV are continuously exposed postnatally. In addition, there may be sex-specific effects for certain exposures, as was demonstrated by De Rooij et al. and Alves et al. (Alves et al., 2020; de Rooij et al., 2016). Nevertheless, outside of the diet category, included studies scarcely explored sex-specificity of their results. Exploring sex-specificity of the impact of prenatal exposures on brain development may provide valuable insights, especially considering that male fetuses are more vulnerable to prenatal exposures and may therefore respond differently (Bale, 2016).

Furthermore, numerous study groups included multi-exposures, which may be problematic for determining the effect of a single, specific exposure. In particular, prenatal exposure to alcohol, smoking and/or illicit drugs were often observed in combination. Correcting for multi-exposures remains challenging, especially when exposure information is based on self-report. Toxic effects of multiple exposures

may amplify their impact, resulting in larger effect sizes. Of note, exposure to multiple, interrelated exposures is common in real life, and studying their combined impact may improve the external validity of the study (Buss and Genueit, 2022). Thereby, both studies of single exposures and studies investigating multi-exposures should be considered to obtain a more complete understanding of the impact of prenatal exposures.

Most studies measured the outcome in childhood, leaving a large knowledge gap of the outcomes in (late) adulthood. Despite the limited number of studies that measured the outcome in adulthood, the majority of brain development occurs in early development, and brain volumetric measures remain relatively stable thereafter until the onset of neurodegeneration (Dobbing and Sands, 1973; Prayer et al., 2006). Large changes in effect size in later life are, therefore, not expected.

The effect size (Δexposed-unexposed, %) in the included studies ranged between -40% and +19%, although many studies failed to report any indication of effect size or brain volumes. The approximated average effect of alcohol (~-10%) on brain volumes was roughly twice as large as the average effect of illicit drugs (~-6%) or smoking (~-5%) in the studies included in this review. These effect sizes are likely to be relevant alterations to the brain reserve, as studies generally report a 10-15% smaller HV in MCI patients and a 15-40% smaller HV in AD patients compared to healthy controls (Bosscher and Scheltens, 2002; Pini et al., 2016). Thereby, having a 5-10% smaller brain volume may significantly impact the brain's capacity to buffer AD-related neurodegeneration.

4.3 Mechanisms

Several biological pathways through which adverse prenatal exposures could result in altered brain development have been proposed. These pathways are mainly associated with teratogenic effects on the developing fetus or nutrient shortage limiting developmental processes (Martin-Gronert and Ozanne, 2012).

For instance, a prenatal exposure or nutrient shortage may alter DNA methylation patterns of genes associated with prenatal brain development and growth in general (Tobi et al., 2014). In addition, prenatal malnutrition has been shown to affect neurogenesis, cell migration and differentiation (Morgane et al., 1993). Comparable processes have been observed for prenatal alcohol toxicity disrupting neuronal proliferation and migration, causing cell death. Furthermore, alcohol-induced hypoxia and altered hormone and protein synthesis levels can result in growth retardation, and alcohol can disrupt growth factor signaling and increase oxidative stress on the embryo (Lebel et al., 2011). Similarly, prenatal tobacco exposure can induce neural cell loss and hypertrophy (Scott-Goodwin et al., 2016). Rodent studies have highlighted the effects of prenatal exposures on brain reserve through alterations in dendritic morphology, spine number, and synaptic plasticity and function (Lesuis et al., 2018). Moreover, a primate study of fetal nutrient restriction related resulting cerebral developmental disturbances to mechanisms including impaired cell proliferation, glial maturation and neuronal process formation (Antonow-Schlorke et al., 2011).

4.4 Methodological remarks

After thorough evaluation of the included studies, several methodological aspects deserve mentioning.

First, many studies analyzed HV corrected for WBV or ICV, without reporting an uncorrected analysis or any information on WBV in the study participants. Consequently, these studies provide little information on the impact of the exposure of interest on brain development as a whole, as a reduction in HV dependent on WBV would still be of interest. Furthermore, additional reporting on WBV would greatly improve the insight on the brain development in exposed individuals.

Reporting on study outcomes was incomplete or unclear for many studies. Numerous studies failed to report brain volumes, uncorrected analyses and effect sizes. As a result, we were limited to a mere report of statistical significance if no additional information was provided. As statistical significance does not give any insight in effect size or potential clinical relevance, we extracted outcome details if provided and used this as context for all studies in the exposure category. In addition, we calculated a % difference between exposed and unexposed groups, when possible, to enable some interpretation of effect size. Furthermore, terminology for WBV was confusing. Reporting of WBV, total brain volume, intracranial volume with or without ventricles or cerebellar volume was often inaccurate and could easily be misunderstood. Studies regularly failed to report whether HV was reported or analyzed unilaterally, bilaterally or as an average of both hemispheres. Since studies have previously identified specific effects for either left HV or right HV, clear reporting of the analysis approach and rationale is of utmost importance.

Additionally, there was considerable overlap in the study samples of numerous studies. Several large cohort studies were used for the analysis of multiple exposures or different outcomes on the same exposure. Also, some manuscripts combined samples from previous studies to explore a new research question in a larger study sample. In the case of considerable overlap in study sample, exposure and outcome, the study with the lowest number of participants was excluded. However, if, despite an overlap in study participants, new information was provided by the study in terms of outcome or age at outcome assessment, studies were not excluded. We aimed to clearly report on these details in both text and tables to enable an unbiased interpretation of the study results.

Moreover, many included studies obtained information on exposure through maternal self-report or retrospective reports sometimes collected years after the prenatal period. This approach reduces the reliability of the exposure data and increases the chances of potential underreporting and misclassification of exposure. Nevertheless, although increasing the risk of bias in a study, underreporting and misclassification would presumably lead to an underestimation of effects. Therefore, the overall pattern of reduced brain volumes after harmful exposures reported supports the hypothesis of an association despite this limitation.

In addition, some exposure categories only included a small number of studies, and the evidence for many specific exposures was limited to a single study. Overall, the number of studies per specific exposure type should be increased to improve the certainty of evidence, especially in categories with single studies per exposure.

Lastly, within exposure categories, we identified considerable differences between studies in exposure definition and severity limiting comparability between

studies. Also, most studies in the alcohol and illicit drug exposure categories used a relatively severe definition of exposure and occasionally included mildly exposed individuals in the unexposed control group. Additionally, many prenatal alcohol exposure studies investigated a specific population of children with FAS, a syndrome defined by significant brain damage. Combined, these factors limit the external validity to societies where pregnant women generally restrict their substance use to for instance an occasional glass of wine. Future studies should shed light on the impact and effect size of sporadic substance use versus complete abstinence on offspring brain development.

4.5 Strengths and limitations

In this systematic review, we provide an overview of the existing body of literature on prenatal exposures and outcomes of WBV, HV and TLV. By selecting studies based on these outcomes instead of AD diagnosis, we were able to identify a large number of studies with outcomes highly relevant for AD, which have not been related to risk of developing AD. This innovative approach resulted in valuable insights for future research strategies, and substantiates previous suggestions of a potential contribution of the prenatal environment to the risk of developing AD. Nevertheless, only a limited number of studies was identified investigating the outcomes in older age (N=3 above 50 years), and more longitudinal studies are needed to map the impact of prenatal exposures on brain health in later life.

Several limitations are the result of the nature of the exposures and outcomes of interest and our study design. First, several of the exposures discussed above are not specific to the prenatal period. For instance, maternal mental health problems or environmental exposures may continue postnatally, and disentangling

738 these effects is challenging. Secondly, the outcomes included in this systematic
739 review are established MRI neuroimaging biomarkers for AD. They may, however,
740 lack specificity for AD, as they are also associated with other types of dementia and
741 neurodegeneration. For instance, HV atrophy is also observed in non-AD forms of
742 dementia including Parkinson, vascular, frontotemporal lobar and semantic
743 dementia (Pini et al., 2016; Whalley et al., 2006). As a result, despite having limited
744 specificity for AD, the conclusions of this systematic review may also be applicable to
745 other types of dementia and late-life neurodegenerative disease. Lastly, we were
746 unable to perform a meaningful meta-analysis because of the large variation in
747 exposures, outcomes and age at outcome assessment in the included studies. These
748 limitations also restricted the comparability between studies. Nevertheless,
749 grouping the studies per exposure category facilitated comparison within categories.
750 The large range in exposures and outcomes did result in a substantial body of
751 literature with a broad external validity, enabling general conclusions for a broad
752 population.

753 The nature of the research topic and the observational designs of included
754 studies restricts conclusions on causality. It is nearly impossible to rule out all
755 potential confounders and randomized controlled trials are scarce. One included
756 study did adopt a randomized controlled trial design, and reported a higher WBV in
757 men after essential brain specific fatty acid supplementation, providing evidence for
758 a causal relationship (Ogundipe et al., 2018).

759

760 ## 4.6 Recommendations for future research

761 This systematic review demonstrated a clear association between prenatal
762 exposures and brain development. Our conclusions on the progression of these

outcomes over time and late-life brain health are, however, speculative. As the number of studies that longitudinally assessed the outcomes of interest was limited, and only a small number of studies assessed the outcomes past childhood. Cross-sectional studies provide a limited view of brain development, since measuring at a single time point does not provide any information on potential growth retardations and catch-up effects. There is a need for longitudinal studies stretching across a broader age range to explore the impact of prenatal exposures throughout life. Furthermore, core outcome sets and reporting guidelines could greatly improve the usability of future studies. Ideally, studies should include both WBV and HV as outcomes, and report on volumes, effect size and uncorrected models in addition to corrected models.

Finally, we urge investigators in future studies to adopt a life-long perspective in studying AD. The evidence summarized in this systematic review endorses the hypothesis that the prenatal environment may be an essential factor in the development of brain regions associated with AD risk in late life. Embedding this realization in research into both prenatal development and brain aging may promote collaborations among researchers in both fields and facilitate breakthroughs which can significantly move the field forward.

4.7 Conclusions

Adverse prenatal exposures are associated with alterations in brain development measured in structural brain outcomes related to AD in late life. Specifically, prenatal exposure to alcohol, opioids, cocaine, nutrient shortage, placental dysfunction and maternal anemia were associated with smaller whole brain, temporal lobe and hippocampal volumes. This altered development may result in

decreased brain reserve which is associated with an increased risk of dementia. Despite the relatively high overall quality of the included studies, there was a considerable range of exposures, outcomes, study designs and ages at outcome assessment, and reporting was inconsistent. Following existing neuroimaging reporting guidelines such as the OHBM COBIDAS Report is highly recommended (https://www.humanbrainmapping.org/files/2016/COBIDASreport.pdf; Pernet et al., 2020). In addition, core outcome sets and reporting guidelines for this field could improve the comparability between studies, overall research quality and applicability of research in this field. Thereby, the field of neuroimaging after prenatal exposures may offer a true life course perspective on the development of AD and other neurodegenerative diseases in later life.

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References

Acosta, H., Kantojarvi, K., Hashempour, N., Pelto, J., Scheinin, N.M., Lehtola, S.J., Lewis, J.D., Fonov, V.S., Collins, D.L., Evans, A., Parkkola, R., Lahdesmaki, T., Saunavaara, J., Karlsson, L., Merisaari, H., Paunio, T., Karlsson, H., Tuulari, J.J., 2020. Partial Support for an Interaction Between a Polygenic Risk Score for Major Depressive Disorder and Prenatal Maternal Depressive Symptoms on Infant Right Amygdalar Volumes. Cerebral Cortex 17, 17.

Akyuz, N., Kekatpure, M.V., Liu, J., Sheinkopf, S.J., Quinn, B.T., Lala, M.D., Kennedy, D., Makris, N., Lester, B.M., Kosofsky, B.E., 2014. Structural brain imaging in children and adolescents following prenatal cocaine exposure: preliminary longitudinal findings. Developmental Neuroscience 36, 316-328.

Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., FitzGerald, J.M., 2015. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. PLoS One 10, e0136065.

Alves, J.M., Luo, S., Chow, T., Herting, M., Xiang, A.H., Page, K.A., 2020. Sex differences in the association between prenatal exposure to maternal obesity and hippocampal volume in children. Brain and Behavior 10, e01522.

Anblagan, D., Jones, N.W., Costigan, C., Parker, A.J., Allcock, K., Aleong, R., Coyne, L.H., Deshpande, R., Raine-Fenning, N., Bugg, G., Roberts, N., Pausova, Z., Paus, T., Gowland, P.A., 2013. Maternal smoking during pregnancy and fetal organ growth: a magnetic resonance imaging study. PLoS ONE [Electronic Resource] 8, e67223.

Antonow-Schlorke, I., Schwab, M., Cox, L.A., Li, C., Stuchlik, K., Witte, O.W., Nathanielsz, P.W., McDonald, T.J., 2011. Vulnerability of the fetal primate brain to moderate reduction in maternal global nutrient availability. Proc Natl Acad Sci U S A 108, 3011-3016.

Archibald, S.L., Fennema-Notestine, C., Gamst, A., Riley, E.P., Mattson, S.N., Jernigan, T.L., 2001. Brain dysmorphology in individuals with severe prenatal alcohol exposure. Developmental Medicine & Child Neurology 43, 148-154.

Ars, C.L., Nijs, I.M., Marroun, H.E., Muetzel, R., Schmidt, M., Steenweg-de Graaff, J., van der Lugt, A., Jaddoe, V.W., Hofman, A., Steegers, E.A., Verhulst, F.C., Tiemeier, H., White, T., 2019. Prenatal folate, homocysteine and vitamin B₁₂ levels and child brain volumes, cognitive development and psychological functioning: the Generation R Study. British Journal of Nutrition 122, S1-S9.
Astley, S.J., Aylward, E.H., Olson, H.C., Kerns, K., Brooks, A., Coggins, T.E., Davies, J., Dorn, S., Gendler, B., Jirikowic, T., Kraegel, P., Maravilla, K., Richards, T., 2009. Magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Alcoholism: Clinical & Experimental Research 33, 1671-1689.
Ausó, E., Gómez-Vicente, V., Esquiva, G., 2020. Biomarkers for Alzheimer's Disease Early Diagnosis. J Pers Med 10.
Bale, T.L., 2016. The placenta and neurodevelopment: sex differences in prenatal vulnerability. Dialogues Clin Neurosci 18, 459-464.
Banderali, G., Martelli, A., Landi, M., Moretti, F., Betti, F., Radaelli, G., Lassandro, C., Verduci, E., 2015. Short and long term health effects of parental tobacco smoking during pregnancy and lactation: a descriptive review. J Transl Med 13, 327.
Basu, S., Kumar, D., Anupurba, S., Verma, A., Kumar, A., 2018. Effect of maternal iron deficiency anemia on fetal neural development. Journal of Perinatology 38, 233-239.
Biffen, S.C., Warton, C.M.R., Dodge, N.C., Molteno, C.D., Jacobson, J.L., Jacobson, S.W., Meintjes, E.M., 2020. Validity of automated FreeSurfer segmentation compared to manual tracing in detecting prenatal alcohol exposure-related subcortical and corpus callosal alterations in 9- to 11-year-old children. NeuroImage Clinical 28, 102368.
Biffen, S.C., Warton, C.M.R., Lindinger, N.M., Randall, S.R., Lewis, C.E., Molteno, C.D., Jacobson, J.L., Jacobson, S.W., Meintjes, E.M., 2017. Reductions in Corpus Callosum Volume Partially Mediate Effects of Prenatal Alcohol Exposure on IQ. Frontiers in Neuroanatomy 11, 132.
Björnebekk, A., Siqveland, T.S., Haabrekke, K., Moe, V., Slinning, K., Fjell, A.M., Walhovd, K.B., 2015. Development of children born to mothers with mental health problems: subcortical volumes and cognitive performance at 41/2 years. European Child & Adolescent Psychiatry 24, 115-118.
Borenstein, A.R., Copenhaver, C.I., Mortimer, J.A., 2006. Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord 20, 63-72.
Bosscher, L., Scheltens, P., 2002. Evidence-Based Dementia Practice.
Buss, C., Davis, E.P., Shahbaba, B., Pruessner, J.C., Head, K., Sandman, C.A., 2012. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proceedings of the National Academy of Sciences of the United States of America 109, E1312-E1319.
Caputo, C., Wood, E., Jabbour, L., 2016. Impact of fetal alcohol exposure on body systems: A systematic review. Birth Defects Res C Embryo Today 108, 174-180.
Catena, A., Martinez-Zaldivar, C., Diaz-Piedra, C., Torres-Espinola, F.J., Brandi, P., Perez-Garcia, M., Decsi, T., Koletzko, B., Campoy, C., 2019. On the relationship between head circumference, brain size, prenatal long-chain PUFA/5-methyltetrahydrofolate supplementation and cognitive abilities during childhood. British Journal of Nutrition 122, S40-S48.
Chang, L., Smith, L.M., LoPresti, C., Yonekura, M.L., Kuo, J., Walot, I., Ernst, T., 2004. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. Psychiatry Research 132, 95-106.

886 Chen, X., Coles, C.D., Lynch, M.E., Hu, X., 2012. Understanding specific effects of
887 prenatal alcohol exposure on brain structure in young adults. Human Brain Mapping
888 33, 1663-1676.
889 Coles, C.D., Goldstein, F.C., Lynch, M.E., Chen, X., Kable, J.A., Johnson, K.C., Hu, X.,
890 2011. Memory and brain volume in adults prenatally exposed to alcohol. Brain &
891 Cognition 75, 67-77.
892 De Guio, F., Mangin, J.F., Riviere, D., Perrot, M., Molteno, C.D., Jacobson, S.W.,
893 Meintjes, E.M., Jacobson, J.L., 2014. A study of cortical morphology in children with
894 fetal alcohol spectrum disorders. Human Brain Mapping 35, 2285-2296.
895 de Rooij, S.R., 2022. Are Brain and Cognitive Reserve Shaped by Early Life
896 Circumstances? Front Neurosci 16, 825811.
897 de Rooij, S.R., Caan, M.W., Swaab, D.F., Nederveen, A.J., Majoie, C.B., Schwab, M.,
898 Painter, R.C., Roseboom, T.J., 2016. Prenatal famine exposure has sex-specific
899 effects on brain size. Brain 139, 2136-2142.
900 de Rooij, S.R., Wouters, H., Yonker, J.E., Painter, R.C., Roseboom, T.J., 2010. Prenatal
901 undernutrition and cognitive function in late adulthood. Proc Natl Acad Sci U S A
902 107, 16881-16886.
903 de Zeeuw, P., Zwart, F., Schrama, R., van Engeland, H., Durston, S., 2012. Prenatal
904 exposure to cigarette smoke or alcohol and cerebellum volume in attention-
905 deficit/hyperactivity disorder and typical development. Transl Psychiatry Psychiatry
906 2, e84.
907 Derauf, C., Lester, B.M., Neyzi, N., Kekatpure, M., Gracia, L., Davis, J., Kallianpur, K.,
908 Efird, J.T., Kosofsky, B., 2012. Subcortical and cortical structural central nervous
909 system changes and attention processing deficits in preschool-aged children with
910 prenatal methamphetamine and tobacco exposure. Developmental Neuroscience
911 34, 327-341.
912 Dobbing, J., Sands, J., 1973. Quantitative growth and development of human brain.
913 Arch Dis Child 48, 757-767.
914 Dodge, N.C., Thomas, K.G.F., Meintjes, E.M., Molteno, C.D., Jacobson, J.L., Jacobson,
915 S.W., 2020. Reduced Hippocampal Volumes Partially Mediate Effects of Prenatal
916 Alcohol Exposure on Spatial Navigation on a Virtual Water Maze Task in Children.
917 Alcoholism: Clinical & Experimental Research 44, 844-855.
918 Donald, K.A., Fouche, J.P., Roos, A., Koen, N., Howells, F.M., Riley, E.P., Woods, R.P.,
919 Zar, H.J., Narr, K.L., Stein, D.J., 2016. Alcohol exposure in utero is associated with
920 decreased gray matter volume in neonates. Metabolic Brain Disease 31, 81-91.
921 Dudek, J., Skocic, J., Sheard, E., Rovet, J., 2014. Hippocampal abnormalities in youth
922 with alcohol-related neurodevelopmental disorder. Journal of the International
923 Neuropsychological Society 20, 181-191.
924 Ekblad, M., Korkeila, J., Lehtonen, L., 2015. Smoking during pregnancy affects foetal
925 brain development. Acta Paediatr 104, 12-18.
926 El Marroun, H., Schmidt, M.N., Franken, I.H., Jaddoe, V.W., Hofman, A., van der Lugt,
927 A., Verhulst, F.C., Tiemeier, H., White, T., 2014. Prenatal tobacco exposure and brain
928 morphology: a prospective study in young children. Neuropsychopharmacology 39,
929 792-800.
930 El Marroun, H., Tiemeier, H., Franken, I.H., Jaddoe, V.W., van der Lugt, A., Verhulst,
931 F.C., Lahey, B.B., White, T., 2016. Prenatal Cannabis and Tobacco Exposure in
932 Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children.
933 Biological Psychiatry 79, 971-979.
934 Ellman, L.M., Deicken, R.F., Vinogradov, S., Kremen, W.S., Poole, J.H., Kern, D.M.,
935 Tsai, W.Y., Schaefer, C.A., Brown, A.S., 2010. Structural brain alterations in

schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. Schizophrenia Research 121, 46-54.
Franke, K., Ziegler, G., Klöppel, S., Gaser, C., 2010. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. Neuroimage 50, 883-892.
Freedman, D., Deicken, R., Kegeles, L.S., Vinogradov, S., Bao, Y., Brown, A.S., 2011. Maternal-fetal blood incompatibility and neuromorphologic anomalies in schizophrenia: Preliminary findings. Progress in Neuro-Psychopharmacology & Biological Psychiatry 35, 1525-1529.
Frisoni, G.B., Fox, N.C., Jack, C.R., Jr., Scheltens, P., Thompson, P.M., 2010. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 6, 67-77.
Fryer, S.L., Mattson, S.N., Jernigan, T.L., Archibald, S.L., Jones, K.L., Riley, E.P., 2012. Caudate volume predicts neurocognitive performance in youth with heavy prenatal alcohol exposure. Alcoholism: Clinical & Experimental Research 36, 1932-1941.
Gautam, P., Lebel, C., Narr, K.L., Mattson, S.N., May, P.A., Adnams, C.M., Riley, E.P., Jones, K.L., Kan, E.C., Sowell, E.R., 2015. Volume changes and brain-behavior relationships in white matter and subcortical gray matter in children with prenatal alcohol exposure. Human Brain Mapping 36, 2318-2329.
Ghassabian, A., El Marroun, H., Peeters, R.P., Jaddoe, V.W., Hofman, A., Verhulst, F.C., Tiemeier, H., White, T., 2014. Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. Journal of Clinical Endocrinology & Metabolism 99, 2383-2390.
Grant, K.S., Petroff, R., Isoherranen, N., Stella, N., Burbacher, T.M., 2018. Cannabis use during pregnancy: Pharmacokinetics and effects on child development. Pharmacol Ther 182, 133-151.
Gross, L.A., Moore, E.M., Wozniak, J.R., Coles, C.D., Kable, J.A., Sowell, E.R., Jones, K.L., Riley, E.P., Mattson, S.N., Cifasd, 2018. Neural correlates of verbal memory in youth with heavy prenatal alcohol exposure. Brain Imaging & Behavior 12, 806-822.
Guxens, M., Lubczynska, M.J., Muetzel, R.L., Dalmau-Bueno, A., Jaddoe, V.W.V., Hoek, G., van der Lugt, A., Verhulst, F.C., White, T., Brunekreef, B., Tiemeier, H., El Marroun, H., 2018. Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children. Biological Psychiatry 84, 295-303.
Hane, F.T., Lee, B.Y., Leonenko, Z., 2017. Recent Progress in Alzheimer's Disease Research, Part 1: Pathology. J Alzheimers Dis 57, 1-28.
Hoffmann, C., Grossman, R., Bokov, I., Lipitz, S., Biegon, A., 2010. Effect of cytomegalovirus infection on temporal lobe development in utero: quantitative MRI studies. European Neuropsychopharmacology 20, 848-854.
Hulshoff Pol, H.E., Hoek, H.W., Susser, E., Brown, A.S., Dingemans, A., Schnack, H.G., van Haren, N.E., Pereira Ramos, L.M., Gispen-de Wied, C.C., Kahn, R.S., 2000. Prenatal exposure to famine and brain morphology in schizophrenia. American Journal of Psychiatry 157, 1170-1172.
Jabes, A., Thomas, K.M., Langworthy, S., Georgieff, M.K., Nelson, C.A., 2015. Functional and Anatomic Consequences of Diabetic Pregnancy on Memory in Ten-Year-Old Children. Journal of Developmental & Behavioral Pediatrics 36, 529-535.
Janulewicz, P.A., Killiany, R.J., White, R.F., Martin, B.M., Winter, M.R., Weinberg, J.M., Aschengrau, A., 2013. Structural Magnetic Resonance Imaging in an adult cohort following prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water. Neurotoxicology & Teratology 38, 13-20.
Joseph, J., Warton, C., Jacobson, S.W., Jacobson, J.L., Molteno, C.D., Eicher, A., Marais, P., Phillips, O.R., Narr, K.L., Meintjes, E.M., 2014. Three-dimensional surface

deformation-based shape analysis of hippocampus and caudate nucleus in children with fetal alcohol spectrum disorders. Human Brain Mapping 35, 659-672.
Korevaar, T.I.M., Muetzel, R., Medici, M., Chaker, L., Jaddoe, V.W.V., de Rijke, Y.B., Steegers, E.A.P., Visser, T.J., White, T., Tiemeier, H., Peeters, R.P., 2016. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: A population-based prospective cohort study. The Lancet Diabetes and Endocrinology 4, 35-43.
Krueger, A.M., Roediger, D.J., Mueller, B.A., Boys, C.A., Hendrickson, T.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Riley, E.P., Lim, K.O., Wozniak, J.R., 2020. Para-limbic Structural Abnormalities Are Associated With Internalizing Symptoms in Children With Prenatal Alcohol Exposure. Alcoholism: Clinical & Experimental Research 44, 1598-1608.
Lebel, C., Mattson, S.N., Riley, E.P., Jones, K.L., Adnams, C.M., May, P.A., Bookheimer, S.Y., O'Connor, M.J., Narr, K.L., Kan, E., Abaryan, Z., Sowell, E.R., 2012. A longitudinal study of the long-term consequences of drinking during pregnancy: heavy in utero alcohol exposure disrupts the normal processes of brain development. Journal of Neuroscience 32, 15243-15251.
Lebel, C., Rasmussen, C., Wyper, K., Walker, L., Andrew, G., Yager, J., Beaulieu, C., 2008. Brain diffusion abnormalities in children with fetal alcohol spectrum disorder. Alcoholism: Clinical & Experimental Research 32, 1732-1740.
Lebel, C., Roussotte, F., Sowell, E.R., 2011. Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain. Neuropsychol Rev 21, 102-118.
Lehtola, S.J., Tuulari, J.J., Scheinin, N.M., Karlsson, L., Parkkola, R., Merisaari, H., Lewis, J.D., Fonov, V.S., Louis Collins, D., Evans, A., Saunavaara, J., Hashempour, N., Lahdesmaki, T., Acosta, H., Karlsson, H., 2020. Newborn amygdalar volumes are associated with maternal prenatal psychological distress in a sex-dependent way. NeuroImage Clinical 28, 102380.
Lesuis, S.L., Hoeijmakers, L., Korosi, A., de Rooij, S.R., Swaab, D.F., Kessels, H.W., Lucassen, P.J., Krugers, H.J., 2018. Vulnerability and resilience to Alzheimer's disease: early life conditions modulate neuropathology and determine cognitive reserve. Alzheimers Res Ther 10, 95.
Liu, J., Lester, B.M., Neyzi, N., Sheinkopf, S.J., Gracia, L., Kekatpure, M., Kosofsky, B.E., 2013. Regional brain morphometry and impulsivity in adolescents following prenatal exposure to cocaine and tobacco. JAMA Pediatrics 167, 348-354.
Luo, J., Abaci Turk, E., Bibbo, C., Gagoski, B., Roberts, D.J., Vangel, M., Tempany-Afdhal, C.M., Barnewolt, C., Estroff, J., Palanisamy, A., Barth, W.H., Zera, C., Malpica, N., Golland, P., Adalsteinsson, E., Robinson, J.N., Grant, P.E., 2017. In Vivo Quantification of Placental Insufficiency by BOLD MRI: A Human Study. Scientific Reports 7, 3713.
Mareckova, K., Marecek, R., Bencurova, P., Klanova, J., Dusek, L., Brazdil, M., 2018. Perinatal stress and human hippocampal volume: Findings from typically developing young adults. Scientific Reports 8, 4696.
Martin-Gronert, M.S., Ozanne, S.E., 2012. Mechanisms underlying the developmental origins of disease. Rev Endocr Metab Disord 13, 85-92.
McLachlan, K., Zhou, D., Little, G., Rasmussen, C., Pei, J., Andrew, G., Reynolds, J.N., Beaulieu, C., 2020. Current Socioeconomic Status Correlates With Brain Volumes in Healthy Children and Adolescents but Not in Children With Prenatal Alcohol Exposure. Frontiers in Human Neuroscience 14, 223.
Meintjes, E.M., Narr, K.L., van der Kouwe, A.J., Molteno, C.D., Pirnia, T., Gutman, B., Woods, R.P., Thompson, P.M., Jacobson, J.L., Jacobson, S.W., 2014. A tensor-based

morphometry analysis of regional differences in brain volume in relation to prenatal alcohol exposure. NeuroImage Clinical 5, 152-160.
Morgane, P.J., Austin-LaFrance, R., Bronzino, J., Tonkiss, J., Díaz-Cintra, S., Cintra, L., Kemper, T., Galler, J.R., 1993. Prenatal malnutrition and development of the brain. Neurosci Biobehav Rev 17, 91-128.
Morton, S.U., Vyas, R., Gagoski, B., Vu, C., Litt, J., Larsen, R.J., Kuchan, M.J., Lasekan, J.B., Sutton, B.P., Grant, P.E., Ou, Y., 2020. Maternal Dietary Intake of Omega-3 Fatty Acids Correlates Positively with Regional Brain Volumes in 1-Month-Old Term Infants. Cerebral Cortex 30, 2057-2069.
Nardelli, A., Lebel, C., Rasmussen, C., Andrew, G., Beaulieu, C., 2011. Extensive deep gray matter volume reductions in children and adolescents with fetal alcohol spectrum disorders. Alcoholism: Clinical & Experimental Research 35, 1404-1417.
Nwosu, E.C., Robertson, F.C., Holmes, M.J., Cotton, M.F., Dobbels, E., Little, F., Laughton, B., van der Kouwe, A., Meintjes, E.M., 2018. Altered brain morphometry in 7-year old HIV-infected children on early ART. Metab Brain Dis 33, 523-535.
Nygaard, E., Slinning, K., Moe, V., Due-Tonnessen, P., Fjell, A., Walhovd, K.B., 2018. Neuroanatomical characteristics of youths with prenatal opioid and poly-drug exposure. Neurotoxicology & Teratology 68, 13-26.
Ogundipe, E., Tusor, N., Wang, Y., Johnson, M.R., Edwards, A.D., Crawford, M.A., 2018. Randomized controlled trial of brain specific fatty acid supplementation in pregnant women increases brain volumes on MRI scans of their newborn infants. Prostaglandins Leukotrienes & Essential Fatty Acids 138, 6-13.
Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst Rev 5, 210.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 372, n71.
Passera, S., Contarino, V., Scarfone, G., Scola, E., Fontana, C., Peccatori, F., Cinnante, C., Counsell, S., Ossola, M., Pisoni, S., Pesenti, N., Grossi, E., Amant, F., Mosca, F., Triulzi, F., Fumagalli, M., 2019. Effects of in-utero exposure to chemotherapy on fetal brain growth. International Journal of Gynecological Cancer 29, 1195-1202.
Paul, R., Prasitsuebsai, W., Jahanshad, N., Puthanakit, T., Thompson, P., Aurpibul, L., Hansudewechakul, R., Kosalaraksa, P., Kanjanavanit, S., Ngampiyaskul, C., Luesomboon, W., Lerdlum, S., Pothisri, M., Visrutaratna, P., Valcour, V., Nir, T.M., Saremi, A., Kerr, S., Ananworanich, J., 2018. Structural Neuroimaging and Neuropsychologic Signatures in Children With Vertically Acquired HIV. Pediatr Infect Dis J 37, 662-668.
Paul, S.E., Hatoum, A.S., Fine, J.D., Johnson, E.C., Hansen, I., Karcher, N.R., Moreau, A.L., Bondy, E., Qu, Y., Carter, E.B., Rogers, C.E., Agrawal, A., Barch, D.M., Bogdan, R., 2021. Associations Between Prenatal Cannabis Exposure and Childhood Outcomes: Results From the ABCD Study. JAMA Psychiatry 78, 64-76.
Pernet, C., Garrido, M.I., Gramfort, A., Maurits, N., Michel, C.M., Pang, E., Salmelin, R., Schoffelen, J.M., Valdes-Sosa, P.A., Puce, A., 2020. Issues and recommendations from the OHBM COBIDAS MEEG committee for reproducible EEG and MEG research. Nat Neurosci 23, 1473-1483.
Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., Galluzzi, S., Marizzoni, M., Frisoni, G.B., 2016. Brain atrophy in Alzheimer's Disease and aging. Ageing Res Rev 30, 25-48.

Popova, S., Dozet, D., Shield, K., Rehm, J., Burd, L., 2021. Alcohol's Impact on the Fetus. Nutrients 13.
Prayer, D., Kasprian, G., Krampl, E., Ulm, B., Witzani, L., Prayer, L., Brugger, P.C., 2006. MRI of normal fetal brain development. Eur J Radiol 57, 199-216.
Qiu, A., Rifkin-Graboi, A., Chen, H., Chong, Y.S., Kwek, K., Gluckman, P.D., Fortier, M.V., Meaney, M.J., 2013. Maternal anxiety and infants' hippocampal development: timing matters. Transl Psychiatry Psychiatry 3, e306.
Rajaprakash, M., Chakravarty, M.M., Lerch, J.P., Rovet, J., 2014. Cortical morphology in children with alcohol-related neurodevelopmental disorder. Brain and Behavior 4, 41-50.
Ratsep, M.T., Paolozza, A., Hickman, A.F., Maser, B., Kay, V.R., Mohammad, S., Pudwell, J., Smith, G.N., Brien, D., Stroman, P.W., Adams, M.A., Reynolds, J.N., Croy, B.A., Forkert, N.D., 2016. Brain Structural and Vascular Anatomy Is Altered in Offspring of Pre-Eclamptic Pregnancies: A Pilot Study. Ajnr: American Journal of Neuroradiology 37, 939-945.
Riggins, T., Cacic, K., Buckingham-Howes, S., Scaletti, L.A., Salmeron, B.J., Black, M.M., 2012. Memory ability and hippocampal volume in adolescents with prenatal drug exposure. Neurotoxicology & Teratology 34, 434-441.
Riikonen, R.S., Nokelainen, P., Valkonen, K., Kolehmainen, A.I., Kumpulainen, K.I., Kononen, M., Vanninen, R.L., Kuikka, J.T., 2005. Deep serotonergic and dopaminergic structures in fetal alcoholic syndrome: a study with nor-beta-CIT-single-photon emission computed tomography and magnetic resonance imaging volumetry. Biological Psychiatry 57, 1565-1572.
Rivkin, M.J., Davis, P.E., Lemaster, J.L., Cabral, H.J., Warfield, S.K., Mulkern, R.V., Robson, C.D., Rose-Jacobs, R., Frank, D.A., 2008. Volumetric MRI study of brain in children with intrauterine exposure to cocaine, alcohol, tobacco, and marijuana. Pediatrics 121, 741-750.
Robey, A., Buckingham-Howes, S., Salmeron, B.J., Black, M.M., Riggins, T., 2014. Relations among prospective memory, cognitive abilities, and brain structure in adolescents who vary in prenatal drug exposure. Journal of Experimental Child Psychology 127, 144-162.
Roussotte, F., Soderberg, L., Warner, T., Narr, K., Lebel, C., Behnke, M., Davis-Eyler, F., Sowell, E., 2012a. Adolescents with prenatal cocaine exposure show subtle alterations in striatal surface morphology and frontal cortical volumes. Journal of Neurodevelopmental Disorders 4, 22.
Roussotte, F.F., Sulik, K.K., Mattson, S.N., Riley, E.P., Jones, K.L., Adnams, C.M., May, P.A., O'Connor, M.J., Narr, K.L., Sowell, E.R., 2012b. Regional brain volume reductions relate to facial dysmorphology and neurocognitive function in fetal alcohol spectrum disorders. Human Brain Mapping 33, 920-937.
Salminen, L.E., Wilcox, R.R., Zhu, A.H., Riedel, B.C., Ching, C.R.K., Rashid, F., Thomopoulos, S.I., Saremi, A., Harrison, M.B., Ragothaman, A., Knight, V., Boyle, C.P., Medland, S.E., Thompson, P.M., Jahanshad, N., 2019. Altered Cortical Brain Structure and Increased Risk for Disease Seen Decades After Perinatal Exposure to Maternal Smoking: A Study of 9000 Adults in the UK Biobank. Cerebral Cortex 29, 5217-5233.
Sammallahti, S., Tiemeier, H., Louwen, S., Steegers, E., Hillegers, M., Jaddoe, V.W.V., White, T., 2020. Fetal-placental blood flow and neurodevelopment in childhood: a population-based neuroimaging study. Ultrasound in Obstetrics & Gynecology 27, 27.
Scott-Goodwin, A.C., Puerto, M., Moreno, I., 2016. Toxic effects of prenatal exposure to alcohol, tobacco and other drugs. Reprod Toxicol 61, 120-130.

Seifan, A., Schelke, M., Obeng-Aduasare, Y., Isaacson, R., 2015. Early Life Epidemiology of Alzheimer's Disease--A Critical Review. Neuroepidemiology 45, 237-254.
Singer, L.T., Min, M.O., Minnes, S., Short, E., Lewis, B., Lang, A., Wu, M., 2018. Prenatal and concurrent cocaine, alcohol, marijuana, and tobacco effects on adolescent cognition and attention. Drug Alcohol Depend 191, 37-44.
Sirnes, E., Oltedal, L., Bartsch, H., Eide, G.E., Elgen, I.B., Aukland, S.M., 2017. Brain morphology in school-aged children with prenatal opioid exposure: A structural MRI study. Early Human Development 106, 33-39.
Sowell, E.R., Thompson, P.M., Mattson, S.N., Tessner, K.D., Jernigan, T.L., Riley, E.P., Toga, A.W., 2002. Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. Cerebral Cortex 12, 856-865.
Spottiswoode, B.S., Meintjes, E.M., Anderson, A.W., Molteno, C.D., Stanton, M.E., Dodge, N.C., Gore, J.C., Peterson, B.S., Jacobson, J.L., Jacobson, S.W., 2011. Diffusion tensor imaging of the cerebellum and eyeblink conditioning in fetal alcohol spectrum disorder. Alcoholism: Clinical & Experimental Research 35, 2174-2183.
Stern, Y., 2012. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 11, 1006-1012.
Thomas, J., Graziosi, S., Brunton, J., Ghouze, Z., O'Driscoll, P., Bond, M., 2020. EPPI-Reviewer: advanced software for systematic reviews, maps and evidence synthesis. EPPI-Centre Software. London: UCL Social Research Institute.
Tobi, E.W., Goeman, J.J., Monajemi, R., Gu, H., Putter, H., Zhang, Y., Slieker, R.C., Stok, A.P., Thijssen, P.E., Müller, F., van Zwet, E.W., Bock, C., Meissner, A., Lumey, L.H., Eline Slagboom, P., Heijmans, B.T., 2014. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun 5, 5592.
Treit, S., Chen, Z., Zhou, D., Baugh, L., Rasmussen, C., Andrew, G., Pei, J., Beaulieu, C., 2017. Sexual dimorphism of volume reduction but not cognitive deficit in fetal alcohol spectrum disorders: A combined diffusion tensor imaging, cortical thickness and brain volume study. NeuroImage Clinical 15, 284-297.
Treit, S., Lebel, C., Baugh, L., Rasmussen, C., Andrew, G., Beaulieu, C., 2013. Longitudinal MRI reveals altered trajectory of brain development during childhood and adolescence in fetal alcohol spectrum disorders. Journal of Neuroscience 33, 10098-10109.
Treit, S., Zhou, D., Chudley, A.E., Andrew, G., Rasmussen, C., Nikkel, S.M., Samdup, D., Hanlon-Dearman, A., Loock, C., Beaulieu, C., 2016. Relationships between Head Circumference, Brain Volume and Cognition in Children with Prenatal Alcohol Exposure. PLoS ONE [Electronic Resource] 11, e0150370.
Uban, K.A., Kan, E., Wozniak, J.R., Mattson, S.N., Coles, C.D., Sowell, E.R., 2020. The Relationship Between Socioeconomic Status and Brain Volume in Children and Adolescents With Prenatal Alcohol Exposure. Frontiers in Human Neuroscience 14, 85.
van den Dries, M.A., Lamballais, S., El Marroun, H., Pronk, A., Spaan, S., Ferguson, K.K., Longnecker, M.P., Tiemeier, H., Guxens, M., 2020. Prenatal exposure to organophosphate pesticides and brain morphology and white matter microstructure in preadolescents. Environmental Research, 110047.
Wade, B.S.C., Valcour, V.G., Puthanakit, T., Saremi, A., Gutman, B.A., Nir, T.M., Watson, C., Aurpibul, L., Kosalaraksa, P., Ounchanum, P., Kerr, S., Dumrongpisutikul, N., Visrutaratna, P., Srinakarin, J., Pothisri, M., Narr, K.L., Thompson, P.M., Ananworanich, J., Paul, R.H., Jahanshad, N., Predict, Resilience Study, G., 2019. Mapping abnormal subcortical neurodevelopment in a cohort of Thai children with HIV. NeuroImage Clinical 23, 101810.

Walhovd, K.B., Moe, V., Slinning, K., Due-Tonnessen, P., Bjornerud, A., Dale, A.M., van der Kouwe, A., Quinn, B.T., Kosofsky, B., Greve, D., Fischl, B., 2007. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. Neuroimage 36, 1331-1344.

Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., Black, S.E., Brayne, C., Breteler, M., Chabriat, H., Decarli, C., de Leeuw, F.E., Doubal, F., Duering, M., Fox, N.C., Greenberg, S., Hachinski, V., Kilimann, I., Mok, V., Oostenbrugge, R., Pantoni, L., Speck, O., Stephan, B.C., Teipel, S., Viswanathan, A., Werring, D., Chen, C., Smith, C., van Buchem, M., Norrving, B., Gorelick, P.B., Dichgans, M., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12, 822-838.

Warton, F.L., Meintjes, E.M., Warton, C.M.R., Molteno, C.D., Lindinger, N.M., Carter, R.C., Zollei, L., Wintermark, P., Jacobson, J.L., van der Kouwe, A., Jacobson, S.W., 2018. Prenatal methamphetamine exposure is associated with reduced subcortical volumes in neonates. Neurotoxicology & Teratology 65, 51-59.

Wells, G., Shea, B., O'Connell, D., Peterson, j., Welch, V., Losos, M., Tugwell, P., 2000. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. .

Whalley, L.J., Dick, F.D., McNeill, G., 2006. A life-course approach to the aetiology of late-onset dementias. Lancet Neurol 5, 87-96.

Willford, J., Day, R., Aizenstein, H., Day, N., 2010. Caudate asymmetry: a neurobiological marker of moderate prenatal alcohol exposure in young adults. Neurotoxicology & Teratology 32, 589-594.

Willoughby, K.A., McAndrews, M.P., Rovet, J.F., 2014. Effects of maternal hypothyroidism on offspring hippocampus and memory. Thyroid 24, 576-584.

Willoughby, K.A., Sheard, E.D., Nash, K., Rovet, J., 2008. Effects of prenatal alcohol exposure on hippocampal volume, verbal learning, and verbal and spatial recall in late childhood. Journal of the International Neuropsychological Society 14, 1022-1033.

Wu, Y., Kapse, K., Jacobs, M., Niforatos-Andescavage, N., Donofrio, M.T., Krishnan, A., Vezina, G., Wessel, D., du Plessis, A., Limperopoulos, C., 2020a. Association of Maternal Psychological Distress With In Utero Brain Development in Fetuses With Congenital Heart Disease. JAMA Pediatrics, e195316.

Wu, Y., Lu, Y.C., Jacobs, M., Pradhan, S., Kapse, K., Zhao, L., Niforatos-Andescavage, N., Vezina, G., du Plessis, A.J., Limperopoulos, C., 2020b. Association of Prenatal Maternal Psychological Distress With Fetal Brain Growth, Metabolism, and Cortical Maturation. JAMA Network Open 3, e1919940.

Yadav, S.K., Gupta, R.K., Garg, R.K., Venkatesh, V., Gupta, P.K., Singh, A.K., Hashem, S., Al-Sulaiti, A., Kaura, D., Wang, E., Marincola, F.M., Haris, M., 2017. Altered structural brain changes and neurocognitive performance in pediatric HIV. NeuroImage Clinical 14, 316-322.

Yuan, Q., Rubic, M., Seah, J., Rae, C., Wright, I.M., Kaltenbach, K., Feller, J.M., Abdel-Latif, M.E., Chu, C., Oei, J.L., group, B.O.B.C., 2014. Do maternal opioids reduce neonatal regional brain volumes? A pilot study. Journal of Perinatology 34, 909-913.

Zhou, D., Rasmussen, C., Pei, J., Andrew, G., Reynolds, J.N., Beaulieu, C., 2018. Preserved cortical asymmetry despite thinner cortex in children and adolescents with prenatal alcohol exposure and associated conditions. Human Brain Mapping 39, 72-88.

Zou, R., El Marroun, H., McGrath, J.J., Muetzel, R.L., Hillegers, M., White, T., Tiemeier, H., 2020. A prospective population-based study of gestational vitamin D status and brain morphology in preadolescents. Neuroimage 209, 116514.
Zou, R., Tiemeier, H., Van Der Ende, J., Verhulst, F.C., Muetzel, R.L., White, T., Hillegers, M., El Marroun, H., 2019. Exposure to maternal depressive symptoms in fetal life or childhood and offspring brain development: A population-based imaging study. American Journal of Psychiatry 176, 702-710.

Figure Captions

Figure 1. PRISMA 2020 flow diagram of study selection.

Figure 2. Newcastle Ottawa Scale risk of bias assessment score per exposure category and study design. Orange indicates no points (-), light blue indicates 1 point (*) and dark blue indicates 2 points (**), only applicable for the comparability category) on the NOS.

Supplementary Figure 1. Interactive bubble map of the evidence according to exposure category, outcome and direction of effect.

Tables

Tables and Supplementary Tables were uploaded as separate files.

Supplement

Supplement A. Prisma 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page (1)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6,7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6, supplement
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7,8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7,8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7,8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8,9,30
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8,30
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9,10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8,9

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10,12
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10
Study characteristics	17	Cite each included study and present its characteristics.	Table 1-3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10-24
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	32-34
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	25-29
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	29-31
	23b	Discuss any limitations of the evidence included in the review.	32-34
	23c	Discuss any limitations of the review processes used.	34,35
	23d	Discuss implications of the results for practice, policy, and future research.	36,37
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	38
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	8

Supplement B. Search strategy.

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to August 28, 2020

Search Strategy: **2020-08-30**

#	Searches	Results
1	prenatal exposure delayed effects/ or prenatal injuries/ or maternal exposure/ or paternal exposure/	36757
2	gestational weight gain/ or maternal age/ or parity/ or paternal age/ or maternal-fetal exchange/ or maternal-fetal relations/ or fetal distress/ or exp pregnancy, multiple/ or exp maternal nutritional physiological phenomena/ or obesity, maternal/ or "disorders of sex development"/ or apgar score/	106242
3	fetal diseases/ or exp fetal membranes, premature rupture/ or fetal alcohol spectrum disorders/ or fetal growth retardation/ or fetal hypoxia/ or asphyxia neonatorum/ or fetal macrosomia/ or fetal nutrition disorders/ or placental insufficiency/ or congenital hypothyroidism/	73652
4	(pregnancy complications/ or diabetes, gestational/ or exp hypertension, pregnancy-induced/ or hyperemesis gravidarum/ or placenta diseases/ or pregnancy complications, cardiovascular/ or pregnancy complications, hematologic/ or pregnancy complications, infectious/ or pregnancy complications, parasitic/ or exp pregnancy complications, neoplastic/ or pregnancy in diabetics/ or pregnant women/px or (HELPP or preeclam* or eclamp* or GDM or ((pregnan* or gestation* or gravid* or maternal) adj6 (hyperten* or blood pressur* or an?emi* or diabet* or obes* or weight gain))).tw,kf.) and (offspring* or progeny or born or neonat* or neo-nat* or new*born* or new-born* or postnat* or post-nat* or perinat* or peri-nat* or infant* or child or children).mp.	102316
5	(seasons/ or residence characteristics/ or geography/ or rural population/ or suburban population/ or urban population/ or rural health/ or suburban health/ or urban health/ or urbanization/ or *"emigrants and immigrants"/ or life change events/ or socioeconomic factors/ or economic status/ or exp educational status/ or exp parents/ed or employment/ or unemployment/ or income/ or occupations/ or exp poverty/ or social class/ or education/ or exp educational measurement/ or sex characteristics/ or sexual development/ or sex determination processes/ or sex differentiation/ or exp mining/ or exp occupational diseases/ or exp environmental pollution/ or environmental health/ or exp toxic actions/ or exp metals, heavy/ or exp particulate matter/ or occupational health/ or mental disorders/ or exp anxiety disorders/ or exp "bipolar and related disorders"/ or mood disorders/ or depressive disorder/ or maternal behavior/ or anxiety/ or psychological distress/ or fear/ or behavioral symptoms/ or affective symptoms/ or depression/ or paranoid behavior/ or exp stress, psychological/ or exp substance-related disorders/ or drug-seeking behavior/ or drinking behavior/ or alcohol drinking/ or binge drinking/ or exp "marijuana use"/ or exp smoking/ or exp "tobacco use"/ or exp narcotics/ or exp illicit drugs/ or alcohols/ or ethanol/ or exp alcoholic beverages/ or tobacco/ or exp serotonin uptake inhibitors/ or exp tranquilizing agents/ or exp glucocorticoids/ or exp adrenal cortex hormones/bl, an, ae, me, df or exp testosterone congeners/bl, an, ae, me, df or exp thyroid hormones/bl, an, ae, me, df or *hormones/ or hypothyroidism/ or exp disease outbreaks/ or infectious disease transmission, vertical/ or "influenza a virus"/ or influenza, human/ or cytomegalovirus infections/ or cytomegalovirus/ or exp flavivirus infections/ or exp flavivirus/ or inflammation/ or interleukins/ or interleukin-6/ or interleukin-8/ or exp nutrition disorders/ or famine/ or hunger/) and	134649

	(parturition/ or birth rate/ or live birth/ or uterus/ or fetus/ or ((midtrimest* or midpregnan* or midgestat* or pregnanc* or pregnant or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat*) and (offspring* or progeny or born or neonat* or neo-nat* or new*born* or new-born* or postnat* or post-nat* or infant* or child or children)).mp.)	
6	fingers/ah, pa	3372
7	((cephalometry/ or head/ah) and infant, newborn/) not (syndrom* or crani*synost* or synosto* or vault distract* or macrocran* or myelomeningoc* or mutat*).ti.	2129
8	birth weight/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/	66863
9	birth certificates/ or birth intervals/ or birth order/ or exp birth setting/	9819
10	(f?etal or f?etus* or f?etopath* or intra-uterin* or intrauterin* or in-utero or antenat* or ante-nat* or prenat* or pre-nat* or perinat* or peri-nat* or pre-birth* or prebirth* or before-birth or ((pre or peri) adj2 (postnat* or post-nat*))).tw,kf.	503984
11	(FASD or ARND or (PAE and alcohol*)).tw,kf.	1656
12	((pregnan* or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat*) adj6 expos*).tw,kf.	19724
13	(DOHAD* or FOAD* or early origin*).tw,kf. or (development* adj3 origin* adj4 (health* or diseas* or adult or dement* or alzheimer*)).tw,kf,jw.	2766
14	(((early-life or pregnan* or gestation* or developmental or neurodevelop* or nutrit*) adj15 (programming or malprogramming)) or (feto* adj6 (priming or epigenet*)) or (early adj3 (programming or malprogramming or priming or epigenet*))).tw,kf.	5167
15	((early life or obstetric*) adj3 (factor* or variabl* or parameter* or circumstanc* or condition*)).tw,kf.	5278
16	(chorioamn* or amnio* or intraamnio* or funisit*).tw,kf.	48185
17	(IUGR* or FGR* or SFGR* or SIUGR* or (placent* adj3 (insufficien* or d*sfunct* or inflammat*))).tw,kf.	11425
18	((PROM and ruptur* and membran*) or PPROM* or EPPROM*1 or ((prematur* or pre-matur* or i?matur* or preterm* or pre-term* or pre-labo?r or prelabo?r) adj6 ruptur* adj4 membran*) or (((ruptur* adj2 membran*) or ROM) and (pregnan* or gestat* or gravidit*))).tw,kf.	8616
19	((small adj2 gestat* adj2 (age or ages)) or (SGA adj3 (infant* or neonat* or newborn* or neo-nat* or new*-born* or pregnan* or gestat* or birth* or weight*))).tw,kf.	11074
20	(((gestat* or age) adj2 ("at birth" or "at deliver*")) or birth age or birth gestation* age).tw,kf.	8878
21	(((birth or births) adj1 (underweight* or weight or weights or overweight* or size)) or birthweight* or LBW* or VLBW* or ELBW*).tw,kf.	77642
22	(((head adj2 circumfere*) or cephalometr*) adj6 (birth or births or childbirth* or baby or babies or neonat* or neo-nat* or new*born* or new*-born* or postnat* or post-nat*)).tw,kf.	2168
23	(interpregnan* or inter-pregnan* or ((pregnan* or gestat* or gravidit* or birth) adj interval*) or ((interval* or period*) adj between adj3 (pregnan* or gestat* or gravidit* or births or (subsequent adj (children or infants))))).tw,kf.	2890
24	((neonat* or neo-nat* or new*born* or new*-born* or babies or baby or birth or term) adj6 asphyx*).tw,kf.	6914
25	((maternal or mother* or pregnant women or (during adj (pregnan* or gestat* or gravidit*))) adj4 (expos* or addict* or substance abus* or substance-us* or smoking or tobacco or cigarett* or nicotin* or drinking or alcohol* or ethanol or Etoh or caffein*	93914

	or drug* or psychotrop* or narcotic* or mari*uana or hash* or cocain* or amphetamin* or amfetamin* or metamphetamin* or metamfetamin* or MDMA or opium or opiat* or opioid* or heroin* or GHB or ketamin* or LSD or antidepres* or anti-depres* or SSRI* or SNRI* or (serotonin* adj3 reuptake inhibitor*) or cipramil or lexapro or prozac or fevarin* or seroxat or zoloft or cymbalta or efexor or effexor or pristiq or fetzima or ixel or savella or milnacipran or monoamine oxidase inhibitor* or MAOIs or MAO-inhibitor* or analgesic* or painkiller* or anti-inflammator* or aspirin* or ((cox* or cyclooxygenase or cyclo-oxygenas*) adj3 (inhibitor* or block* or antagon*)) or coxib* or celecoxib or diclofenac or ibuprofen or indomethicin* or naproxen or acetaminophen* or acetylsalicylic or aspirin* or antidiabetic* or metformin* or chemo* or cytostatic* or anthracyclin* or cyclophosphamid* or epirubicin* or radiat* or irradiat* or radiotherap* or radio-therap* or hormon* or testosteron* or androgen* or estrogen* or oestrogen* or free-T4 or fT4 or f-T4 or free-T3 or fT3 or f-T3 or thyr* or triiodothyronin* or TSH or corticosteroid* or cortisol or hydrocort* or steroid* or gl#costeroid* or gl#cocortico* or dexameth* or prednis* or betameth* or hypothyr* or autoantibod* or auto-antib* or TPO or thyroperoxidase or autoimmun* or auto-immun* or (immune adj2 (repons* or attack* or system* or hypothes*)) or immunit* or inflammat* or IL-6 or IL6 or IL-8 or IL8 or IL-1 or IL1 or interleukin* or cytokin* or infect* or toxoplasm* or influenz* or virus* or viral or CMV or cytomegalovir* or toxin* or heavy-metal* or lead or Pb or mercury or Hg or arsen* or cadmium or chromium or Nickel or pollut* or chemic* or endocrine disrupt* or BPA or BPAs or bisphenol* or PFOA or PFOAS or PFTE or teflon or perfluoro* or per-fluoro* or polychlor* or PCB or PCBs or tetrachlor* or PCE or biphenyl* or phalat* or perchlorat* or plastic or plastics or pesticid* or asbest* or solvent* or Rhesus or Rh or ABO or (blood adj2 incompatib*) or hyperoxygenat* or hyper-oxygenat* or hypo-oxygenat* or hypox* or nutrit* or (nutrient* adj2 (transfer or restrict*)) or undernutrit* or malnutrit* or malnourish* or nourish* or famine or hunger or food or supplement* or vitamin* or multivitam* or vit-D or vit-B12 or vit-B6 or vit-C or vit-A or vit-E or retinol or ascorbic* or ascorbat* or tocopherol* or alphatocopherol* or tocotrienol* or cobalamin* or pyridoxin* or folic acid or folate or methylhydrofolat* or methyltetrahydrofolat* or hydrofolat* or iron or calcium or polyunsaturat* or poly-unsaturat* or monounsaturat* or mono-unsaturat* or MUFA or MUFAs or PUFA or PUFAs or LCPUFA* or LCP or LCPs or docosahex?eno* or DHA or eicosapent?en* or icosapent?en* or EPA or omega-3* or omega-6* or omega3* or omega6* or n3 or n6 or n-3 or n-6 or linolenic or linolenate* or alphalinolen* or gammalinolen* or GLA or DGLA or arachidon* or ARA or diet or diets or dietary or behavio?r or stress* or distress* or anxiet* or depression or depressive or GPRSMDD or mental or mood or schizophren* or psychosis or psychiat*)).tw,kf. and (parturition/ or uterus/ or (pregnanc* or pregnant or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat* or prepart* or pre-part* or peripart* or peri-part*).mp.)	
26	((birth or births) adj2 (record* or chart* or certificat* or index)).tw,kf.	5676
27	(((maternal or paternal) adj2 (age or ages)) or ((maternal or paternal or parent* or mother* or father*) adj2 mean adj2 (age or ages)) or ((maternal or paternal or parental or mother* or father*) adj2 (age or ages) adj2 birth)).tw,kf.	22889
28	((born or birth or child* or infant*) adj3 (older or old or young*) adj2 (mother* or father* or parent*)).tw,kf.	3994
29	((maternal or mother*) adj6 (parity or multipar* or nullipar* or primipar*)).tw,kf.	7291
30	(((maternal or paternal or parent* or mother* or father*) adj3 (educat* or school* or academic*)) or ((famil* or maternal or paternal or parental or parents or mother* or father*) adj4 (social status or socioeconom* or econom* or SEP or cSEP or SES or cSES	59329

	or income*1 or poverty or occupat* or employ* or unemploy* or mining or miners or coal or industr*)) or ((condition* or characteristic* or circumstanc* or origin* or expos* or etiol* or aetiol* or factor* or environment* or social status or socioeconom* or econom* or SEP or cSEP or SES or cSES) adj6 (born or birth or births or childbirth*)) or ((condition* or characteristic* or circumstanc* or origin* or expos* or etiol* or aetiol* or caus* or social-status or socioeconom* or econom* or SEP or SES or cSES or program* or hunger or famine or nutritional deficien* or program* or event*) adj3 early-life) or (early life adj1 (factor* or variable* or environment* or precursor* or stress or residence)) or early life risk factor* or early exposur* or early life expos* or early famine or ((Chinese or China or Dutch* or war or wars or worldwar* or warfar* or outbreak* or pandemic* or endemic* or epidemiol* or (early adj2 expos*)) adj5 (famin* or starvat* or hunger or undernutr* or malnutrit* or malnourish* or influenz*))).tw,kf. and (parents/ or fathers/ or mothers/ or uterus/ or parturition/ or birth rate/ or live birth/ or (birth or births or childbirth* or born or pregnanc* or pregnant or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat*).mp.)	
31	(((season* or winter* or summer* or autumn* or spring or springtime or quarter*) adj8 (birth or births or birthrate* or childbirth* or born)) or birth-month*).tw,kf.	4270
32	birth year.tw,kf.	1637
33	((order adj2 (birth or births or childbirth* or borns or born or sibling* or sibship*)) or ((first or 1st or second* or 2nd or third or 3rd or fourth or 4th) adj (born* or sibling*)) or ((sibship* or sibling*) adj (number or size)) or firstborn* or (each-additional adj2 (child or infant* or born))).tw,kf.	6775
34	(((state or states or country or countries or county or counties or place or residenc* or ((area or areas) not (surface adj3 area*)) or location* or overseas or foreign* or nativ* or rural or urban or cities or suburban or residential or industrial or mine or mines or coalmine*) adj3 (birth or births or childbirth* or born)) or birthplace*).tw,kf.	16401
35	(((second-to-fourth or index-to-ring) adj4 (finger* or digit*)) or ((digit or finger length*) adj3 (ratio* or 2d-4d or 2d?4d)) or ((2d-4d or 2d?4d or index finger* or ring finger*) adj4 (ratio or ratios or length* or male* or female* or gender))).tw,kf.	1184
36	or/1-35 [prenatal origin/exposure]	834597
37	((((brain or brains) not brain natriuretic peptid*) or brainag* or intracran* or intra-cran* or hippocamp* or parahippocamp* or subiculum or (ammon* adj3 horn*) or ((CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj3 (region* or sector* or area* or field*)) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or (corn* adj2 amon*) or ((temporal* or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit*) adj9 (lobe or lobes or pole or poles or subplate* or planum or cortex or cortical or cortices or region* or ROI or ROIs or sector* or area* or field* or horn* or sulc* or gyr* or opercul* or lateral* or BA-20)) or (planum adj2 polare*) or ((fusiform* or fusi-form* or dentat*) adj9 gyr*) or (fimbria* adj2 forni*) or ((lateral or third or 3rd or fourth or 4th) adj3 ventric*) or (cerebr* adj3 aqu#duct*) or ((white or gr#y) adj3 matter)) and (sMRI* or MRI* or MR-imag* or ((magnetic or neuro or brain*) adj2 (resonan* or imag*)) or neuroimag* or susceptibility weighted imaging or (weighted adj3 (T1 or T2 or T-1 or T-2)) or HT1 or HT2 or T1W* or T2W* or T1-W or T2-W or FLAIR or 3dFLAIR or Freesurfer or whole-brain or brain-volum* or ((intracran* or intra-cran* or subcortical or sub-cortical or subcortex or sub-cortex or hippocamp* or temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or horn* or sulc* or gyr* or fornix or fornices or (planum adj2 polare*)	296090

	or ((lateral or third or 3rd or fourth or 4th) adj3 ventric*)) adj6 volum*) or (visual adj2 (scor* or rating)))).mp. [BRAIN_MRI FILTER]	
38	**36 and 37 [prenatal origin/exposure + brain/MRI filter]**	**8394**
39	*brain/pa, ab and *aging/	1288
40	organ size/ and (*brain/ or *cerebral cortex/ or cerebral ventricles/ or cerebral aqueduct/ or fourth ventricle/ or lateral ventricles/ or third ventricle/ or exp hippocampus/ or temporal lobe/)	6826
41	atrophy/ and (*brain/ or cerebral ventricles/ or cerebral aqueduct/ or fourth ventricle/ or lateral ventricles/ or third ventricle/ or exp hippocampus/ or temporal lobe/)	6696
42	(exp hippocampus/ or temporal lobe/ or cerebral ventricles/ or cerebral aqueduct/ or fourth ventricle/ or lateral ventricles/ or third ventricle/) and (prenatal exposure delayed effects/ or maternal exposure/ or fetal alcohol spectrum disorders/ or exp maternal nutritional physiological phenomena/ or obesity, maternal/ or fetal nutrition disorders/)	1521
43	(brainag* or (brain adj (age or ages or ag?ing)) or ((prematur* or pre-matur* or early or gap or gaps) adj4 brain adj2 ag?ing)).tw,kf.	3071
44	(sMRI* or qMRI* or Freesurfer or ((structural or volumetr* or quantitativ* or (weighted adj3 (T1 or T2 or T-1 or T-2)) or T1W* or T2W* or T1-W or T2-W or FLAIR or 3dFLAIR or whole-brain or (brain adj1 morph*)) adj3 (MRI* or MR-imag* or ((magnetic or neuro or brain*) adj2 (resonan* or imag*)) or neuroimag*))).tw,kf.	36713
45	(((brain or brains or intracran* or intra-cran* or subcortic* or sub-cortic*) adj2 (size* or shape)) or (((brain adj1 (region* or ROI or ROIS or area* or deep or whole or total* or "all" or overall or complet* or entir* or absolute)) or hippocamp* or parahippocamp* or subiculum or ((ammon* or corn*) adj3 horn*) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or (fimbria* adj2 forni*) or ventric* or aqu#duct*) adj4 size*)).tw,kf.	11652
46	((brain or brains or intracran* or intra-cran* or subcort* or sub-cort*) adj3 (volume or volumes or volumetr*)).tw,kf.	14523
47	(((brain adj1 (region* or ROI or ROIs or area* or deep or whole or total* or "all" or overall or complet* or entir* or absolute or structures)) or hippocamp* or parahippocamp* or subiculum or ((ammon* or corn*) adj3 horn*) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or (temporal* adj6 (lobe or lobes or pole or poles or subplate* or planum or cortex or cortices or cortical or region* or ROI or ROIs or sector* or area* or field* or horn* or sulc* or gyr* or opercul* or lateral* or BA-20 or parietal or frontal or ((gr#y or white) adj3 matter))) or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or (fimbria* adj2 forni*) or ventric* or aqu#duct* or CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj30 volum*).tw,kf.	51440
48	((hippocamp* or parahippocamp* or subiculum or ((ammon* or corn*) adj3 horn*) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or (fimbria* adj2 forni*) or ((lateral or third or 3rd or fourth or 4th) adj2 ventric*) or aqu#duct* or CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj12 (atroph* or hypoplas*)).tw,kf.	7099
49	((brain or brains) adj2 (atroph* or hypoplas*)).tw,kf.	6039
50	((cortex or cortical or subcort* or sub-cort* or (gr#y adj3 matter) or GM) adj6 (volum* or thick* or thin* or small* or enlarg* or larger or dilat* or atroph* or hypoplas*)).tw,kf. and (hippocamp* or parahippocamp* or subiculum or (ammon*	9549

	adj3 horn*) or ((CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj3 (region* or sector* or area* or field*)) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or (corn* adj2 amon*) or ((temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit*) adj9 (lobe or lobes or pole or poles or cortex or cortical or region* or sector* or area* or field* or horn* or sulc* or gyr* or opercul* or lateral* or BA-20)) or (planum adj2 polare*) or ((fusiform* or fusi-form* or dentat*) adj9 gyr*) or (fimbria* adj2 forni*) or ((lateral or third or 3rd or fourth or 4th) adj3 ventric*) or (cerebr* adj3 aqu#duct*)).mp.	
51	cerebral small vessel diseases/ or stroke, lacunar/	1359
52	(infarction/ or exp stroke/ or hemorrhage/ or exp intracranial hemorrhages/ or cerebral veins/ or brain injury/ or hypoxia, brain/ or white matter/) and (exp asymptomatic diseases/ or undiagnosed diseases/)	454
53	hemosiderin/	1476
54	((((white adj2 matter) or WM) adj9 (hyperintens* or hyper-intens* or (signal adj1 (abnormal* or intens*)) or ((high or increas*) adj2 intens*) or HT2 or T2 or T-2 or T2WI* or FLAIR or 3dFLAIR or (visual adj2 (scor* or rating)))) or WMH or WMHs or DEHSI).tw,kf.	7391
55	(((white matter or WM) adj2 l?esion*) or WML or WMLs or PWML or PWMLs).tw,kf.	5895
56	((small adj2 (vessel* or arter* or capillar* or vein or venous) adj2 (diseas* or l?esion* or infarct* or stroke or strokes)) or ((cereb* or burden or score*) adj3 SVD*) or cSVD*).tw,kf.	5017
57	((lacun* adj9 (stroke or strokes or infarct* or (small adj (vessel* or arter* or capillar* or vein or venous)) or l?esion* or bleed* or h?emorrhag* or presenc*)) or SVLL or SVLLs).tw,kf.	4882
58	(((perivascul* or peri-vascul*) adj3 space*) or ((enlarg* or larg* or dilat* or wide* or prominent* or edem* or oedem*) adj3 PVS) or PVSs or EPVS* or (Virchow* adj3 Robin*) or (VRS and Virchow*) or VRSs).tw,kf.	2789
59	((((silent not silent verb) or unnotic*) adj15 infarct*) or ((silent not silent verb) adj3 (stroke or strokes)) or (SCI and infarct*) or SCIs or microinfarct* or micro-infarct*).tw,kf.	3881
60	((discrete or separate or distinct or punctat* or delineat* or focally or dispers* or isolated) adj6 infarct*).tw,kf.	2342
61	(microbleed* or microh?emorrhag* or ((micro or subtle or SWI) adj2 (h?emorrhag* or bleed*)) or susceptibilit*-weight* imaging).tw,kf.	4334
62	(h*sideros* or sideros* or h?emosiderin*).tw,kf.	7585
63	**or/39-62 [structural MRI brain biomarkers]**	**153175**
64	**38 and 63 [prenatal factors/exposures and structural MRI brain biomarkers]**	**2048**
65	(exp animals/ not humans/) or (animal* or veterinar*).jw. or exp veterinary medicine/ or exp animals, genetically modified/ or (transgenic* or ((primates or ape or apes or monkey* or baboon* or macaq* or pig or pigs or piglet* or porcine or goat or goats* or sheep or lamb or lambs or ovine or cattle or bovine or cow or cows or horse or horses or mare or calve or calves or dog or dogs or canine or bitch* or (cat not cat-scan) or cats or feline or rodent* or rabbit* or mice or mouse or murine* or C57BL* or Balb-c or Balbc or rat or rats or wistar or sprague or dawley or frog or frogs or zebra* or drosophil* or chick* or bee or bees or dam or dams or pups or pup or ewe or ewes or sow or sows) not human*)).ti,ot.	5216375
66	**64 not 65 [human studies on prenatal factors/exposures and structural MRI brain biomarkers]**	**1689**

67	(editorial or "systematic review").pt. or (editorial or reply or (case-report not case-report-survey) or two-cases).ti. or cochrane.jw. or ((review.pt. or case reports/ or (review or overview).ti. or (search* adj15 (literatur* or ((electronic* or medical or biomedical) adj3 database*) or medline or pubmed or embase or psyc?info or exhaustiv* or systematic*)).tw,kf,kw.) not (exp records/ or exp cohort studies/ or cross-sectional studies/ or case-control studies/ or (case-control* or cohort* or retrospectiv* or prospectiv* or crosssection* or cross-section* or population-based or ((chart* or record* or retrospectiv*) adj3 review*)).tw,kf,kw.)) [filter for original studies]	5257041
68	**66 not 67 [original human studies on prenatal factors/exposures and structural MRI brain biomarkers]**	**1313**
69	**remove duplicates from 68 [original human studies on prenatal factors/exposures and structural MRI brain biomarkers -deduplicated]**	**1307**

Database(s): **Embase Classic+Embase** 1947 to 2020 August 28

Search Strategy: **2020-08-30**

#	Searches	Results
1	maternal exposure/ or paternal exposure/ or perinatal drug exposure/ or prenatal drug exposure/ or prenatal exposure/	37844
2	exp parental age/ or parity/ or exp parental smoking/ or exp multiple pregnancy/ or gestational weight gain/ or maternal obesity/ or maternal nutrition/ or antenatal depression/ or perinatal depression/ or maternal stress/ or perinatal stress/	125470
3	prenatal disorder/ or fetus disease/ or exp chorioamnionitis/ or fetal alcohol syndrome/ or fetal malnutrition/ or fetotoxicity/ or fetus distress/ or fetus hypoxia/ or newborn hypoxia/ or intrauterine growth retardation/ or selective intrauterine growth restriction/ or macrosomia/ or premature fetus membrane rupture/ or placenta insufficiency/ or congenital hypothyroidism/	104847
4	(maternal disease/ or pregnancy disorder/ or fetomaternal transfusion/ or pregnancy complication/ or intrauterine infection/ or maternal hypertension/ or exp pregnancy diabetes mellitus/ or exp "eclampsia and preeclampsia"/ or hyperemesis gravidarum/ or pregnancy toxemia/ or placenta disorder/ or (HELPP or preeclam* or eclamp* or GDM or ((pregnan* or gestation* or gravid* or maternal) adj6 (hyperten* or blood pressur* or an?emi* or diabet* or obes* or weight gain))).tw,kw.) and (offspring* or progeny or born or neonat* or neo-nat* or new*born* or new-born* or postnat* or post-nat* or perinat* or peri-nat* or infant* or child or children).mp.	106890
5	(exp season/ or geographic distribution/ or environment/ or rural area/ or exp urban area/ or rural population/ or suburban population/ or urban population/ or urban rural difference/ or urbanization/ or *immigrant/ or life event/ or educational status/ or education/ or academic achievement/ or socioeconomics/ or exp economic status/ or exp income group/ or poverty/ or social status/ or social class/ or exp employment status/ or exp mining/ or agricultural worker/ or coal worker/ or industrial worker/ or manual labor/ or income/ or occupation/ or occupational hazard/ or exp occupational disease/ or job stress/ or exp occupational health/ or exp pollution/ or environmental health/ or drug exposure/ or occupational drug exposure/ or exp toxicity/ or exp heavy metal/ or endocrine disruptor/ or endemic disease/ or environmental disease/ or epidemic/ or exp exposure/ or pandemic/ or pesticide/ or particulate matter/ or exp "environmental, industrial and domestic chemicals"/ or exp central stimulant agent/ or exp psychedelic agent/ or exp narcotic agent/ or exp amphetamine derivative/ or exp opiate agonist/ or central depressant agent/ or exp *anticonvulsive	236474

	agent/ or exp narcotic agent/ or exp antidepressant agent/ or tranquilizer/ or exp anxiolytic agent/ or exp *neuroleptic agent/ or alcohol/ or exp alcoholic beverage/ or tobacco/ or addiction/ or exp drug dependence/ or exp "smoking and smoking related phenomena"/ or exp "substance use"/ or exp drug abuse/ or substance abuse/ or "drug use"/ or drinking behavior/ or maternal behavior/ or *mental disease/ or anxiety disorder/ or distress syndrome/ or *mood disorder/ or *behavior disorder/ or maternal behavior/ or anxiety disorder/ or distress syndrome/ or phobia/ or depression/ or mood disorder/ or exp bipolar disorder/ or major depression/ or dysthymia/ or fear/ or anxiety/ or exp stress/ or sexual development/ or sex determination process/ or sex differentiation/ or sexual maturation/ or *hormone/ or exp *glucocorticoid/ or exp *steroid hormone/ec or *corticosteroid/ec or exp hydrocortisone derivative/ec or sex hormone/ or exp testosterone derivative/ or androgen/ or "disorders of hormone metabolism"/ or exp hormone deficiency/ or exp hypothyroidism/ or endocrine function/ or thyroid function/ or "influenza a virus"/ or influenza, human/ or cytomegalovirus infections/ or cytomegalovirus/ or exp flavivirus infections/ or exp flavivirus/ or *inflammation/ or interleukin 6/ec or interleukin 8/ec or hunger/ or nutritional disorder/ or exp malnutrition/ or exp nutritional deficiency/ or exp overnutrition/ or alcohol consumption/ or caffeine intake/ or coffee consumption/ or exp food deprivation/ or exp vitamin intake/ or exp folic acid derivative/ or thiamine/) and (uterus/ or birth/ or birth rate/ or live birth/ or maternal blood/ or fetus/ or ((midtrimest* or midpregnan* or midgestat* or pregnanc* or pregnant or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat*) and (offspring* or progeny or born or neonat* or neo-nat* or new*born* or new-born* or postnat* or post-nat* or infant* or child or children)).mp.)	
6	exp digit ratio/ or "disorder of sex development"/	2406
7	((head circumference/ or leg length/ or cephalometry/) and (baby/ or newborn/)) not (syndrom* or crani*synost* or synosto* or vault distract* or macrocran* or myelomeningoc* or mutat*).ti.	3872
8	"parameters concerning the fetus, newborn and pregnancy"/ or apgar score/ or exp low birth weight/ or birth weight/ or placenta weight/ or mother fetus relationship/	150198
9	birth certificate/ or birthplace/ or birth order/ or birth setting/ or birth season/	10030
10	(f?etal or f?etus* or f?etopath* or intra-uterin* or intrauterin* or in-utero or antenat* or ante-nat* or prenat* or pre-nat* or perinat* or peri-nat* or pre-birth* or prebirth* or before-birth or ((pre or peri) adj2 (postnat* or post-nat*))).tw,kw.	686867
11	(FASD or ARND or (PAE and alcohol*)).tw,kw.	3176
12	((pregnan* or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat*) adj6 expos*).tw,kw.	27460
13	(DOHAD* or FOAD* or early origin*).tw,kw. or (development* adj3 origin* adj4 (health* or diseas* or adult or dement* or alzheimer*)).tw,kw,jw.	3218
14	(((early-life or pregnan* or gestation* or developmental or neurodevelop* or nutrit*) adj15 (programming or malprogramming)) or (feto* adj6 (priming or epigenet*)) or (early adj3 (programming or malprogramming or priming or epigenet*))).tw,kw.	7461
15	((early life or obstetric*) adj3 (factor* or variabl* or parameter* or circumstanc* or condition*)).tw,kw.	7480
16	(chorioamn* or amnio* or intraamnio* or funisit*).tw,kw.	66730
17	(IUGR* or FGR* or SFGR* or SIUGR* or (placent* adj3 (insufficien* or d*sfunct* or inflammat*))).tw,kw.	19567
18	((PROM and ruptur* and membran*) or PPROM* or EPPROM*1 or ((prematur* or pre-matur* or i?matur* or preterm* or pre-term* or pre-labo?r or prelabo?r) adj6 ruptur*	13343

	adj4 membran*) or (((ruptur* adj2 membran*) or ROM) and (pregnan* or gestat* or gravidit*))).tw,kw.	
19	((small adj2 gestat* adj2 (age or ages)) or (SGA adj3 (infant* or neonat* or newborn* or neo-nat* or new*-born* or pregnan* or gestat* or birth* or weight*))).tw,kw.	15603
20	(((gestat* or age) adj2 ("at birth" or "at deliver*")) or birth age or birth gestation* age).tw,kw.	14058
21	(((birth or births) adj1 (underweight* or weight or weights or overweight* or size)) or birthweight* or LBW* or VLBW* or ELBW*).tw,kw.	108137
22	(((head adj2 circumfere*) or cephalometr*) adj6 (birth or births or childbirth* or baby or babies or neonat* or neo-nat* or new*born* or new*-born* or postnat* or post-nat*)).tw,kw.	2990
23	(interpregnan* or inter-pregnan* or ((pregnan* or gestat* or gravidit* or birth) adj interval*) or ((interval* or period*) adj between adj3 (pregnan* or gestat* or gravidit* or births or (subsequent adj (children or infants))))).tw,kw.	3058
24	((neonat* or neo-nat* or new*born* or new*-born* or babies or baby or birth or term) adj6 asphyx*).tw,kw.	8723
25	((maternal or mother* or pregnant women or (during adj (pregnan* or gestat* or gravidit*))) adj4 (expos* or addict* or substance abus* or substance-us* or smoking or tobacco or cigarett* or nicotin* or drinking or alcohol* or ethanol or Etoh or caffein* or drug* or psychotrop* or narcotic* or mari*uana or hash* or cocain* or amphetamin* or amfetamin* or metamphetamin* or metamfetamin* or MDMA or opium or opiat* or opioid* or heroin* or GHB or ketamin* or LSD or antidepres* or anti-depres* or SSRI* or SNRI* or (serotonin* adj3 reuptake inhibitor*) or cipramil or lexapro or prozac or fevarin* or seroxat or zoloft or cymbalta or efexor or effexor or pristiq or fetzima or ixel or savella or milnacipran or monoamine oxidase inhibitor* or MAOIs or MAO-inhibitor* or analgesic* or painkiller* or anti-inflammator* or aspirin* or ((cox* or cyclooxygenase or cyclo-oxygenas*) adj3 (inhibitor* or block* or antagon*)) or coxib* or celecoxib or diclofenac or ibuprofen or indomethicin* or naproxen or acetaminophen* or acetylsalicylic or aspirin* or antidiabetic* or metformin* or chemo* or cytostatic* or anthracyclin* or cyclophosphamid* or epirubicin* or radiat* or irradiat* or radiotherap* or radio-therap* or hormon* or testosteron* or androgen* or estrogen* or oestrogen* or free-T4 or fT4 or f-T4 or free-T3 or fT3 or f-T3 or thyr* or triiodothyronin* or TSH or corticosteroid* or cortisol or hydrocort* or steroid* or gl#costeroid* or gl#cocortico* or dexameth* or prednis* or betameth* or hypothyr* or autoantibod* or auto-antib* or TPO or thyroperoxidase or autoimmun* or auto-immun* or (immune adj2 (repons* or attack* or system* or hypothes*)) or immunit* or inflammat* or IL-6 or IL6 or IL-8 or IL8 or IL-1 or IL1 or interleukin* or cytokin* or infect* or toxoplasm* or influenz* or virus* or viral or CMV or cytomegalovir* or toxin* or heavy-metal* or lead or Pb or mercury or Hg or arsen* or cadmium or chromium or Nickel or pollut* or chemic* or endocrine disrupt* or BPA or BPAs or bisphenol* or PFOA or PFOAS or PFTE or teflon or perfluoro* or per-fluoro* or polychlor* or PCB or PCBs or tetrachlor* or PCE or biphenyl* or phalat* or perchlorat* or plastic or plastics or pesticid* or asbest* or solvent* or Rhesus or Rh or ABO or (blood adj2 incompatib*) or hyperoxygenat* or hyper-oxygenat* or hypo-oxygenat* or hypox* or nutrit* or (nutrient* adj2 (transfer or restrict*)) or undernutrit* or malnutrit* or malnourish* or nourish* or famine or hunger or food or supplement* or vitamin* or multivitam* or vit-D or vit-B12 or vit-B6 or vit-C or vit-A or vit-E or retinol or ascorbic* or ascorbat* or tocopherol* or alphatocopherol* or tocotrienol* or cobalamin* or pyridoxin* or folic acid or folate or methylhydrofolat* or methyltetrahydrofolat* or hydrofolat* or iron or calcium or polyunsaturat* or poly-	122868

	unsaturat* or monounsaturat* or mono-unsaturat* or MUFA or MUFAs or PUFA or PUFAs or LCPUFA* or LCP or LCPs or docosahex?eno* or DHA or eicosapent?en* or icosapent?en* or EPA or omega-3* or omega-6* or omega3* or omega6* or n3 or n6 or n-3 or n-6 or linolenic or linolenate* or alphalinolen* or gammalinolen* or GLA or DGLA or arachidon* or ARA or diet or diets or dietary or behavio?r or stress* or distress* or anxiet* or depression or depressive or GPRSMDD or mental or mood or schizophren* or psychosis or psychiat*)).tw,kw. and (uterus/ or birth/ or (pregnanc* or pregnant or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat* or prepart* or pre-part* or peripart* or peri-part*).mp.)	
26	((birth or births) adj2 (record* or chart* or certificat* or index)).tw,kw.	7311
27	(((maternal or paternal) adj2 (age or ages)) or ((maternal or paternal or parent* or mother* or father*) adj2 mean adj2 (age or ages)) or ((maternal or paternal or parental or mother* or father*) adj2 (age or ages) adj2 birth)).tw,kw.	34546
28	((born or birth or child* or infant*) adj3 (older or old or young*) adj2 (mother* or father* or parent*)).tw,kw.	4993
29	((maternal or mother*) adj6 (parity or multipar* or nullipar* or primipar*)).tw,kw.	10475
30	(((maternal or paternal or parent* or mother* or father*) adj3 (educat* or school* or academic*)) or ((famil* or maternal or paternal or parental or parents or mother* or father*) adj4 (social status or socioeconom* or econom* or SEP or cSEP or SES or cSES or income*1 or poverty or occupat* or employ* or unemploy* or mining or miners or coal or industr*)) or ((condition* or characteristic* or circumstanc* or origin* or expos* or etiol* or aetiol* or factor* or environment* or social status or socioeconom* or econom* or SEP or cSEP or SES or cSES) adj6 (born or birth or births or childbirth*)) or ((condition* or characteristic* or circumstanc* or origin* or expos* or etiol* or aetiol* or caus* or social-status or socioeconom* or econom* or SEP or SES or cSES or program* or hunger or famine or nutritional deficien* or program* or event*) adj3 early-life) or (early life adj1 (factor* or variable* or environment* or precursor* or stress or residence)) or early life risk factor* or early exposur* or early life expos* or early famine or ((Chinese or China or Dutch* or war or wars or worldwar* or warfar* or outbreak* or pandemic* or endemic* or epidemiol* or (early adj2 expos*)) adj5 (famin* or starvat* or hunger or undernutr* or malnutrit* or malnourish* or influenz*))).tw,kw. and (parent/ or expectant mother/ or expectant father/ or mother/ or father/ or uterus/ or birth/ or birth rate/ or live birth/ or (birth or births or childbirth* or born or pregnanc* or pregnant or gestat* or gravidit* or trimester* or midtrimest* or midpregnan* or midgestat*).mp.)	78030
31	(((season* or winter* or summer* or autumn* or spring or springtime or quarter*) adj8 (birth or births or birthrate* or childbirth* or born)) or birth-month*).tw,kw.	5216
32	birth year.tw,kw.	2389
33	((order adj2 (birth or births or childbirth* or borns or born or sibling* or sibship*)) or ((first or 1st or second* or 2nd or third or 3rd or fourth or 4th) adj (born* or sibling*)) or ((sibship* or sibling*) adj (number or size)) or firstborn* or (each-additional adj2 (child or infant* or born))).tw,kw.	8519
34	(((state or states or country or countries or county or counties or place or residenc* or ((area or areas) not (surface adj3 area*)) or location* or overseas or foreign* or nativ* or rural or urban or cities or suburban or residential or industrial or mine or mines or coalmine*) adj3 (birth or births or childbirth* or born)) or birthplace*).tw,kw.	20332
35	(((second-to-fourth or index-to-ring) adj4 (finger* or digit*)) or ((digit or finger length*) adj3 (ratio* or 2d-4d or 2d?4d)) or ((2d-4d or 2d?4d or index finger* or ring finger*) adj4 (ratio or ratios or length* or male* or female* or gender))).tw,kw.	1488

36	**or/1-35 [prenatal factors/exposure]**	**1129795**
37	((((brain or brains) not brain natriuretic peptid*) or brainag* or intracran* or intra-cran* or hippocamp* or parahippocamp* or subiculum or (ammon* adj3 horn*) or ((CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj3 (region* or sector* or area* or field*)) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or (corn* adj2 amon*) or ((temporal* or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit*) adj9 (lobe or lobes or pole or poles or subplate* or planum or cortex or cortical or cortices or region* or ROI or ROIs or sector* or area* or field* or horn* or sulc* or gyr* or opercul* or lateral* or BA-20)) or (planum adj2 polare*) or ((fusiform* or fusi-form* or dentat*) adj9 gyr*) or (fimbria* adj2 forni*) or ((lateral or third or 3rd or fourth or 4th) adj3 ventric*) or (cerebr* adj3 aqu#duct*) or ((white or gr#y) adj3 matter)) and (sMRI* or MRI* or MR-imag* or ((magnetic or neuro or brain*) adj2 (resonan* or imag*)) or neuroimag* or susceptibility weighted imaging or (weighted adj3 (T1 or T2 or T-1 or T-2)) or HT1 or HT2 or T1W* or T2W* or T1-W or T2-W or FLAIR or 3dFLAIR or Freesurfer or whole-brain or brain-volum* or ((intracran* or intra-cran* or subcortical or sub-cortical or subcortex or sub-cortex or hippocamp* or temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or horn* or sulc* or gyr* or fornix or fornices or (planum adj2 polare*) or ((lateral or third or 3rd or fourth or 4th) adj3 ventric*)) adj6 volum*) or (visual adj2 (scor* or rating)))).mp. [BRAIN_MRI FILTER]	496090
38	**36 and 37 [prenatal factors/exposure + brain/MRI filter]**	**16757**
39	volumetry/ and (brain.hw. or brain size/ or brain/ or brain development/ or neuroanatomy/ or subcortex/ or exp dentate gyrus/ or exp hippocampus/ or exp subiculum/ or exp temporal lobe/ or brain ventricle/ or brain aqueduct/ or brain fourth ventricle/ or brain lateral ventricle/ or brain third ventricle/ or lateral brain ventricle/ or (nuclear magnetic resonance imaging/ and (exp brain/ or exp brain ventricle/)))	3659
40	(brain size/ or organ size/) and (*brain/ or brain regions/ or subcortex/ or exp dentate gyrus/ or exp hippocampus/ or exp subiculum/ or exp temporal lobe/ or brain ventricle/ or brain aqueduct/ or brain fourth ventricle/ or brain lateral ventricle/ or brain third ventricle/ or lateral brain ventricle/)	13343
41	(brain size/ or (brain region/ and nuclear magnetic resonance imaging/) or *subcortex/ or exp dentate gyrus/ or exp hippocampus/ or exp subiculum/ or exp temporal lobe/ or brain ventricle/ or brain aqueduct/ or brain fourth ventricle/ or brain lateral ventricle/ or brain third ventricle/ or lateral brain ventricle/) and (perinatal drug exposure/ or prenatal drug exposure/ or prenatal exposure/ or maternal exposure/ or fetal alcohol syndrome/ or fetal malnutrition/ or maternal disease/ or paternal exposure/ or fetotoxicity/ or exp parental smoking/ or maternal obesity/ or maternal nutrition/ or antenatal depression/ or perinatal depression/ or maternal stress/ or perinatal stress/)	2554
42	*brain atrophy/ or *brain atrophy/co, et or ((*atrophy/ or brain atrophy/ or *hypoplasia/) and (*brain/ or brain regions/ or *subcortex/ or exp dentate gyrus/ or exp hippocampus/ or exp subiculum/ or exp temporal lobe/ or brain ventricle/ or brain aqueduct/ or brain fourth ventricle/ or brain lateral ventricle/ or brain third ventricle/ or lateral brain ventricle/))	12663
43	(brainag* or (brain adj (age or ages or ag?ing)) or ((prematur* or pre-matur* or early or gap or gaps) adj4 brain adj2 ag?ing)).tw,kw.	4293
44	(sMRI* or qMRI* or ((structural or volumetr* or quantitativ* or (weighted adj3 (T1 or T2 or T-1 or T-2)) or T1W* or T2W* or T1-W or T2-W or FLAIR or 3dFLAIR or whole-	57014

	brain or (brain adj1 morph*)) adj3 (MRI* or MR-imag* or ((magnetic or neuro or brain*) adj2 (resonan* or imag*)) or neuroimag*))).tw,kw. or Freesurfer.tw,kw,dv.	
45	(((brain or brains or intracran* or intra-cran* or subcortic* or sub-cortic*) adj2 (size* or shape)) or (((brain adj1 (region* or ROI or ROIS or area* or deep or whole or total* or "all" or overall or complet* or entir* or absolute)) or hippocamp* or parahippocamp* or subiculum or ((ammon* or corn*) adj3 horn*) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or (fimbria* adj2 forni*) or ventric* or aqu#duct*) adj4 size*)).tw,kw.	16909
46	((brain or brains or intracran* or intra-cran* or subcort* or sub-cort*) adj3 (volume or volumes or volumetr*)).tw,kw.	23404
47	(((brain adj1 (region* or ROI or ROIs or area* or deep or whole or total* or "all" or overall or complet* or entir* or absolute or structures)) or hippocamp* or parahippocamp* or subiculum or ((ammon* or corn*) adj3 horn*) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or (temporal* adj6 (lobe or lobes or pole or poles or subplate* or planum or cortex or cortices or cortical or region* or ROI or ROIs or sector* or area* or field* or horn* or sulc* or gyr* or opercul* or lateral* or BA-20 or parietal or frontal or ((gr#y or white) adj3 matter))) or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or (fimbria* adj2 forni*) or ventric* or aqu#duct* or CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj30 volum*).tw,kw.	82013
48	((hippocamp* or parahippocamp* or subiculum or ((ammon* or corn*) adj3 horn*) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit* or (fimbria* adj2 forni*) or ((lateral or third or 3rd or fourth or 4th) adj2 ventric*) or aqu#duct* or CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj12 (atroph* or hypoplas*)).tw,kw.	12053
49	((brain or brains) adj2 (atroph* or hypoplas*)).tw,kw.	10298
50	((cortex or cortical or subcort* or sub-cort* or (gr#y adj3 matter) or GM) adj6 (volum* or thick* or thin* or small* or enlarg* or larger or dilat* or atroph* or hypoplas*)).tw,kw. and (hippocamp* or parahippocamp* or subiculum or (ammon* adj3 horn*) or ((CA1 or CA-1 or CA2 or CA-2 or CA3 or CA-3 or CA4 or CA-4 or BA20 or BA-20) adj3 (region* or sector* or area* or field*)) or (dentat* adj3 (gyr* or fasc* or region* or area*)) or (corn* adj2 amon*) or ((temporal or temporale or temporalis or front*tempor* or front*-tempor* or occipit*-tempor* or occipit*temp* or temp*occipit*) adj9 (lobe or lobes or pole or poles or cortex or cortical or region* or sector* or area* or field* or horn* or sulc* or gyr* or opercul* or lateral* or BA-20)) or (planum adj2 polare*) or ((fusiform* or fusi-form* or dentat*) adj9 gyr*) or (fimbria* adj2 forni*) or ((lateral or third or 3rd or fourth or 4th) adj3 ventric*) or (cerebr* adj3 aqu#duct*)).mp.	16426
51	*white matter lesion/	2059
52	lacunar stroke/	3331
53	perivascular space/	1236
54	(cerebrovascular disease/ or brain infarction/ or infarction/ or brain infarction size/ or cerebrovascular accident/ or stroke/ or bleeding/ or brain hemorrhage/ or brain blood vessel/ or brain hypoxia/ or brain ischemia/ or hypoxic ischemic encephalopathy/ or white matter injury/ or white matter lesion/ or white matter/) and (asymptomatic disease/ or undiagnosed disease/ or susceptibility weighted imaging/)	3001
55	hemosiderin/	6059

56	((((white adj2 matter) or WM) adj9 (hyperintens* or hyper-intens* or (signal adj1 (abnormal* or intens*)) or ((high or increas*) adj2 intens*) or HT2 or T2 or T-2 or T2WI* or FLAIR or 3dFLAIR or (visual adj2 (scor* or rating)))) or WMH or WMHs or DEHSI).tw,kw.	12476
57	(((white matter or WM) adj2 l?esion*) or WML or WMLs or PWML or PWMLs).tw,kw.	9747
58	((small adj2 (vessel* or arter* or capillar* or vein or venous) adj2 (diseas* or l?esion* or infarct* or stroke or strokes)) or ((cereb* or burden or score*) adj3 SVD*) or cSVD*).tw,kw.	8930
59	((lacun* adj9 (stroke or strokes or infarct* or (small adj (vessel* or arter* or capillar* or vein or venous)) or l?esion* or bleed* or h?emorrhag* or presenc*)) or SVLL or SVLLs).tw,kw.	8203
60	(((perivascul* or peri-vascul*) adj3 space*) or ((enlarg* or larg* or dilat* or wide* or prominent* or edem* or oedem*) adj3 PVS) or PVSs or EPVS* or (Virchow* adj3 Robin*) or (VRS and Virchow*) or VRSs).tw,kw.	4381
61	((((silent not silent verb) or unnotic*) adj15 infarct*) or ((silent not silent verb) adj3 (stroke or strokes)) or (SCI and infarct*) or SCIs or microinfarct* or micro-infarct*).tw,kw.	6214
62	((discrete or separate or distinct or punctat* or delineat* or focally or dispers* or isolated) adj6 infarct*).tw,kw.	3578
63	(microbleed* or microh?emorrhag* or ((micro or subtle or SWI) adj2 (h?emorrhag* or bleed*)) or susceptibilit*-weight* imaging).tw,kw,dq.	7648
64	(h*sideros* or sideros* or h?emosiderin*).tw,kw.	12026
65	**or/39-64 [structural MRI brain biomarkers]**	**241632**
66	**38 and 65 [prenatal factors/exposures and structural MRI brain biomarkers]**	**3654**
67	((exp animal/ or nonhuman/) not human/) or (animal* or veterinar*).jw. or animal experiment/ or exp animal model/ or exp experimental animal/ or exp transgenic organism/ or (transgenic* or ((primates or ape or apes or monkey* or baboon* or macaq* or pig or pigs or piglet* or porcine or goat or goats* or sheep or lamb or lambs or ovine or cattle or bovine or cow or cows or horse or horses or mare or calve or calves or dog or dogs or canine or bitch* or (cat not cat-scan) or cats or feline or rodent* or rabbit* or mice or mouse or murine* or C57BL* or Balb-c or Balbc or rat or rats or wistar or sprague or dawley or frog or frogs or zebra* or drosophil* or chick* or bee or bees or dam or dams or pups or pup or ewe or ewes or sow or sows) not human*)).ti,ot. [animals not humans]	8289150
68	**66 not 67 [human studies on prenatal factors/exposures and structural MRI brain biomarkers]**	**3022**
69	editorial/ or "systematic review"/ or (editorial or conference abstract or conference review or note).pt. or (editorial or reply or (case-report not case-report-survey) or two-cases).ti. or cochrane.jw. or ((review.pt. or review/ or case report/ or (review or overview).ti. or (search* adj15 (literatur* or ((electronic or medical or biomedical) adj3 database*) or medline or pubmed or embase or psyc?info or exhaustiv* or systematic*)).tw,kw.) not (exp medical record/ or cohort analysis/ or longitudinal study/ or prospective study/ or retrospective study/ or exp case control study/ or cross-sectional study/ or (case-control* or cohort* or retrospectiv* or prospectiv* or crosssection* or cross-section* or population-based or ((chart* or record* or retrospectiv*) adj3 review*)).tw,kw.)) [Filter for original studies]	10620683
70	**68 not 69 [original human studies on prenatal factors/exposures and structural MRI brain biomarkers]**	**1553**

71	**remove duplicates from 70 [original human studies on prenatal factors/exposures and structural MRI brain biomarkers -deduplicated]**	**1507**
72	**71 not medline.cr. [original human studies on prenatal factors/exposures and structural MRI brain biomarkers -deduplicated - embase records only]**	**1364**

1272