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Premature brain aging in humans exposed to maternal nutrient restriction during early gestation

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ABSTRACT

Background: Prenatal exposure to undernutrition is widespread in both developing and industrialized countries, causing irreversible damage to the developing brain, resulting in altered brain structure and decreased cognitive function during adulthood. The Dutch famine in 1944/45 was a humanitarian disaster, now enabling studies of the effects of prenatal undernutrition during gestation on brain aging in late adulthood.
Methods: We hypothesized that study participants prenatally exposed to maternal nutrient restriction (MNR) would demonstrate altered brain structure resembling premature brain aging in late adulthood, expecting the effect being stronger in men. Utilizing the Dutch famine birth cohort (n = 118; mean age: 67.5 ± 0.9 years), this study implements an innovative biomarker for individual brain aging, using structural neuroimaging. *BrainAGE* was calculated using state-of-the-art pattern recognition methods, trained on an independent healthy reference sample, then applied to the Dutch famine MRI sample, to evaluate the effects of prenatal undernutrition during early gestation on individual brain aging in late adulthood.
Results: Exposure to famine in early gestation was associated with *BrainAGE* scores indicative of an older-appearing brain in the male sample (mean difference to subjects born before famine: 4.3 years, $p < 0.05$). Furthermore, in explaining the observed variance in individual *BrainAGE* scores in the male sample, maternal age at birth, head circumference at birth, medical treatment of hypertension, history of cerebral incidences, actual heart rate, and current alcohol intake emerged to be the most influential variables (adjusted $R^2 = 0.63$, $p < 0.01$).
Interpretation: The findings of our study on exposure to prenatal undernutrition being associated with a status of premature brain aging during late adulthood, as well as individual brain structure being shaped by birth- and late-life health characteristics, are strongly supporting the critical importance of sufficient nutrient supply during pregnancy. Interestingly, the status of premature brain aging in participants exposed to the Dutch famine during early gestation occurred in the absence of fetal growth restriction at birth as well as vascular pathology in late-life. Additionally, the neuroimaging brain aging biomarker presented in this study will further enable tracking effects of environmental influences or (preventive) treatments on individual brain maturation and aging in epidemiological and clinical studies.

1. Introduction

Increasing evidence from epidemiological studies as well as experimental animal models proves the significant impact of the intrauterine environment on the general lifespan, individual ageing trajectories, lifelong health, and disease outcomes (Rando and Simmons, 2015; Tarry-Adkins and Ozanne, 2014). More specifically, exposure to maternal nutrient restriction (MNR) during prenatal development has been associated with altered brain structure, developmental delays during childhood, impairments in life-long learning, cognitive deficits, behavioral and psychiatric disorders, as well as later-life neurodegenerative disorders (de Rooij et al., 2010; Faa et al., 2014; Raznahan et al., 2012).

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Several studies in a translational nonhuman primate baboon model of moderate MNR (i.e. nutrient reduction of 30%) during pregnancy indicated subtle but widespread disturbances of early organizational processes in cerebral development on a histological level, resulting in major impairments of fetal brain development (Antonow-Schlorke et al., 2011), and subsequent altered postnatal cognitive and behavioral performances (Keenan et al., 2013; Rodriguez et al., 2012) in the young MNR offspring.

In the context of the "developmental origins of health and disease" (DOHaD) paradigm it has been proposed that MNR during gestation triggers long-lasting influences on the epigenome of the differentiating cell, thus resulting in changes in organ structure and adaptation of its metabolism to ensure immediate survival of the fetus (Barnes and Ozanne, 2011; Lillycrop and Burdge, 2011). The developing brain is highly dependent on the availability of nutrients and a lack of sufficient nutrition forms a serious threat to normal brain development (Ramel and Georgieff, 2014). Furthermore, the accumulation of oxidative stress due to suboptimal *in utero* exposure is suggested to consequently lead to accelerated cellular aging over the life course (Tarry-Adkins and Ozanne, 2014), with long-term (health) outcomes of adverse *in utero* conditions seeming to be more prominent in male than female offspring (Aiken and Ozanne, 2013).

Epidemiologically, MNR during pregnancy and lactation is a worldwide problem, including insufficient intake of calories and protein as well as deficiencies in micronutrients (Black et al., 2008), being caused by a variety of factors, e.g. natural disasters, war, poverty, or cultural habits like women being the last in the family to eat (Roseboom et al., 2011). Furthermore, decreased fetal nutrient delivery is also common in teenage pregnancies (Baker et al., 2009) and pregnancies in women over 35 years of age (Beard et al., 2009), women suffering from severe vomiting or dieting during pregnancy (Roseboom et al., 2011), as well as in multiple pregnancies (Raznahan et al., 2012) and placental insufficiency (Zhang et al., 2015). Therefore, it is relevant to study the effects of prenatal undernutrition due to MNR on the brain and its aging processes as this may help to further understand the factors and preconditions of (precocious) brain aging.

The Dutch Famine Birth Cohort Study has been described as an 'experiment of history' which provides a unique opportunity to investigate the effects of prenatal malnutrition on the aging process. During the winter of 1944–1945, the western part of the Netherlands was struck by a period of severe food scarcity. The previously and subsequently well-nourished Dutch population's daily rations dropped acutely to as little as 400–800 calories during the five months of famine. The famine was a humanitarian disaster, but it now offers an opportunity to study the effects of maternal malnutrition on the offspring's health and aging processes in later life. Studies in the Dutch famine birth cohort have already shown that those who were conceived during the famine – and had thus been undernourished during the earliest stages of their development – have an increased risk for coronary heart disease, diabetes, an atherosclerotic lipid profile, altered clotting, and breast cancer (Roseboom et al., 2006). Additionally, coronary heart disease also occurred about 3 years earlier (Painter et al., 2006), total brain volume was decreased in late adulthood (de Rooij et al., 2016), and cognition may deteriorate faster in comparison to those who had not been undernourished prenatally (de Rooij et al., 2010). Consequently, those who were conceived during the famine, and thus had been exposed to MNR during early gestation, appear to age more quickly in terms of general health as compared to those who had not been undernourished *in utero*.

Aging in general aging is driven by the progressive accumulation of cellular damage throughout life and changes in intercellular communication, with individual rates of aging being modified by various genetic and environmental influences (Lopez-Otin et al., 2013; Rando and Chang, 2012). Brain aging, in particular, is characterized by region-specific and non-linear patterns of atrophy (Resnick et al., 2003). To establish preventive measures for age-related brain diseases, it has become vital to determine and to predict the individual trajectory of brain aging (Lopez-Otin et al., 2013; Rando and Chang, 2012). A number of cell-, tissue- or function-based biomarkers, such as telomere length, the epigenetic clock, magnetic resonance imaging (MRI) based approaches, and neurocognitive measures have been developed (for a recent review see Franke et al., 2017a). These biomarkers are aimed to assess an individual's biological age, which is shaped by the interaction between genes, environment and life burden over time, as opposed to the chronological age, which is measured in calendar units. Determination of the biological brain age would allow to (1) predict individual neurocognitive performance during different stages of live, (2) identify an individual's health and risk patterns for age-related diseases, (3) identify protective or harmful environmental influences on mental health, and (4) apply preventive and interventional strategies that are tailor-made for certain biological ages (Bocklandt et al., 2011). Therefore, developing biomarkers for biological age is enjoying increasing popularity in neuroscience.

Personalized structural and functional biomarkers of biological brain aging either identify deviations from pre-established reference curves for healthy fetal and neonatal neurodevelopment (for a recent review see Levman and Takahashi, 2016), healthy brain maturation during childhood and adolescence (e.g., Brown et al., 2012; Cao et al., 2015; Dosenbach et al., 2010; Erus et al., 2015; Franke et al., 2012b; Khundrakpam et al., 2015; Wang et al., 2014), and healthy brain aging into senescence (e.g., Ashburner, 2007; Cherubini et al., 2016; Cole et al., 2015; Franke et al., 2010; Groves et al., 2012; Han et al., 2014; Kandel et al., 2013; Konukoglu et al., 2013; Liem et al., 2017; Lin et al., 2016; Mwangi et al., 2013; Neeb et al., 2006; Sabuncu and Van Leemput, 2011; Sabuncu et al., 2012; Schnack et al., 2016; Steffener et al., 2016; Tian et al., 2016; Wang and Pham, 2011; Wang et al., 2014), as well as distinguish patients with brain disorders from healthy controls (Arbabshirani et al., 2017; Cohen et al., 2011; Gabrieli et al., 2015; Gaser et al., 2013; Löwe et al., 2016; Varoquaux and Thirion, 2014). At the structural level, most of these methods are MRI-based and use state-of-the-art machine learning techniques to establish the reference model for a given task and to subsequently decode the characteristics of test individuals. At the functional level, cross-sectional studies in different age cohorts and longitudinal studies over restricted time ranges have focused on the changing neurocognitive architecture across the lifespan, both in childhood and during older age (Deary et al., 2013; McAvinue et al., 2012). Regression-based predictive analyses aim to predict the values of continuous variables, such as brain volume, and cognitive or neuropsychological characteristics (Cohen et al., 2011; Kandel et al., 2013; Lei et al., 2017). The individualized biomarkers of brain development and aging derived from these regression analyses are valuable and quantifiable parameters that offer a broad range of implementations, i.e., generating reference curves for healthy brain maturation and aging, predicting individual brain development and aging trajectories based on the pre-established reference curves, and disentangling age-related changes from disease-related changes in brain structure and function.

Similar to the assessment of "biological age" based on DNA methylation status, telomere length or allostatic load, establishing magnetic resonance imaging (MRI)-based biomarkers of brain aging exemplifies an important new trend in neuroscience in order to provide risk-assessments and predictions for age-associated neurological and neuropsychiatric impairments on a single-subject level (Bzdok, 2016). In contrast to univariate analyses, brain-aging biomarkers are capable of detecting and quantifying subtle and widespread variations in regional brain structure throughout the whole brain for a given age (e.g., Cole et al., 2017a, 2017b; Franke et al., 2017b; Habes et al., 2016b; Hodgson et al., 2017; Schnack et al., 2016; Steffener et al., 2016). Deviations from age-typical atrophy patterns were already shown to be related to mortality (Cole et al., 2017a), individual health and lifestyle variables and medical drug use (Franke et al., 2014; Habes et al., 2016b), with advanced brain aging emerging in traumatic brain injury (Cole et al., 2015), HIV (Cole et al., 2017b), diabetes (Franke et al., 2013), schizophrenia (Koutsouleris et al., 2014; Schnack et al., 2016), and predicting the onset of cognitive decline

(Franke et al., 2012a; Gaser et al., 2013).

The aim of this study was to investigate whether exposure to fetal undernutrition during early gestation, induced by MNR during the Dutch famine, has an effect on the personal status of brain aging in late-life. Utilizing our well-validated MRI-based brain-aging biomarker (Franke et al., 2010), the age prediction model was trained with an independent sample of healthy subjects and subsequently applied to the MRI subsample of the Dutch famine birth cohort. Individual *BrainAGE* scores were calculated as the difference between the calculated brain age and the person's chronological age, with *BrainAGE* scores above zero suggesting precocious/advanced brain aging. We hypothesized that exposure to famine in early gestation is associated with a status of precocious brain aging in later life, illustrated by increased *BrainAGE* scores in participants, who were exposed to the Dutch famine during early gestation. In line with the sexual dimorphism hypothesis in the DOHaD paradigm, we expected the effect of MNR on the individual status of brain aging being stronger in males. Furthermore, the influence of a number of birth measures and health characteristics in later life on the observed variance in late-life *BrainAGE* scores was examined. Additionally, the relation between *BrainAGE* and cognitive and neuropsychiatric test scores was explored.

2. Methods

2.1. The Dutch famine

The Dutch famine was a consequence of a cascade of events that happened at the end of World War II, with food stocks in the western cities of The Netherlands that ran out rapidly and rations that fell below 1000 calories per person on November 26th, 1944. The amount of protein, carbohydrate, and fat decreased more or less proportionately. The rations varied between about 400 and 800 calories from December 1944 to April 1945, and rose above 1000 calories again after May 12th, 1945. In addition to the official rations, food also came from other sources (e.g., church organizations, central kitchens, and the black market). People may have had access up to double the rationed amount at the peak of the famine, but the rations do adequately reflect the variation in food availability over time. Children younger than 1 year of age were relatively protected, as their rations never fell below 1000 calories. Before the famine pregnant women received extra rations, but during the famine these extra supplies were no longer available (de Rooij et al., 2010).

2.2. The Dutch famine birth cohort

The Dutch famine birth cohort comprises 2414 men and women who were born as term singletons during the period 1 November 1943 and 28 February 1947 in the Wilhelmina Gasthuis in Amsterdam, the Netherlands. People were included in the cohort if they were born alive as a singleton after pregnancy duration of at least 259 days and if a medical birth record could be retrieved. Preterm babies were thus excluded. A total of 1527 persons were included in the cohort at the start of the general Dutch famine birth cohort study in 1995. The current MRI study was aimed at investigating aging outcomes in 150 cohort members, which would provide enough statistical power to detect meaningful differences in a variety of aging outcomes. The selection procedure of the cohort has been described in detail elsewhere (de Rooij and Roseboom, 2013). At the start of the MRI study in 2012, 1307 (54%) cohort members were eligible. They were alive, still living in the Netherlands, and their current address was known to the investigators. Birth weight and head circumference at birth did not differ between these eligible and non-eligible cohort members (3357 vs. 3333 g, $p = 0.22$; 32.8 vs. 32.9 cm, $p = 0.22$). 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.

2.3. Experimental design

The official daily food-rations for the general population of 21 years and older were used to define exposure to famine. A person was considered prenatally exposed to famine if the average daily food-ration of the mother during any 13-week period of gestation contained less than 1000 calories. Based on this definition, babies born between 7 January 1945 and 8 December 1945 had been exposed *in utero*. In correspondence with previous publications on this cohort, we delineated periods of 16 weeks each to differentiate between those exposed in late gestation (born between 7 January and 28 April 1945), in mid gestation (born between 29 April and 18 August 1945) and in early gestation (born between 19 August and 8 December 1945). People born before 7 January 1945 and people conceived after 8 December 1945 were considered as unexposed to famine *in utero* and acted as control groups. As the effect of famine exposure on congenital anomalies of the CNS affected only those exposed during early gestation and the majority of effects of prenatal famine exposure on later life health which we have previously shown occurred in those who were exposed in early gestation, we focused the current study on this group and did not include those exposed to famine in late or mid gestation (Roseboom et al., 2011; Stein et al., 1975).

2.4. Sample selection

For the 2012 study consisting of a home visit and a MRI session in the hospital, we aimed to include a total of 150 people: 50 of those born before the famine, 50 of those exposed to famine in early gestation and 50 of those conceived after the famine. We randomly drew equal samples from each of the groups until the number of 50 people agreeing to participate was reached. A total number of 151 participants of an eligible group of 268 cohort members (56%) were visited at home. Participation rates were similar in the born before famine and exposed in early gestation groups (54% vs. 51%) and higher in the conceived after famine group (66%). All 151 participants were invited to the MRI part of the study. A total of eight subjects refrained from further participation due to anxiety of being in the MR scanner. Another 15 subjects were excluded for MR scanning because of the presence of metal in their bodies and nine subjects declined to visit the hospital. Of one person who participated in the MRI protocol, data had accidentally not been stored. We therefore arrived at a total number of 118 MRI participants (mean age 67.5 $\pm$ 0.9 years) of whom 30% was born before the famine, 35% was exposed to famine in early gestation and 35% was conceived after the famine. Of the 33 excluded subjects, 52% had been born before the famine, 24% was prenatally exposed to famine and 24% was conceived after the famine. Two MRI participants have had a CVA that was diagnosed by a physician. None had ever been diagnosed with a depressive disorder, anxiety disorder, psychosis, schizophrenia, bipolar disorder, or obsessive-compulsive disorder.

2.5. Study parameters

Maternal characteristics and birth characteristics were extracted from medical birth records (i.e., maternal age at birth, gestational age, birth weight, birth length, head circumference, ponderal index (PI) at birth, with PI being calculated as a relationship between mass and height, thus measuring fetal growth). Participants conducted a standardized interview, took anthropometric measurements and performed several medical and cognitive tests, measuring different cognitive domains. The interview yielded information about current smoking, medical history and use of medication. The Alice Heim Test 4th version (AH4) (Heim, 1970) measures general intelligence, comprising 65 verbal and mathematical reasoning items of increasing difficulty. The test score refers to the percentage of correct responses. Episodic memory was tested with the 15 words test and a paragraph encoding and recall test with participants being told to reproduce immediately (immediate recall) and 30 min later (delayed recall). The percentage retained from immediate to delayed

recall condition was calculated (retrieval). A short computerized version of the Stroop task (Stroop, 1935) was administered to measure executive functioning, specifically selective attention. The name of a color was presented in one of four different ink colors (i.e., the word "blue" printed in yellow ink). Participants had 5 s to name the color of the ink and to choose the correct option out of four names of colors printed in different ink colors. Total test time was 5 min. Time of responding to each item in seconds was recorded (reaction time), as well as percentage of correct answers (score). The Trail Making Test (Tombaugh, 2004) was administered to measure cognitive processing speed (part A) and mental flexibility (part B). Participants were asked to connect a sequence of 25 consecutive targets in a sequential order, the targets being all numbers (part A) or alternating between numbers and letters (part B). If the test taker was making an error, it had to be corrected before moving on to the next dot. Time of finishing each part in seconds was recorded. Anxiety and depression symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), with mild depression being assumed for HADS scores between 8 and 10, moderate depression being assumed for HADS scores between 11 and 14, severe depression being assumed for HADS scores >14.

2.6. MRI data acquisition

Participants underwent a standardized MRI scan of the brain performed on a 3T MRI scanner (Philips Ingenia, Best, the Netherlands) with a 16-channel DStream Head-Spine coil. For the present study, we analyzed data from T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE). The MPRAGE protocol consisted of a sagittal sequence with the following parameters: voxel size = 1.1 × 1.1 × 1.2 mm, field of view (FOV) = 256 × 256 mm, repetition time (TR) = 6.8 ms and echo time (TE) = 3.1 ms. Images were visually inspected for gross structural abnormalities and presence of artifacts and double-checked by a radiologist in case of abnormal findings.

2.7. Preprocessing of MRI Data & Data Reduction

As described previously (Franke et al., 2010), preprocessing of the T1-weighted images was done using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm/) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de), running under MATLAB (www.mathworks.com). All T1-weighted images were corrected for bias-field inhomogeneities, then spatially normalized and segmented into GM, WM, and CSF within the same generative model (Ashburner and Friston, 2005). The segmentation procedure was further extended by accounting for partial volume effects (Tohka et al., 2004), by applying adaptive maximum a posteriori estimations (Rajapakse et al., 1997), and by using a hidden Markov random field model (Cuadra et al., 2005). Preprocessing the images further included affine registration and smoothing with 4 mm full-width-at-half-maximum (FWHM) smoothing kernels. Spatial resolution was set to 4 mm. Data were further reduced by applying principal component analysis (PCA) in order to reduce computational costs, to avoid severe overfitting, as well as to get a robust and widely applicable age estimation model, utilizing the "Matlab Toolbox for Dimensionality Reduction" (http://ict.ewi.tudelft.nl/~lvandermaaten/Home.html).

2.8. BrainAGE model training sample

To train the age estimation framework, we used MRI data of 313 healthy subjects [127 male] from the publicly accessible IXI cohort (http://www.brain-development.org; data downloaded in September 2011) aged 45–86 years [mean (SD) = 61.4 (9.1) years], which were collected on three different scanners (i.e., Philips 1.5T, General Electric 1.5T, Philips 3.0T). Written informed consent was provided by all participants according to procedures for the protection of human subjects, approved by the local institutional committees (i.e., Hammersmith Hospital London, UK; Guy's Hospital London, UK; Institute of Psychiatry London, UK). T1-weighted images were preprocessed with the same pipeline as described in Preprocessing of MRI Data & Data Reduction.

2.9. BrainAGE framework

The *BrainAGE* framework utilizes a machine-learning pattern recognition method, namely relevance vector regression (RVR) (Tipping, 2000, 2001). It was recently developed to model healthy brain aging and subsequently estimate individual brain ages based on T1-weighted images (Franke et al., 2010). As suggested previously, a linear kernel was chosen, since age estimation accuracy was shown not to improve when choosing non-linear kernels (Franke et al., 2010). Thus and in contrast to support vector machines, parameter optimization during the training procedure was not necessary. In general, the age regression model is trained with chronological age and preprocessed whole brain structural MRI data (as described above) of the training sample, resulting in a complex model of healthy brain aging (Fig. 1A, left panel). Put in other words, the algorithm uses those whole-brain MRI data from the training sample that represent the prototypical examples within the specified regression task (i.e., healthy brain aging). Additionally, voxel-specific weights are calculated that represent the importance of each voxel within the specified regression task (i.e., healthy brain aging). For an illustration of the most important features (i.e., the importance of voxel locations for regression with age) that were used by the RVR to model

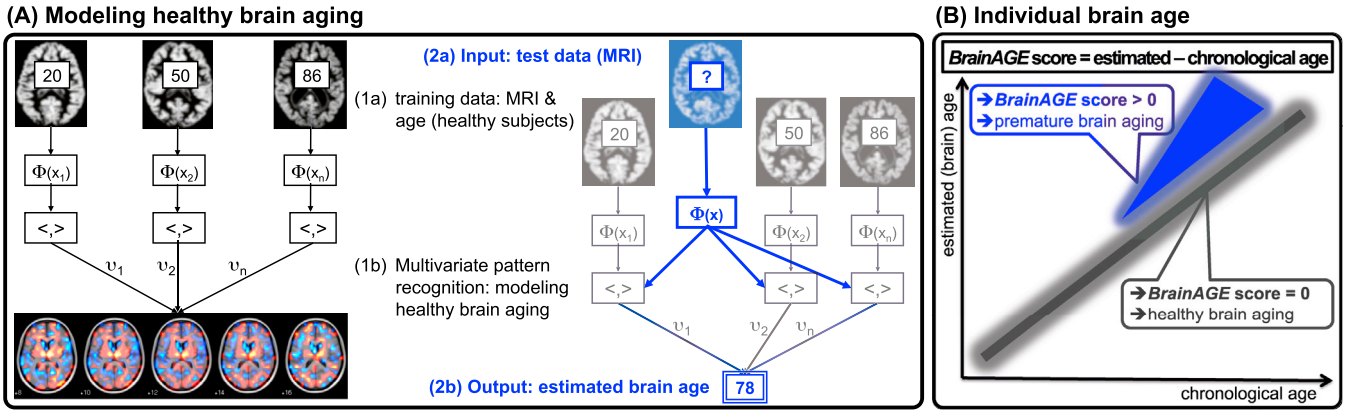

Fig. 1. Depiction of the *BrainAGE* concept. A: The model of healthy brain aging is trained with the chronological age and preprocessed structural MRI data of a training sample (left; with an illustration of the most important voxel locations that were used by the age regression model). Subsequently, the individual brain ages of previously unseen test subjects are estimated, based on their MRI data. B: The difference between the estimated and chronological age results in the *BrainAGE* score, positive *BrainAGE* scores indicate advanced brain aging. (Image reproduced from Franke et al., 2012a), with permission from Hogrefe Publishing, Bern.

Table 1
Birth and adult health characteristics and descriptive statistics for the Dutch famine exposure groups.

	Female sample ($n = 66$)				Male sample ($n = 52$)				*Female vs. Male sample p*
	Exposure to famine				Exposure to famine				
	Born before	*In early gestation*	*Conceived after*	*p*	*Born before*	*In early gestation*	*Conceived after*	*p*	
Characteristics at birth									
Maternal age at birth (years)	26.1 (5.7)	27.8 (5.6)	30.4 (5.6)	**0.04**	27.7 (6.5)	25.2 (6.2)	26.7 (6.6)	0.53	0.13
Gestational age (days)	287.4 (10.8)	286.6 (14.2)	287.7 (13.0)	0.96	278.8 (9.0)	291.1 (12.7)	284.6 (7.9)	**0.02**	0.41
Birth weight (g)	3248 (570)	3295 (483)	3554 (532)	0.12	3366 (456)	3398 (449)	3640 (456)	0.16	0.25
Birth length (cm)	54.4 (15.3)	50.4 (1.8)	53.4 (10.3)	0.44	50.5 (1.5)	51.3 (2.0)	50.9 (2.1)	0.51	0.23
Head circumference (cm)	32.3 (1.4)	32.3 (1.3)	33.1 (1.2)	0.07	32.4 (1.3)	32.6 (1.6)	33.8 (1.5)	**0.02**	0.13
Ponderal index (kg/m^3)	26.2 (2.1)	25.6 (2.4)	26.4 (2.0)	0.48	26.1 (2.4)	25.2 (2.5)	27.5 (2.0)	<**0.01**	0.60
Late-life health characteristics									
Body mass index (kg/m^2)	27.4 (4.0)	27.8 (4.7)	31.8 (5.8)	<**0.01**	27.5 (2.4)	28.8 (5.2)	28.6 (4.9)	0.68	0.47
Systolic blood pressure (mmHg)	148.2 (14.7)	146.6 (15.7)	148.1 (16.4)	0.94	150.2 (16.5)	148.0 (13.9)	156.4 (16.6)	0.26	0.18
Diastolic blood pressure (mmHg)	80.1 (8.1)	81.4 (10.7)	85.2 (10.1)	0.20	84.8 (16.6)	84.4 (9.3)	89.2 (9.7)	0.43	0.06
Heart rate (beats/min)	74.7 (9.5)	74.2 (8.2)	73.5 (10.8)	0.92	66.4 (14.4)	70.7 (8.3)	73.0 (11.7)	0.28	0.06
Non-fasting blood glucose (mg/dl)	5.57 (1.50)	5.75 (1.04)	5.96 (1.59)	0.85	7.00 (1.77)	6.59 (1.44)	6.28 (1.64)	0.46	<**0.01**
Cholesterol (mg/dl)	6.14 (1.02)	5.66 (1.57)	5.86 (0.90)	0.44	5.15 (0.80)	5.02 (0.95)	5.63 (1.16)	0.16	<**0.01**
HDL (mg/dl)	1.70 (0.37)	1.87 (0.64)	1.75 (0.58)	0.60	1.60 (0.46)	1.35 (0.39)	1.35 (0.30)	0.14	<**0.001**
LDL (mg/dl)	3.70 (0.96)	3.15 (1.52)	3.43 (0.85)	0.31	2.90 (0.69)	2.90 (0.92)	3.39 (1.05)	0.21	0.07
Triglycerides (mg/dl)	1.65 (0.68)	1.43 (1.19)	1.52 (0.72)	0.75	1.45 (0.66)	1.72 (1.10)	2.20 (1.59)	0.21	0.16
Diabetes (%)	14.3	19.0	14.3	0.88	21.4	35.7	28.6	0.92	0.27
Hypertension (%)	47.6	33.3	38.1	0.66	28.6	50.0	57.1	0.66	0.79
Hypercholesterolaemia (%)	23.8	23.8	38.1	0.70	42.9	57.1	35.7	0.59	0.33
History of CVA or TIA (%)	0.0	0.0	4.8	0.39	7.1	7.1	21.4	0.52	<**0.05**
Current smokers (%)	4.8	23.8	14.3	0.23	0.0	7.1	21.4	0.22	0.31

Data are given as means (SD), except where given as numbers and percentages *P*-values are reported from ANOVAs comparing the three famine exposure groups and Students' t-tests testing women vs. men (last column). Bold type indicates statistical significance. CVA = cerebrovascular accident; HDL = high density lipoprotein; LDL = low density lipoprotein; TIA = transient ischaemic attack.

normal brain aging and more detailed information please refer to Franke et al. (2010). Subsequently, the brain age of a test subject can be estimated using the individual tissue-classified MRI data (as described above), aggregating the complex, multidimensional aging pattern across the whole brain into one single value (Fig. 1A, right panel). In other words, all the voxels of the test subject's MRI data are weighted by applying the voxel-specific weighting matrix. Then, the brain age is calculated by applying the regression pattern of healthy brain aging and aggregating all voxel-wise information across the whole brain. The difference between estimated and chronological age will reveal the individual brain age gap estimation (*BrainAGE*) score, with positive values indicating advanced structural brain aging and negative values indicating decelerated structural brain aging. Consequently, the *BrainAGE* score directly quantifies the amount of acceleration or deceleration of brain aging (Fig. 1B). For example, if a 70 yrs old individual has a *BrainAGE* score of +5 yrs, this means that this individual shows the typical atrophy pattern of a 75 yrs old individual. Recent work has demonstrated that this method provides reliable and stable estimates. Specifically, the *BrainAGE* scores calculated from two shortly delayed scans on the same MRI scanner, as well as on separate 1.5T and 3.0T scanners, produced intraclass correlation coefficients (ICC) of 0.93 and 0.90, respectively (Franke et al., 2012a). Within this study, the *BrainAGE* framework was applied using the preprocessed GM images. For training the model as well as for predicting individual brain ages, we used "The Spider" (http://www.kyb.mpg.de/bs/people/spider/main.html), a freely available toolbox including several machine learning algorithms running under MATLAB. Individual *BrainAGE* scores can be found in *SI Data Spreadsheet*.

2.10. Statistical analysis

Descriptive statistics were used to summarize sample characteristics, i.e. birth and late-life health characteristics (Table 1), fractional brain tissue volumes, neuropsychiatric test scores, and *BrainAGE* scores (Table 2). Fractional brain volumes were calculated as a ratio of individual ICVs. Analysis of variance (ANOVA) was used to test for differences between the three famine exposure groups (i.e., 'born before', 'in early gestation', 'conceived after'), separately in both genders. Effect size was calculated using η^2. Student's t-tests were performed to test for differences between the female and male samples.

Gender-specific standard least squares linear regression analyses were performed explore the importance of each variable, i.e., chronological age, famine exposure (as this variable has three states, it was dummy coded as 'born before' [0/1] and 'in early gestation' [0/1]), birth characteristics (i.e., maternal age at birth, gestational age, birth weight, birth length, head circumference, ponderal index), and late-life health characteristics (i.e., body mass index, blood pressure, heart rate, blood glucose, cholesterol, HDL, LDL, triglycerides, diabetes, medical treatment of hypertension, medical treatment of hypercholesterolaemia, history of cerebral incidences, current smoking, current alcohol intake) in order to explain the observed of variance in late-life *BrainAGE* scores. Results are additionally reported with false discovery rate (FDR)-corrected p-values for each variable.

Finally, all cognitive and neuropsychiatric variables are clustered by constructing components, which are linear combinations of those variables in a cluster of similar variables, i.e. groups of highly correlated variables. The cluster components are constructed using the first principal component of the variables in that cluster, thus explaining as much of the variation as possible among the variables in that cluster. Variable clustering in order to avoid statistical error 1 inflation was chosen over PCA because of better interpretability of the new cluster-based variables. Then, least squares regression analyses were performed on the clusters, including *BrainAGE* scores, gender, famine exposure as predictors, in order to explore, whether individual *BrainAGE* scores or exposure to famine *in utero* had any effects on cognitive and neuropsychiatric measures.

Table 2
Group characteristics and descriptive statistics for the Dutch famine exposure groups.

	Female sample ($n = 66$)				Male sample ($n = 52$)				*Female vs. Male sample p*
	Exposure to famine				Exposure to famine				
	Born before	*In early gestation*	*Conceived after*	*p*	*Born before*	*In early gestation*	*Conceived after*	*p*	
n	21	22	23	–	14	19	19	–	
Age at MR scan (years)	68.7 (0.5)	67.4 (0.2)	66.7 (0.4)	<**0.001**	68.6 (0.4)	67.4 (0.1)	66.7 (0.4)	<**0.001**	0.57
Intracranial Volume (ICV) and Fractional Brain Tissue Volumes									
ICV volume (ml)	1274 (95)	1294 (90)	1260 (101)	0.49	1438 (116)	1411 (118)	1518 (88)	**0.01**	<**0.001**
Fractional GM volume (/ICV)	0.44 (0.02)	0.44 (0.02)	0.44 (0.02)	0.85	0.43 (0.02)	0.42 (0.02)	0.42 (0.02)	0.49	<**0.001**
Fractional WM volume (/ICV)	0.36 (0.02)	0.37 (0.02)	0.37 (0.01)	0.46	0.37 (0.02)	0.37 (0.02)	0.37 (0.02)	0.87	0.41
Fractional CSF volume (/ICV)	0.20 (0.02)	0.20 (0.02)	0.19 (0.01)	0.22	0.21 (0.01)	0.21 (0.02)	0.21 (0.02)	0.65	<**0.001**
***BainAGE* score**									
BainAGE score (years)	−0.09 (4.28)	0.91 (3.97)	−0.09 (5.27)	0.71	−1.81 (3.51)	2.53 (5.25)	0.53 (4.59)	**0.03**	0.66
Neuropsychological Data									
AH4: Score (%)	62.8 (13.5)	63.5 (17.0)	60.4 (17.4)	0.80	70.8 (9.2)	68.3 (10.8)	66.4 (12.8)	0.54	**0.02**
Episodic memory: 15 Word test (sum)	33.7 (8.9)	35.0 (8.9)	32.3 (7.9)	0.57	29.0 (6.0)	26.3 (9.0)	26.3 (8.7)	0.57	<**0.001**
Episodic memory: Immediate recall (sum)	23.0 (4.8)	22.1 (7.0)	20.7 (7.0)	0.49	22.6 (5.9)	18.7 (7.3)	18.6 (8.2)	0.23	0.10
Episodic memory: Delayed recall (sum)	16.3 (6.0)	16.8 (6.2)	15.5 (6.8)	0.79	17.1 (6.9)	13.4 (7.2)	13.4 (8.3)	0.30	0.17
Episodic memory: Retrieval (%)	69.4 (18.0)	75.1 (14.8)	73.6 (18.4)	0.54	72.9 (22.3)	67.1 (30.3)	71.2 (26.5)	0.81	0.52
Stroop task: Reaction time (sec)	3.51 (0.46)	3.52 (0.64)	3.43 (0.60)	0.85	3.21 (0.37)	3.20 (0.48)	3.23 (0.55)	0.98	**0.009**
Stroop task: Score (%)	50.1 (26.3)	42.9 (29.7)	35.4 (28.4)	0.23	55.4 (35.1)	55.2 (31.9)	66.1 (30.7)	0.52	**0.003**
Trail Making Test A (sec)	38.7 (11.9)	36.5 (8.8)	38.5 (15.8)	0.82	35.4 (5.3)	35.8 (8.8)	36.1 (14.7)	0.98	0.33
Trail Making Test B (sec)	93.1 (36.5)	80.3 (27.9)	87.1 (35.9)	0.46	83.6 (32.1)	85.6 (28.7)	64.8 (17.1)	**0.05**	0.14
HADS: Anxiety score (sum)	4.00 (2.49)	4.95 (2.93)	6.00 (3.38)	0.09	3.00 (2.00)	4.11 (3.03)	3.67 (2.99)	0.53	**0.01**
HADS: Depression score (sum)	2.19 (2.36)	1.89 (1.91)	2.78 (3.32)	0.54	1.21 (0.97)	2.95 (3.31)	3.39 (5.27)	0.25	0.61

Data are displayed as mean (SD). *P*-values are reported from ANOVAs comparing the three famine exposure groups and Students' t-tests testing women vs. men (last column). Bold type indicates statistical significance.

Data processing and statistical analyses were performed using MATLAB and JMP 13.

3. Results

3.1. Group characteristics

The MRI study sample from the Dutch famine cohort included offspring who were considered as prenatally exposed to MNR due to the Dutch famine during early gestation ($n = 41$) as well as two control groups, i.e. offspring born before the Dutch famine ($n = 35$) and offspring who were conceived after the Dutch famine ($n = 42$). In total, the MRI study sample included 66 women and 52 men, aged between 65.9 and 69.6 yrs at the time of MRI scanning (mean age ± standard deviation (SD): 67.5 ± 0.9 yrs). As would be expected due to grouping based on date of birth, age at MRI scan differed between the famine exposure groups ($F = 272.2$, $p < 0.001$), but not between females and males (Table 2). Additionally, maternal age and body mass index (BMI) in late-life differed between famine exposure groups in the female sample; gestational age, head circumference at birth, and ponderal index (PI) differed between famine exposure groups in the male sample (Table 1). Interestingly, risk factors for a vascular pathology in late life did not differ between famine exposure groups, in neither females, nor males.

3.2. Brain characteristics

As the focus of our study was on *BrainAGE* analyses, we only give a rough overview of the general brain characteristics. More detailed analyses on regional brain volumes and white matter integrity in the same MRI study sample were published recently (de Rooij et al., 2016). In late adulthood, total intracranial volume (ICV) differed between the famine exposure groups in the male sample (Table 2), with significantly decreased ICV in offspring who had been exposed to the Dutch famine during early gestation ($p < 0.05$). In the female sample, ICV did not differ between groups, but were significantly lower as compared to the male sample ($p < 0.001$; Table 2). Absolute brain tissue volumes were corrected for individual ICV to account for differences in head size. Fractional gray matter volume (GM) was higher in the female as compared to the male sample ($t = 4.39$, $p < 0.001$), whereas fractional cerebro-spinal fluid volume (CSF) volume was higher in the male as compared to the female sample ($t = -3.53$, $p < 0.001$). Fractional white matter volumes (WM) did not differ between genders ($t = -0.82$, *n.s.*). Exposure to famine had no effect on fractional brain tissue volumes in late adulthood (Table 2). As comprehensively analyzed in a recent study on brain size and structure in the Dutch famine birth cohort (de Rooij et al., 2016), birth weight, head circumference at birth and at age 68 were all significantly positively associated with ICV and total brain volume/ICV ratio was strongly associated with smoking status and history of cerebrovascular accident or transient ischaemic attack.

3.3. Brain aging in late adulthood

BrainAGE scores, which quantify individual neuroanatomical aging in relation to age-specific atrophy patterns, differed significantly between the famine exposure groups in the male sample ($F = 3.6$, $p < 0.05$, $\eta^2 = 0.13$), but not in the female sample ($F = 0.3$, *n.s.*; Table 2). Post-hoc tests (incl. Bonferroni correction) showed significantly increased *BrainAGE* scores in male offspring who had been exposed to the Dutch famine during early gestation as compared to subjects born before the famine by about 4.3 years ($p < 0.05$; Fig. 2), but not as compared to subjects received after the famine (2.0 years, *n.s.*). *BrainAGE* scores did not differ between male and female samples ($F = 0.04$, *n.s*; Table 2).

In the female sample, the least squares regression model, including measures at birth and actual health characteristics as predictors, could not explain the observed variance in individual *BrainAGE* scores (adjusted $R^2 = 0.09$, $p = 0.30$; Fig. 3). Because the regression model did not reach statistical significance, we do not report further details on the predictor variables in the female sample.

In the male sample, the least squares regression model explaining the observed variance in individual *BrainAGE* scores showed very good

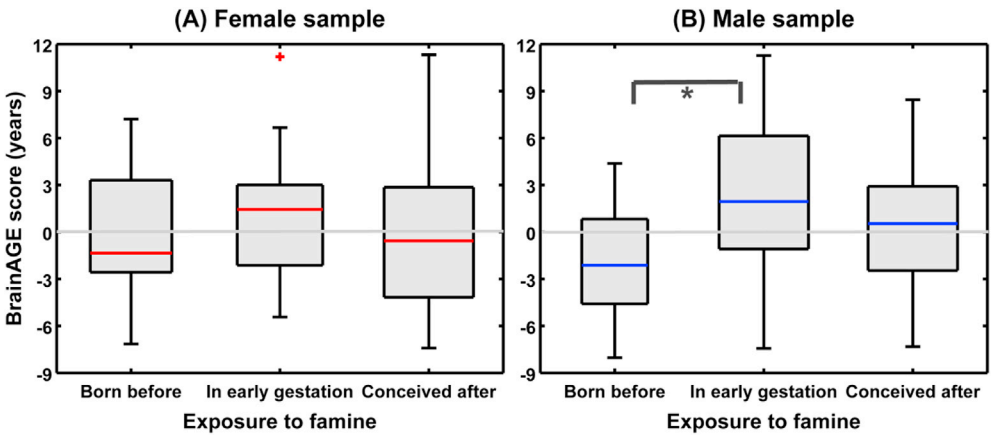

Fig. 2. Neurostructural aging in the Dutch famine birth cohort study. *BrainAGE* scores differed significantly between the three groups only in the (B) male, but not in the female (A) sample. In the male sample, post-hoc tests showed significantly increased scores in subjects with exposure to famine in early gestation ($p < 0.05$; asterisk). The gray boxes contain the values between the 25th and 75th percentiles of the groups, including the median (red/blue lines for female/male samples). Black lines extending above and below each box symbolize data within 1.5 times the interquartile range (outliers are displayed with a +). The width of the boxes depends on the group size.

performance (adjusted $R^2 = 0.63$, $p = 0.007$; Fig. 3). After FDR-correction, maternal age at birth, head circumference at birth, medical treatment of hypertension, history of cerebral incidences, actual heart rate, and current alcohol intake emerged to be the most influential variables (Table 3).

3.4. Relationship between individual brain aging and neuropsychiatric parameters

Cognitive and Neuropsychiatric test scores in late adulthood did not differ between the Dutch famine exposure groups, except for *Trail Making Test B*, measuring mental flexibility, in the male sample, with significantly better performances in men conceived after the famine ($F = 3.2$, $p < 0.05$; Table 2). As compared to women, men performed better in *AH4 test*, measuring general intelligence, and *Stroop test*, measuring selective attention (Table 2). Additionally, men showed lower anxiety scores (*HADS*). Women performed better in *15 Words Test,* measuring episodic memory (Table 2).

To explore, whether individual *BrainAGE* scores or exposure to famine *in utero* had any effects on cognitive and neuropsychiatric measures, least squares regression analyses were performed, including *BrainAGE* scores, gender, famine exposure, and the interaction between *BrainAGE* and famine exposure as predictors. Before performing regression analyses, variable clustering resulted in three clusters (Table 4). Cluster 1 represents cognitive attention and explained 57% of the variance in the included test scores. Cluster 2 represents episodic memory and explained 62% of the variance in the included test scores. Cluster 3 represents psychiatric measures and explained 80% of the variance in the included test scores. Altogether, variable clustering explained 63% of the variance in the neuropsychiatric data. The regression analyses resulted in significant models only for clusters 1 and 2, with model effects due to gender in both models (Table 5). After Bonferroni correction for multiple testing only the results for cluster 1 remained significant.

4. Discussion

The present study evaluates the long-term effects of MNR during early gestation in humans on neuroanatomical aging and its behavioral correlates in late adulthood. It combines our recently presented non-invasive *in vivo* MRI biomarker for brain aging with the unique Dutch Famine Birth Cohort Study in order to analyze MNR related differences in individual brain aging in old age. Indicated by increased *BrainAGE* scores resulting from increased subtle changes in brain structure, our results provide *in vivo* evidence for a status of premature brain aging in late adulthood, particularly in men who had been exposed to famine *in utero*. The effects of MNR on *BrainAGE* occurred without effects on size or weight of the baby at birth and vascular pathology in late life, which stresses the significance of early nutritional conditions in life-long developmental programming even more.

The *BrainAGE* approach was designed to indicate deviations in age-related spatiotemporal brain changes. Though "healthy" brain aging has been found to follow highly coordinated and sequenced patterns of brain tissue loss and CSF expansion (Raz and Rodrigue, 2006; Resnick et al., 2003; Terribilli et al., 2011), multiple factors affect and modify those individual trajectories. Applying the *BrainAGE* method results in a single global estimation score of the individual "brain age", while

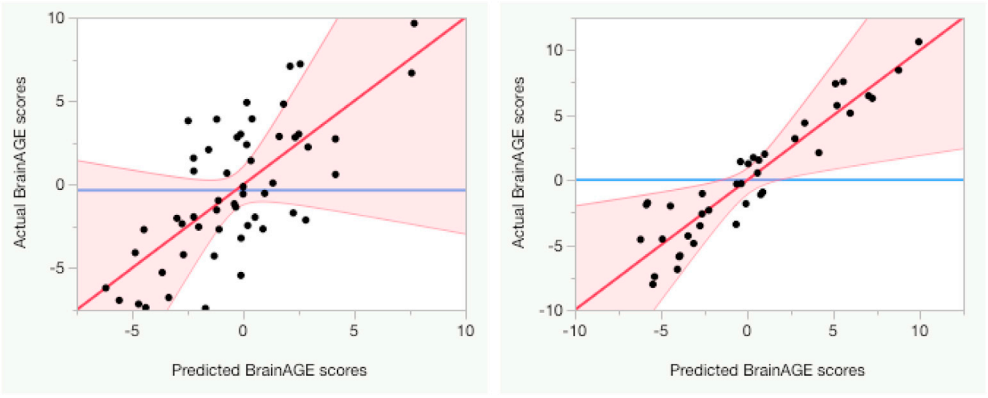

Fig. 3. Least squares regression models for explaining the observed variance in individual *BrainAGE* scores by famine exposure, birth, and actual health measures as predictors. Actual vs. predicted *BrainAGE* scores resulting from the regression analyzes for female (left) and male (right) offspring at age 68 years. In females (left panel), the observed variance in individual *BrainAGE* scores could not be explained by famine exposure, birth, and actual health measures (adj. $R^2 = 0.09$, $p = 0.30$). In males (right panel) the observed variance in individual *BrainAGE* scores was explained by famine exposure, birth, and actual health measures as predictors (adj. $R^2 = 0.63$, $p = 0.007$). Black dots show individual data points (i.e., observed *BrainAGE* scores vs. scores predicted by the sex-specific least squares regression model), the red line shows the best fitting regression line, and the light red area shows the range of possible regression lines.

Table 3
Standardized regression coefficients resulting from the least square regression model for late-life *BrainAGE* scores in the male sample of the Dutch famine MRI study.

	Male sample		
	Standardized regression coefficient β	*p-value (before FDR-correction)*	*p-value (after FDR-correction)*
Chronological age	−1.10	***0.02***	0.07
Famine exposure group ('born before')	−1.40	***0.02***	0.06
Famine exposure group ('in early gestation')	−0.34	0.18	0.30
Birth characteristics			
Maternal age	−0.47	***0.007***	**0.04**
Gestational age	−0.09	0.54	0.76
Birth weight	−3.14	0.08	0.20
Birth length	2.50	0.10	0.22
Head circumference	1.03	***0.0007***	**0.02**
Ponderal index	1.76	0.14	0.26
Late-life health characteristics			
Body mass index	0.36	0.12	0.23
Systolic blood pressure	0.17	0.43	0.69
Diastolic blood pressure	0.00	0.98	0.98
Heart rate	0.58	***0.01***	**<0.05**
Non-fasting blood glucose	0.10	0.69	0.83
Cholesterol	−0.50	0.48	0.72
HDL	−0.04	0.91	0.95
LDL	0.13	0.84	0.92
Triglycerides	−0.08	0.75	0.86
Diabetes	−0.09	0.69	0.83
Medical treatment of Hypertension	0.47	***0.006***	**0.04**
Medical treatment of Hypercholesterolaemia	−0.08	0.62	0.83
History of CVA or TIA	−0.35	***0.01***	0.05
Current smokers	−0.27	0.06	0.16
Alcohol intake (>1 glass/week)	−0.47	***0.005***	**0.04**

CVA = cerebrovascular accident; TIA = transient ischaemic attack.

accounting for the multidimensional aging pattern across all voxels in the brain. With correlations of $r = 0.92$ between chronological age and estimated brain age in healthy adults, the *BrainAGE* framework has proven to be a straightforward method to accurately and reliably estimate structural brain age with minimal preprocessing and parameter optimization (Franke et al., 2010). Individuals with increased *BrainAGE* scores may thus be at risk for several neurodegenerative diseases and related functional declines. Profound relationships have already been observed between *BrainAGE* and disease severity, prospective worsening of cognitive functions (Franke et al., 2012a), conversion to Alzheimer's disease (Gaser et al., 2013), as well as diabetes mellitus type 2 (Franke et al., 2013). Furthermore, in elderly people, increased *BrainAGE* scores

Table 5
Least squares regression analyses for clusters of cognitive and neuropsychiatric measures, including *BrainAGE* scores, gender, and famine exposure as predictors.

	Model fit		Model parameter estimates (Standard error)		
	Adj. R^2	*p*	*BrainAGE score*	*Gender*	*Famine exposure*
Cluster 1 (AH4: Score, Trail Making Test A, Trail Making Test B, Stroop task: Reaction time, Stroop task: Score)	0.07	**0.016**	0.04 (0.06)	−1.02 (0.32) **	−0.00 (0.34)
Cluster 2 (Episodic memory: Immediate recall, Delayed recall, Retrieval, 15 Word test)	0.04	**0.05**#	−0.11 (0.06)	−0.67 (0.32)*	0.04 (0.34)
Cluster 3 (HADS: Anxiety score, Depression score)	0.00	0.73	0.03 (0.05)	−0.26 (0.26)	0.04 (0.27)

Bold type indicates statistical significance, with # denoting loss of significance after Bonferroni correction. *$p < 0.05$ **$p < 0.01$.

were explained by sex-specific sets of health parameters (Franke et al., 2014). Similar approaches for evaluating individual age-related atrophy scores also showed accelerated brain aging in schizophrenia ("schizophrenia gap"; Schnack et al., 2016), traumatic brain injury ("Predicted Age Difference" [PAD]; Cole et al., 2015), mild cognitive impairment and Alzheimer's disease ("Gaussian Process model [GP] z-scores"; Ziegler et al., 2014), as well as significant associations of individual brain aging with several health- and lifestyle-related risk factors in the general population ("Spatial Pattern of Atrophy for Recognition of Brain Aging" [SPARE-BA]; Habes et al., 2016b).

In adulthood, moderate dietary restriction was shown to elongate lifespan in a number of species, including humans (Fontana et al., 2010). However, increasing evidence suggests dietary restriction during prenatal life having the opposite effect, i.e. being related to a shortened lifespan as well as increased prevalence for non-communicable diseases in later life, including glucose intolerance, diabetes mellitus, cardio-vascular diseases, metabolic syndrome, hypertension, and obesity (Lillycrop and Burdge, 2011; Ozanne and Hales, 2004; Tarry-Adkins and Ozanne, 2014). This is probably due to a mechanism of permanent alteration of organ structure and metabolism occurring in the fetus in order to ensure survival of the organism under suboptimal conditions, as postulated by the thrifty phenotype hypothesis (Hales and Barker, 2001). Especially when confronted with a postnatal environment of adequate nutrition or even overnutrition, this early life programming to a suboptimal nutritional supply has tremendous effects on the lifespan and life-long health, as recently demonstrated in several epidemiological and

Table 4
Results of variable clustering for neuropsychiatric measures.

	Cluster 1 [$R^2 = 0.57$]		Cluster 2 [$R^2 = 0.62$]		Cluster 3 [$R^2 = 0.80$]	
	R^2 with own cluster	*coefficients*	*R^2 with own cluster*	*coefficients*	*R^2 with own cluster*	*coefficients*
AH4: Score	0.57	−0.446	–	–	–	–
Episodic memory: 15 Word test	–	–	0.40	0.400	–	–
Episodic memory: Immediate recall	–	–	0.68	0.524	–	–
Episodic memory: Delayed recall	–	–	0.94	0.613	–	–
Episodic memory: Retrieval	–	–	0.47	0.436	–	–
Stroop task: Reaction time	0.57	0.446	–	–	–	–
Stroop task: Score	0.60	−0.458	–	–	–	–
Trail Making Test A	0.49	0.415	–	–	–	–
Trail Making Test B	0.63	0.469	–	–	–	–
HADS: Anxiety score	–	–	–	–	0.80	0.707
HADS: Depression score	–	–	–	–	0.80	0.707

Underlining marks the most representative variable in each cluster.

experimental studies (Ozanne and Hales, 2004; Tarry-Adkins and Ozanne, 2014). As decreased fetal nutrient delivery due to MNR is not only common in developing but also industrialized countries (Baker et al., 2009; Beard et al., 2009; Black et al., 2008; Raznahan et al., 2012; Roseboom et al., 2006, 2011; Zhang et al., 2015), it is therefore relevant to study the effects of a suboptimal environment *in utero* on brain structure and its aging processes as this may help to further understand the factors and preconditions of individual brain aging trajectories and individual susceptibility to neurodegenerative diseases like Alzheimer's disease (Gaser et al., 2013).

Only few studies in humans have directly measured the effects of prenatal undernutrition on neuroanatomy (for a recent review please see Franke et al., 2017c), instead investigating the associations between brain morphology and size or weight at birth, which is an indirect measure for the fetal environment, with small size and low weight at birth resulting from prenatal undernutrition due to maternal undernutrition, placental insufficiency, extreme maternal vomiting or a multiple pregnancy. In a number of human samples, small size at birth and low birth weight has already been associated with altered brain morphology during gestation, in childhood, adolescence and well into older age. These alterations, including smaller total and regional brain volumes, reductions in cortical surface area and prefrontal cortical thickness, have also been demonstrated to correlate with neurobehavioral outcomes and impaired cognitive function, like slower processing speed and reduced executive functioning (Rogne et al., 2015). However, the effects of MNR on neuroanatomical aging in humans had not been explored yet, but a recent study in the Dutch famine cohort showed that prenatal exposure to famine in men is associated with smaller total brain volume in late adulthood (de Rooij et al., 2016). Utilizing the *BrainAGE* approach, which accounts for the multidimensional aging pattern across the brain, this study shows that prenatal famine exposure in men is also associated with a status of premature aging of the brain. Interestingly, the effects of MNR during early gestation on individual brain aging occurred in the absence of fetal growth restriction at birth, which stresses the significance of early nutritional conditions in life-long developmental programming.

In statistically explaining the observed variance in late-life *BrainAGE* scores in males, a combination of birth measures (i.e., maternal age, head circumference) and health characteristics (i.e., heart rate, hypertension, alcohol intake) emerged to be the most important predictors. This result is in line with recent (epidemiological large-scale) studies that demonstrated an association between lifestyle and health markers, especially markers of cardio-vascular disease and the metabolic syndrome, and differences in rate of brain atrophy and individual brain aging (Cole et al., 2017a; Debette et al., 2011; Franke et al., 2014; Habes et al., 2016a). However, all these predictors did not differ between male offspring, who were exposed to the Dutch famine during early gestation vs. those male offspring, who were born before the Dutch famine. Thus, the observed MNR-related increase in late-life *BrainAGE* scores in the male offspring, who were exposed to the Dutch famine during early gestation, can not be explained by increased cardio-vascular and diabetes pathology, although those incidences have previously been shown to be associated with exposure to MNR during early gestation (Painter et al., 2006; Roseboom et al., 2006). Rather, disturbances during early brain development due to fetal undernutrition in early gestation might additionally affecting individual brain structure in late-life, resembling patterns of premature brain aging. Given previously reported subtle but widespread MNR-induced disturbances of early organizational processes in cerebral development that result in major impairments of fetal brain development (Antonow-Schlorke et al., 2011; King et al., 2004), the brain microstructures might be more vulnerable to aging-related changes, thus leading to advanced atrophy. Since this study is a cross-sectional study, this issue needs to be illuminated further in future studies, including longitudinal studies and employing to-be-developed region-specific brain aging models.

As hypothesized and being in line with recent developmental programming models suggesting that long-term (health) outcomes of adverse *in utero* conditions will be more prominent in male than female offspring (Aiken and Ozanne, 2013), gender-specific *BrainAGE* analyses showed stronger effects of MNR due to exposure to famine during gestation on late-life *BrainAGE* scores in the male offspring. More specifically, in adult male offspring, who had been exposed to MNR during early gestation, *BrainAGE* scores were increased by more than 4 years as compared to men born before the famine, whereas adult female offspring, who had been exposed to MNR *in utero,* showed increases in *BrainAGE* of about one year only.

A potential alternative explanation for the sex differences we found may be that of selective survival of cohort members in the present study. We have previously demonstrated excess mortality up to the age of 63 years in female offspring exposed to famine in early gestation in the whole Dutch famine birth cohort (van Abeelen et al., 2012), which may have resulted in selective participation of women who were alive and in sufficient condition to be selected for participation in the present MRI study at age 67 years. Data on late-life health characteristics are somewhat inconclusive, showing increased cholesterol and HDL levels, but also revealing lower blood-glucose levels as well as fewer incidences of cerebrovascular accidents and transient ischaemic attacks in the female sample. This might lead to an underestimation of the effect of MNR on *BrainAGE* scores in the exposed female offspring due to better health conditions of the surviving females in the whole Dutch famine birth cohort compared to males. Therefore and because of the longer living of females in general, the effect of MNR on brain aging may take longer to evolve and thus to be discovered in the (surviving) female sample.

In human and animal studies, MNR-induced alterations in brain structure have also been associated with cognitive and behavioral deficits, behavioral and psychiatric disorders, as well as later-life neurodegenerative disorders (Ars et al., 2016; de Rooij et al., 2010; Faa et al., 2014; Keenan et al., 2013; Raznahan et al., 2012; Rodriguez et al., 2012). Also, advanced brain aging has been shown to be associated with increased cognitive decay and the risk of neurodegenerative diseases (Cole et al., 2017a; Debette et al., 2011; Franke et al., 2012a, 2013; Gaser et al., 2013; Habes et al., 2016a; Löwe et al., 2016). However, and in line with the study on differences of brain volumes in the same cohort (de Rooij et al., 2016), this study did not reveal any associations between *BrainAGE* scores or famine exposure to cognitive or neuropsychiatric measures. Again, an explanation for this may be that the Dutch famine birth cohort MRI subsample study was hampered by selective participation – as compared to the general population – of more healthy subjects, of whom nobody has ever been diagnosed with a depressive disorder, anxiety disorder, psychosis, schizophrenia, bipolar disorder, or obsessive-compulsive disorder.

There are a few limitations to the present study: First, neither the extent to which individual exposure to famine differed, nor the individual limitation of specific nutrient intake (like protein, folate, unsaturated fatty acids, and other micronutrients), shown to differently disrupt processes of early brain development (Georgieff, 2007; Ramel and Georgieff, 2014), is known. Second, it is not possible to disentangle the effects of the variable degrees of maternal stress or other prenatal environmental influences, and other influences, which may have affected fetal brain development (Symonds et al., 2000). Third, the conditions of the (immediate) postnatal environment and nutrition supply are also affecting general health and individual brain aging trajectories. After the Dutch famine, food situations improved over time, which may have positively affected brain development in later gestation, but did not compensate for the disturbances in early developmental programming and brain development due to undernutrition in early gestation. In the cross-sectional comparison analyses presented here, these potential influences during the life course on individual brain maturation and aging could not been separated from the life-lasting effects of perinatal nutrient delivery on neurodevelopment. However, direct effects of fetal undernutrition on the development of the central nervous system (CNS) were shown by a study, which reported that babies who had been exposed to the Dutch famine

during the first gestational trimester showed an increase in the prevalence of congenital anomalies of the CNS, including spina bifida and hydrocephalus (Stein et al., 1975). Additionally, the associations of individual *BrainAGE* scores with cognitive and neuropsychiatric performances are still indistinct in cognitively healthy and non-diseased samples. Further research will investigate this issue in epidemiological samples. Fourth, condensing whole-brain voxel-wise information into a single number by brain age prediction models is eventually criticised as being overly 'black box'. Especially, critics are stressing that by lumping together all information derived from brain scans for predicting age or being unclear about exactly which features brain age prediction is based on, important neuroscientific information may be disregarded. However, no one single part of the brain is the sole driver of aging as age-related changes to the brain are subtle, non-linear, spatially distributed and vary between individuals. Thus, the advantage of brain age paradigms is that the machine learning algorithm can be trained with a wide range of different phenotypes of healthy/normal brain structure, which avoids reductively focusing on some group average – most likely being unrepresentative of any single individual. Additionally, large areas of relatively small changes in age-related brain structure might actually contribute as much to the model of healthy/normal brain aging as small areas of relatively large changes in age-related brain structure, thus only considering large changes would result in reduced accuracy of the brain age prediction model (for a more thorough discussion of this issue please refer to Cole and Franke, 2017).

In conclusion, prenatal undernutrition is associated with a status resembling premature aging of brain structure in men during late adulthood. Future work should explore the effects of several factors of maternal stress during pregnancy (e.g. malnutrition, maternal obesity and diabetes, smoking during pregnancy, twin pregnancy, placental insufficiency, anxiety) on neuroanatomical maturation and aging in order to identify subtle, yet clinically-significant, changes in brain structure, thus contributing to a better understanding of the consequences of prenatal environment on life-long brain health as well as to an early diagnosis of neurodegenerative diseases and facilitating early treatment or preventative interventions, e.g. by adequately feeding women during pregnancy in order to prevent chronic diseases in future generations. Additionally, gender-specific mechanisms should be taken into account in future studies.

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