REPORT

Prenatal famine exposure has sex-specific effects on brain size

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Early nutritional deprivation might cause irreversible damage to the brain. Prenatal exposure to undernutrition has been shown to be associated with increased central nervous system anomalies at birth and decreased cognitive function in adulthood. Little is known about the potential effect on the brain in older age. We investigated brain size and structure at age 68 years after prenatal famine exposure. T1-weighted structural magnetic resonance images of the brain were made in 118 Dutch famine birth cohort members. Of these 118 (44% male, age range 65–69 years), 41 had been exposed to famine in early gestation and 77 had been prenatally unexposed. Structural volumes were automatically assessed using FreeSurfer. Diffusion tensor imaging was performed and anisotropy and diffusivity were computed. Fluid attenuated inversion recovery was performed to assess white matter hyperintensities. Exposure to famine in early gestation was associated with smaller intracranial volume in males, but not females. Volumes of total brain, grey and white matter were also smaller in early exposed males, but these differences disappeared after adjusting for intracranial volume. Prenatally exposed males but not females, had a smaller intracranial and total brain volume compared to unexposed subjects. Our findings show that prenatal undernutrition permanently affected brain size.

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Abbreviations: ICV = intracranial volume; TBV = total brain volume; WMH = white matter hyperintensity

Introduction

Development of the foetal brain depends amongst others on the availability of nutrients. Foetal undernutrition therefore poses a serious threat to normal foetal brain development (Ramel and Georgieff, 2014). Experimental studies in animals have shown that nutrient restriction during gestation may have long-term effects on brain development and morphology. Rats and baboons that were prenatally protein restricted showed several changes in brain structure and a range of effects on brain maturation (Morgane et al., 1993; Antonow-Schlorke et al., 2011).
Prenatal famine and brain size and structure

The Dutch famine was a 5-month period at the end of World War II during which the western part of the Netherlands was struck by severe famine. Direct devastating effects of prenatal famine exposure were demonstrated in babies that had been exposed during the first trimester. They had increased rates of congenital anomalies of the CNS, including spina bifida and hydrocephalus (Stein et al., 1975). Long-term follow-up studies have shown that prenatal famine exposure is associated with a higher occurrence of mental disorders and poorer performance on a selective attention task at age 58, suggesting that maternal malnutrition during foetal life may negatively affect cognitive function in later life (de Rooij et al., 2010; Susser and St Clair, 2013).

Little is known about the effects of prenatal undernutrition on brain size and structure in later life. A small study showed that intracranial volume (ICV) was decreased in 51-year-old famine-exposed schizophrenia patients. Prenatal famine exposure alone was related to increased brain abnormalities, predominantly white matter hyperintensities (WMHs) (Hulshoff Pol et al., 2000).

We investigated brain size and structure in a subsample of the Dutch famine birth cohort. We aimed to assess the effects of undernutrition during early gestation on brain size, structure and white matter integrity at 68 years.

Materials and methods

The Dutch famine birth cohort

The Dutch famine birth cohort comprises 2414 males and females born as term singletons between 1 November 1943 and 28 February 1947 in the Wilhelmina Gasthuis in Amsterdam, The Netherlands. The current study was aimed at investigating ageing outcomes in 150 cohort members, which would provide enough statistical power to detect meaningful differences in a variety of ageing outcomes, including WMHs. The selection procedure and inclusion of the current sample has been described elsewhere (Ravelli et al., 1998; de Rooij et al., 2015). For more details on methods, see the online Supplementary material. The study was approved by the local medical ethics committee and carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Experimental design

A person was considered prenatally exposed to famine if the average official daily food-ration of the mother during any 13-week period of gestation contained <1000 calories. Using this definition, babies born between 7 January 1945 and 8 December 1945 had been exposed in utero. As the effect of famine exposure on congenital CNS anomalies affected only those exposed during early gestation and the majority of previously shown effects of prenatal famine exposure on later life health occurred in those exposed in early gestation, we focused the current study on this group, who were born between 19 August and 8 December 1945 (Stein et al., 1975; Roseboom et al., 2011).

Sample

A total of 151 participants were invited to the MRI study of whom 33 withdrew due to magnetic resonance scanner anxiety (n=8), metal in the body (n=15), not wanting to visit the hospital (n=9) and loss of data (n=1). Of the total 118 MRI participants, 30% were born before the famine, 35% were exposed to famine in early gestation and 35% were conceived after the famine. For detailed information on the collection of maternal characteristics, birth outcomes and adult characteristics see Supplementary material.

MRI

Participants underwent a standardized MRI-brain scan performed on a 3 T MRI scanner with a 16-channel dStreamHead-Spine coil. We analysed data from three different scanning protocols performed: T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE: voxel size = 1.1 × 1.1 × 1.2 mm, field of view = 256 × 256 mm, repetition time = 6.8 ms, echo time = 3.1 ms), 3D fluid attenuated inversion recovery (FLAIR; voxel size = 1.1 × 1.1 × 1.2 mm, field of view = 250 × 250 mm, repetition time = 4800 ms, echo time = 336 ms) and diffusion tensor imaging (DTI: transverse sequence with voxel size = 2 × 2 × 2 mm, field of view = 224 × 224 mm, repetition time = shortest, echo time = 92 ms, b = 1000 s/mm2, 46 gradient directions, four acquisitions without diffusion weighting).

Images were visually inspected for gross structural abnormalities and presence of artefacts and double-checked by a radiologist in case of abnormal findings. Structural volumes were automatically assessed using FreeSurfer-software (version 5.3.0) (Fig. 1A) (Fischl, 2012). ICV represents the total brain volume (TBV) plus ventricular volume.

Head motion and deformations induced by eddy currents were corrected for by affine registration of the diffusion-weighted images to the non-diffusion weighted image. The gradient directions were corrected by the transformation rotation component (Leemans and Jones, 2009). Rician noise in the diffusion-weighted images was reduced by an adaptive noise filtering method (Caan et al., 2010). Diffusion tensors were calculated using a non-linear least squares estimation. Fractional anisotropy maps were then aligned into a common space (Andersson et al., 2007), averaged and skeletonized (fractional anisotropy was thresholded at 0.2) (Smith et al., 2006). Aligned fractional anisotropy and mean diffusion maps were projected onto this fractional anisotropy skeleton and averaged to obtain white matter summary statistics invariant to possible partial voluming effects (Fig. 1B). 3D-FLAIR data were segmented using a ‘random forest’ classifier, trained on an independent manually segmented dataset of 20 elderly individuals (Fig. 1C). An additional atlas white matter probability map, warped to the T1-weighted scan, was used in the classification, as well as a spatial prior (Breiman, 2001; Steenwijk et al., 2013).
Statistical analysis

We compared those prenatally exposed to famine to those prenatally unexposed to famine (born before famine or conceived after famine). We used linear and logistic regression analyses to compare maternal, birth, general adult characteristics and MRI outcomes between groups. As there are known sex differences in brain volumes as well as in effects of foetal programming, we tested for sex interactions by adding a sex/exposure interaction term to our models.

Results

Study group characteristics

Of 118 subjects, WMH measurements were excluded for two participants (one FLAIR scan failed, one extreme outlier). Table 1 shows maternal, birth and adult characteristics, which were not significantly different between groups.

Brain volumes

ICV and TBV were larger in males than in females [119 ml (95% confidence interval: 88–150) and 116 ml (86–146)]. Birth weight, head circumference at birth and at age 68 were all significantly positively associated with ICV and TBV (all P < 0.05). TBV/ICV ratio was not significantly associated with age, but strongly associated with smoking status (smaller, P = 0.01) and history of cerebrovascular accident or transient ischaemic attack (smaller, P = 0.03).

There were significant exposure × sex interactions for ICV, TBV, total grey matter volume (all P = 0.01) and total white matter volume (P = 0.02). Therefore, we stratified by sex in further volume analyses.

Males exposed to famine during early gestation had smaller ICV than unexposed males with a mean difference of 58 ml (98% confidence interval: 11–106), corresponding to a difference of ~5% (Table 2). They also had smaller TBV [65 ml (17–113)], total grey matter volume [32 ml (7–57)], and total white matter volumes [32 ml (4–60)]. Adjusting for age, head circumference at birth and at age 68 left these effects largely unaltered [50 ml (12–89); 57 ml (17–98); 30 ml (6–53); and 28 ml (4–52), respectively]. Additionally adjusting for ICV in case of TBV, grey and white matter abolished the effects. Volumes of cerebellar grey matter, thalamus, caudate nucleus, accumbens area and grey and white matter volumes in another large number of specific brain areas were also smaller in exposed than in unexposed males. Adjusting for ICV made all differences disappear.

There were no differences between exposed and unexposed females in ICV, TBV, total grey matter and white matter and TBV/ICV and also not in white matter volumes in specific areas. Only 2 of almost 40 specific areas tested showed grey matter volume differences between exposed and unexposed females. In exposed females, grey matter volume was smaller in the transverse temporal (P = 0.03) and temporal pole area (P = 0.01). The latter remained significant after adjusting for ICV (P = 0.02).

White matter integrity

Fractional anisotropy, mean diffusion and total WMH did not differ significantly between the sexes. Fractional anisotropy was positively and mean diffusion negatively associated with ICV. Mean diffusion was positively associated with age. Fractional anisotropy was smaller and mean diffusion and WML were larger in smokers (all P < 0.05).

There were no significant exposure × sex interactions for fractional anisotropy (P = 0.22), WMH volume (P = 0.59) and mean diffusion (P = 0.07). There were no exposure group differences in mean diffusion, fractional anisotropy and WMH volume, also not after adjustment for ICV (Table 3).
Table 1  Maternal birth and adult characteristics according to famine exposure status

<table>
<thead>
<tr>
<th>Exposure to famine</th>
<th>n</th>
<th>Born before</th>
<th>In early gestation</th>
<th>Conceived after</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristics, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>118</td>
<td>68.7</td>
<td>67.4</td>
<td>66.7</td>
<td>67.5 (0.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Female (%)</td>
<td>118</td>
<td>60.0</td>
<td>53.7</td>
<td>54.8</td>
<td>55.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Maternal and birth characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation head household manual (%)</td>
<td>96</td>
<td>76.0</td>
<td>62.2</td>
<td>64.7</td>
<td>66.7</td>
<td>0.72</td>
</tr>
<tr>
<td>Maternal weight at last antenatal visit (kg)</td>
<td>100</td>
<td>64.7</td>
<td>69.1</td>
<td>70.9</td>
<td>68.4 (9.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>103</td>
<td>285</td>
<td>287</td>
<td>287</td>
<td>286 (12)</td>
<td>0.53</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>118</td>
<td>3375</td>
<td>3483</td>
<td>3390</td>
<td>3418 (503)</td>
<td>0.31</td>
</tr>
<tr>
<td>Adult characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educationa</td>
<td>118</td>
<td>4.7</td>
<td>4.6</td>
<td>4.5</td>
<td>4.6 (2.1)</td>
<td>0.98</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>118</td>
<td>50</td>
<td>48</td>
<td>49</td>
<td>49 (14)</td>
<td>0.57</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>118</td>
<td>2.9</td>
<td>14.6</td>
<td>14.3</td>
<td>11.0</td>
<td>0.36</td>
</tr>
<tr>
<td>Alcohol consumers &gt; 1 glass/week (%)</td>
<td>118</td>
<td>65.7</td>
<td>78.0</td>
<td>69.0</td>
<td>71.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Sports participation (%)</td>
<td>118</td>
<td>85.7</td>
<td>75.6</td>
<td>81.0</td>
<td>80.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>118</td>
<td>27.4</td>
<td>28.3</td>
<td>30.3</td>
<td>28.8 (4.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117</td>
<td>149</td>
<td>147</td>
<td>152</td>
<td>149 (16)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>117</td>
<td>82</td>
<td>83</td>
<td>87</td>
<td>84 (11)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>118</td>
<td>40.0</td>
<td>34.1</td>
<td>40.5</td>
<td>38.1</td>
<td>0.52</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>118</td>
<td>31.4</td>
<td>34.1</td>
<td>33.3</td>
<td>33.1</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>118</td>
<td>17.1</td>
<td>22.0</td>
<td>16.7</td>
<td>16.8</td>
<td>0.50</td>
</tr>
<tr>
<td>History of CVA or TIA (%)</td>
<td>118</td>
<td>2.9</td>
<td>2.4</td>
<td>9.5</td>
<td>5.1</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data are given as means (SD), except where given as numbers and percentages; P-values for difference between the exposed and combined unexposed groups based on regression analysis. CVA = cerebrovascular accident; TIA = transient ischaemic attack.

aEducational level measured on a 10-point scale (1 = primary education not completed, 10 = university completed).

Table 2  Volumetric head and brain characteristics in males and females according to famine exposure status

<table>
<thead>
<tr>
<th>Exposure to famine</th>
<th>Males (n)</th>
<th>Born before</th>
<th>In early gestation</th>
<th>Conceived after</th>
<th>Total (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circumference at birth (cm)</td>
<td>14</td>
<td>32.7</td>
<td>33.1</td>
<td>33.5</td>
<td>33.2 (1.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Adult head circumference (cm)</td>
<td>57.1</td>
<td>57.6</td>
<td>58.7</td>
<td>57.9 (1.5)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>ICV (ml)</td>
<td>1138</td>
<td>1101</td>
<td>1176</td>
<td>1138 (85)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>TBV (excl ventr.) (ml)</td>
<td>1092</td>
<td>1049</td>
<td>1131</td>
<td>1090 (88)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>TBV/ICV</td>
<td>0.959</td>
<td>0.953</td>
<td>0.959</td>
<td>0.957 (0.26)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Total ventricular volume (ml)</td>
<td>34.2</td>
<td>33.3</td>
<td>36.3</td>
<td>34.6 (14.3)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Total grey matter (ml)</td>
<td>603</td>
<td>581</td>
<td>620</td>
<td>601 (46)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Total white matter (ml)</td>
<td>488</td>
<td>469</td>
<td>510</td>
<td>489 (50)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Cortical thickness (mm)</td>
<td>4.81</td>
<td>4.82</td>
<td>4.81</td>
<td>4.82 (0.18)</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females (n)</th>
<th>Born before</th>
<th>In early gestation</th>
<th>Conceived after</th>
<th>Total (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circumference at birth (cm)</td>
<td>21</td>
<td>32.1</td>
<td>32.5</td>
<td>32.4 (1.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Adult head circumference (cm)</td>
<td>55.0</td>
<td>55.0</td>
<td>54.7</td>
<td>54.9 (1.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>ICV (ml)</td>
<td>1010</td>
<td>1041</td>
<td>1006</td>
<td>1019 (82)</td>
<td>0.13</td>
</tr>
<tr>
<td>TBV (excl ventr.) (ml)</td>
<td>966</td>
<td>990</td>
<td>967</td>
<td>972 (77)</td>
<td>0.25</td>
</tr>
<tr>
<td>TBV/ICV</td>
<td>0.956</td>
<td>0.951</td>
<td>.962</td>
<td>0.957 (0.16)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total ventricular volume (ml)</td>
<td>28.5</td>
<td>30.4</td>
<td>26.6</td>
<td>28.4 (13.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Total grey matter (ml)</td>
<td>540</td>
<td>551</td>
<td>538</td>
<td>543 (37)</td>
<td>0.22</td>
</tr>
<tr>
<td>Total white matter (ml)</td>
<td>425</td>
<td>439</td>
<td>429</td>
<td>431 (44)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cortical thickness (mm)</td>
<td>4.85</td>
<td>4.85</td>
<td>4.91</td>
<td>4.87 (0.17)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Data are given in means (SD); P-values for difference between the exposed and combined unexposed groups based on regression analysis.
Discussion

We found a sex-specific effect of prenatal famine exposure on brain volume at age 68 years. Males exposed to famine during early gestation had significantly smaller ICV and TBV compared to unexposed males. They also had smaller volumes of total cortical grey matter, cortical white matter, cerebellar grey matter, thalamus, caudate nucleus and accumbens area and a large number of more specific cortical grey matter and white matter areas. These differences disappeared after correction for ICV, suggesting that prenatal famine exposure had an overall diminishing effect on brain size in males. In females, prenatal famine exposure was not associated with large structural volume differences. Volumes of 2 of 40 small specific areas, the temporal pole and transverse temporal area, were significantly smaller in exposed females. However, we did not perform statistical correction for the large number of tests performed.

A decreased ICV in those exposed to the Dutch famine in early gestation was also reported by a previous, smaller study (Hulshoff Pol et al., 2000). But this difference in ICV was only found among schizophrenic patients, and not in the healthy controls, nor were sex differences reported. This is potentially due to the small size of the groups (n = 36).

ICV is largely dependent on brain growth and reaches its maximum size at ∼7 years of age (Rushton and Ankney, 1996). While brain volume decreases with increasing age, ICV is deemed to generally stay the same and therefore a reflection of the peak volume the brain has attained (Rushton and Ankney, 1996; Wolf et al., 2003). The smaller ICV we found in exposed males may have been the consequence of an early interruption of brain development caused by nutritional deficiency in the first trimester of gestation. This potentially stunted early brain development may have resulted in a decrease in maximum volumetric brain development still visible after 68 years. This is also in line with the evidence from animal experiments showing that prenatal nutritional deficiencies resulted in developmental disturbances related to brain growth and maturation (Morgane et al., 1993; Antonow-Schlorde et al., 2011).

Alternatively, brain volumes in famine exposed males may have been affected by atrophy to a larger extent. There is evidence that ICV is not invariant but decreases with age as a result of skull thickening. A recent study showed that at age 70–74 years, ICV is ∼7% smaller than it was at its peak size (Royle et al., 2013). The authors suggested that the mechanism behind thickening of the skull may be related to brain tissue loss in older age. Although hypothetical, another or additional explanation for the decrease in ICV and total brain volume may be that prenatal famine exposure in males has somehow led to increased loss of brain tissue in later life affecting ICV as well.

Both ICV and brain volume are strongly correlated with head circumference, which was also the case in our data (r = 0.71 and r = 0.72, respectively) and all three parameters are associated with cognitive ability (Rushton and Ankney, 1996; Shenkin et al., 2009). We previously showed that at age 58, head circumference was smaller in those prenatally exposed to famine (de Rooij et al., 2010). We also showed that smaller head circumference was associated with decreased cognitive performance, although this did not explain the association between prenatal famine exposure and decreased selective attention performance (de Rooij et al., 2010). In the present data we did not find differences in head circumference between exposed and unexposed groups, which may be a consequence of the relatively small sample (n = 118) we measured compared to the sample measured at age 58 (n = 737). At age 68, head circumference and TBV were all associated with cognitive performance at age 58. However, the smaller ICV and TBV in exposed males did not explain the association between famine exposure in early gestation and decreased selective attention performance (data not shown). Without detectable effects of decreased brain volume in the exposed males on cognitive function, it remains to be seen what the clinical importance of our findings is. Several studies have shown that smaller brain size attained in childhood is associated with increased prevalence, an earlier onset of symptoms and increased severity of cognitive deficit in Alzheimer’s disease, although absence of such associations has also been reported (Mortimer et al., 2005). Future studies, preferably involving the entire cohort, may show whether those exposed to famine in early gestation indeed go on to develop Alzheimer’s disease more often or at an earlier age.

The overall smaller size of the brain after prenatal famine exposure was only found in males and not females. Previously, Brown and Susser (1997) showed that only

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Table 3 DTI and FLAIR derived white matter measures according to famine exposure status

<table>
<thead>
<tr>
<th>Exposure to famine</th>
<th>n</th>
<th>Born before</th>
<th>In early gestation</th>
<th>Conceived after</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional anisotropy</td>
<td>118</td>
<td>0.424</td>
<td>0.424</td>
<td>0.432</td>
<td>0.427 (0.022)</td>
<td>0.48</td>
</tr>
<tr>
<td>Mean diffusion × 10⁴ (mm²/s)</td>
<td>118</td>
<td>0.794</td>
<td>0.792</td>
<td>0.781</td>
<td>0.789 (0.036)</td>
<td>0.40</td>
</tr>
<tr>
<td>Total WMH (ml)³</td>
<td>116</td>
<td>2969</td>
<td>2796</td>
<td>2552</td>
<td>2757 (2.1)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Data are given in means (SD) and geometric means (geometric SD); P-values for difference between the exposed and combined unexposed groups based on regression analysis; Fractional anisotropy = DTI fractional anisotropy; mean diffusion = DTI mean diffusivity; WMH = total white matter hyperintensity volume.
males exposed to famine in early gestation were at increased risk for developing spina bifida. This effect was completely absent in exposed females. However, both exposed males and females were at increased risk for other CNS anomalies such as anencephaly. A number of mental disorders, including addiction and depression, are also more common after prenatal exposure to famine in males (Franzek et al., 2008; de Rooij et al., 2011). However, rates of schizophrenia did not seem to differ between exposed males and females (Susser and St Clair, 2013). A study in Chilean children showed that undernutrition in the first year of life had a clear effect on brain volume at age 18 in males and females, but the effect in males was much larger than in females (Ivanovic et al., 2000). So it seems that some outcomes after prenatal undernutrition predominantly affect exposed males, while other outcomes do not show this sex difference, which may depend on interactions between prenatal undernutrition and genetic and epigenetic processes (Douet et al., 2014).

An alternative explanation for the sex differences we found is selective participation of cohort members in the present study. We have previously demonstrated excess mortality up to the age of 63 in females exposed to famine in early gestation, which may have resulted in selective participation (van Abeelen et al., 2012). This might have led to an underestimation of the effect of undernutrition on brain volumes in the exposed females.

We did not find any differences in the age-related white matter measures mean diffusion, fractional anisotropy and WMH. This contradicts the previously mentioned findings by Hulshoff Poll et al. (2000), who showed an increase in WMH at age 51 in people exposed to famine prenatally. Again, selective participation of the more healthy cohort members may provide an explanation for the absence of these anticipated results.

In summary, our results suggest sex-specific effects of famine exposure during early gestation on the brain at age 68. Exposed males, but not females, showed an overall reduction in brain volume of ~5%. Our findings suggest that prenatal famine exposure in males left a mark on the brain that is even visible after 68 years.

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Supplementary material

Supplementary material is available at Brain online.

References