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ORIGINAL ARTICLE

Self-reported depression and anxiety after prenatal famine exposure: mediation by cardio-metabolic pathology?

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Evidence from previous studies suggests an association between prenatal exposure to famine and increased risk for depression. The aim of this study was to investigate whether prenatal exposure to the Dutch famine is associated with self-reported depression/anxiety and whether a potential association is mediated by the presence of cardio-metabolic disease. A total of 819 persons, born as term singletons around the 1944–1945 Dutch famine, filled out the Hospital Anxiety and Depression Scale (HADS) and were asked about their medical history. As indicators of cardio-metabolic disease we included type 2 diabetes (T2D), hypertension and coronary heart disease (CHD). In the total study population, exposure to famine during early gestation was associated with the presence of self-reported mild-to-severe anxiety. Evidence was found for several interactions between exposure in early gestation and sex. Subsequent analyses according to sex showed that men exposed to famine during early gestation scored higher on the HADS depression scale. Self-reported mild-to-severe anxiety symptoms were more prevalent among early exposed men. No such differences were found in women. T2D and hypertension were not correlated with any of the depression and anxiety measures. Adjusting for the presence of CHD did minimally attenuate the size of the reported associations. In conclusion, the present results do not match those previously reported in prenatally famine-exposed individuals. We found only weak evidence for an association between prenatal famine exposure and symptoms of depression and anxiety, which was shown exclusively in men exposed during early gestation.

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Introduction

A number of studies have suggested that exposure to adverse conditions during prenatal life may predispose to depression and anxiety in later life. Offspring of mothers treated with the synthetic non-steroidal estrogen diethylstilbestrol (DES) during a large part of pregnancy, more often suffered from depression and anxiety than offspring of untreated mothers.[1] Exposure to an influenza epidemic during mid gestation was related with an increase in the proportion of hospital diagnoses of major affective disorder.[2] Exposure to severe maternal stress in the form of a major earthquake in China during any period of gestation was associated with increased levels of severe depression and overall depressive symptoms.[3]

During the last winter of World War II between November 1944 and May 1945, a severe food shortage struck the western cities in the Netherlands. Brown *et al*. used the Dutch Psychiatric Registry to investigate the possible role of prenatal exposure to the Dutch famine in the development of major affective disorder.[4,5] Results showed that exposure to famine during mid or late gestation was associated with a higher risk of being hospitalized for major affective disorder. The effect was shown to be larger in men than in women.

Stein *et al*. recently studied quality of life and self-reported depressive symptoms, respectively, with the Short-Form Health Survey and the Center for Epidemiologic Studies Depression Instrument in 923 men and women of whom 411 had been exposed to the Dutch famine before conception or during gestation.[6] It was shown that prenatal famine exposure and especially pre-conceptional famine exposure was associated with poorer mental health-related quality of life and increased self-reported depressive symptoms in men and women.

Prenatal exposure to a poor environment may lead to increased depression and anxiety by means of a process called fetal programming. Poor circumstances *in utero* may elicit permanent physiological and metabolic alterations predisposing to disease in later life.[7] Depression and anxiety may result from fetal programming of the central nervous system,

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particularly of regions and/or hormonal systems contributing to emotional processing.[8] Alternatively, it may result from fetal programming of cardiometabolic disease, indirectly increasing the risk for depression and anxiety disorder.

Among people suffering from diabetes and cardiovascular disease, a large proportion has psychological problems of which depression and anxiety disorder are the most prevalent. Persons with diabetes have a two-fold increased risk of suffering from depression as well as having an increased risk of suffering from anxiety symptoms.[9,10] Diabetes and anxiety symptoms are also largely affecting those with cardiovascular disease.[11] These psychological problems may arise due to the sense of threat and loss related to being diagnosed with the disease as well as the burden of medication use, quality of life hampering disease complications and associated necessary lifestyle changes.[12,13] Another explanation may be that cardiometabolic diseases bring about endocrinological and/or vascular changes which may increase the risk for developing depression and anxiety symptoms.[14,15]

In our own Dutch Famine Birth Cohort (which does not include the same people as the cohort used by Stein *et al.*), we have shown that prenatal famine exposure is associated with increased risk for diabetes and cardiovascular disease.[16] In this study, we set out to investigate whether depression and anxiety symptoms are increased among the prenatally famine-exposed members of the Dutch Famine Birth Cohort. Furthermore, we investigated whether a potential association between prenatal famine exposure and depression and anxiety could be mediated by the increased presence of cardio-metabolic disease.

Method

Participants and selection

All singleton babies born alive in the Wilhelmina Gasthuis (a local hospital in Amsterdam, the Netherlands) between 1 November 1943 and 28 February 1947 were candidates to be included in the Dutch Famine Birth Cohort. We excluded those whose birth records were not available (1%) or those who were born prematurely (8.9%, gestational age below 259 days). In all, 2414 men and women were included in the study. The population registry of Amsterdam traced 2155 (89%) of the 2414 included babies. Of these, 160 babies had not been registered in Amsterdam at birth, 328 people had died, 213 people had emigrated, 157 people refused permission to record their address, 125 people were not traceable to a current address, and eight people requested their address to be removed from the study's database. At the start of the study in 2002, 1423 individuals (66%) were eligible and invited to participate. 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.

Exposure to famine

The official daily food-rations for the general population of 21 years and older were used to define exposure to famine.[17,18] A person was considered to be prenatally exposed to famine if the mother's average daily food-ration during any 13-week period of gestation contained less than 1000 calories. Babies born between 7 January 1945 and 8 December 1945 had accordingly been exposed *in utero*. In correspondence with all 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 between 1 November 1943 and 6 January 1945 and people born between 9 December 1945 and 28 February 1947 were considered unexposed and acted as the control group.

Self-reported depression and anxiety

A Dutch translation of the Hospital Anxiety and Depression Scale (HADS) was administered.[19] The HADS has two subscales: a depression subscale (HADS-D, seven items, range 0–21) and an anxiety subscale (HADS-A, seven items, range 0–21). Cronbach's alpha was 0.80 for the HADS-D items and 0.83 for the HADS-A items, indicating good internal consistency. Mild depressive symptoms were defined as a score of 8–10 points on the HADS-D, moderate depressive symptoms as a score of 11–14 points and severe depressive symptoms as a score of 15–21 points.[19] Anxiety was classified in the same way using HADS-A. Mild-to-severe depressive or anxiety symptoms were thus present in those scoring eight points or higher on the respective scales. This cut-off score has been shown to be the most optimal to detect caseness for both anxiety disorders and depression based on the ICD-9 in a community-based survey, as well as in most other patient-based studies.[20,21]

In a standardized interview, participants were asked whether they had ever during their lifetime been diagnosed with depression by a professional health-care provider. We asked the same question with regard to an anxiety disorder.

Cardio-metabolic disease

As indicators of cardio-metabolic disease, we included type 2 diabetes (T2D), hypertension and coronary heart disease (CHD). T2D was defined as taking anti-diabetic medication or a fasting glucose level of >7.0 mmol/l and/or a 2-h glucose level of >11.0 mmol/l based on a standard oral glucose tolerance test. Hypertension was defined as taking anti-hypertensive medication or a systolic blood pressure of >140 mmHg and/or a diastolic blood pressure of >90 mmHg. Blood pressure was measured in duplo on two occasions (morning and afternoon) using an automated device. Mean blood pressure was defined as the average of all available measurements. CHD was defined as the presence of one or more of the following: angina pectoris according to Rose/WHO questionnaire; Q-waves on an electrocardiogram (ECG; Minnesota codes 1-1 or 1-2) or a history of coronary revascularization (angioplasty or bypass surgery).

Possible confounders and covariates

Information about the mother, the course of the pregnancy and the size of the baby at birth was extracted from the detailed medical birth records.[22] Socio-economic status (SES) at birth was derived from the occupation of the family head dichotomized into manual and non-manual class. Information about current SES and lifestyle was obtained in a standardized interview. We asked the participant whether he or she smoked and whether he or she consumed alcohol. We considered drinking at least one alcoholic consumption per week a positive answer. We asked whether the subject currently participated in sports and considered participating in sports for at least 1 h per 14 days a positive answer. We defined current SES according to ISEI (International Socio-Economic Index)-92, which is based on the participant's or their partner's occupation, whichever status is higher.[23] We measured height and weight and calculated body mass index.

Statistical analyses

We used *t*-tests to analyze the differences in birthweights between the total, eligible and participating groups of cohort members. We applied Spearman's ρ to analyze correlations between the scores on the HADS-D and HADS-A scale, the self-reported history of diagnosis of depression or anxiety disorder, possible confounding variables and cardio-metabolic diseases. To investigate the effects of sex and prenatal famine exposure on HADS scores, HADS categories and the self-reported history of diagnosis of depression or anxiety disorder, we used linear and logistic regression analyses. We tested for possible interactions between sex and famine exposure by introducing an interaction term sex $\times$ famine exposure to the models. Total depression and anxiety scores showed a right-skewed distribution with score zero included. To be able to perform regression analyses on the HADS scores, we performed a log $(x+1)$ transformation, which largely normalized the distributions.

To examine whether presence of cardio-metabolic disease mediated a possible association between famine exposure and depression/anxiety, we added the variables T2D, hypertension and CHD to the models.

As the numbers of our study groups and cases in study groups were small and the amount of possible confounders large, we did not adjust for all possible confounders at the same time, but instead adjusted for maternal characteristics (maternal age, maternal weight at the last antenatal visit, maternal parity, socio-economic status), birth characteristics (birth weight, gestational age) and adult characteristics (marital status, currently being employed, current socio-economic status, smoking, alcohol drinking, practicing sports) separately. Finally, we also constructed a regression model adjusting for all confounders that showed an association with the dependent variable with a $P<0.20$.

We considered differences to be statistically significant if $P<0.05$. Where *P*-values are given, they are two-sided.

Results

Population characteristics

Of the 1423 eligible persons, 740 visited the hospital, 70 were visited at home and 50 were interviewed by telephone (but the HADS questionnaire was filled out at home). Those who participated had mean birth weights similar to those of eligible people not participating (3350 g *v.* 3359 g, $P=0.73$) and similar to those of the original cohort of 2414 people (3350 g *v.* 3344 g, $P=0.77$). The participation rates were 63% for those born before the famine, 71% for those exposed in late gestation, 66% for those exposed in mid gestation, 56% for those exposed in early gestation and 52% for those conceived after the famine. Of the 860 men and women included in the study, 819 had complete data on the HADS questionnaire (Table 1).

Depression and anxiety

Total score on the HADS-D scale was significantly correlated with the self-reported history of diagnosis of depression ($\rho=0.23$, $P<0.001$). Total score on the HADS-A scale was significantly correlated with the self-reported history of diagnosis of an anxiety disorder ($\rho=0.10$, $P<0.01$). Total scores on HADS-D and on HADS-A were also correlated ($\rho=0.57$, $P<0.001$).

Table 2 shows that the mean HADS-D score was 3.3 and the mean HADS-A score was 5.5. HADS-A scores were higher in women ($P<0.01$ based on regression analysis). HADS-D score was significantly correlated with marital status ($\rho=-0.12$, $P<0.01$, meaning that being married was significantly correlated with a lower score), currently being employed (-0.12, $P<0.001$), current SES (-0.16, $P<0.001$), smoking (0.13, $P<0.001$), and sports participation (-0.14, $P<0.001$). HADS-A score was significantly correlated with marital status (-0.10, $P<0.01$), currently being employed (-0.13, $P<0.001$), current SES (-0.09, $P=0.01$) and alcohol consumption (0.07, $P=0.03$). The way in which people participated in the study (hospital visit, home visit or telephone interview) was not correlated with depression or anxiety scores.

The presence of hypertension or T2D was not significantly correlated with depression or anxiety symptom scores ($\rho=0.01$ and 0.05, respectively, for HADS-D and 0.03 and 0.02 for HADS-A). Having CHD was significantly correlated with the HADS-D score (0.11, $P<0.01$), and borderline significantly correlated with the HADS-A score (0.06, $P=0.13$).

Self-reported mild-to-severe depressive symptoms (HADS-D score $\geqslant 8$) were present in 10.7% of the study population and self-reported symptoms of mild-to-severe anxiety (HADS-A score $\geqslant 8$) were present in 22.6%. A total of 9.0% reported ever having been diagnosed with depression. Diagnosis of an anxiety disorder was reported by 2.0%. Women more often had symptoms of mild-to-severe anxiety ($P<0.001$) and more often reported to have been diagnosed with depression ($P=0.05$) or an anxiety disorder ($P=0.02$).

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Table 1. *General, maternal, birth and adult characteristics according to prenatal exposure to the Dutch famine*

Exposure status	Born before famine	Exposed in late gestation	Exposed in mid gestation	Exposed in early gestation	Conceived after famine	All (S.D.)	*N*
General characteristics							
N	253	138	121	75	232	819	819
Men (%)	46.2	44.2	37.2	41.3	49.6	45.1	819
Age (years)	59.3	58.5	58.3	58.0	57.4	58.4 (1.0)	819
Maternal characteristics							
Age at delivery (years)	28.8	31.2*	28.7	27.1*	28.4	28.9 (6.3)	819
Weight gain third trimester (kg)	2.8	0.0*	4.6*	5.0*	3.4	2.9 (2.9)	570
Weight at last antenatal visit (kg)	66.3	62.5*	63.9*	69.0	68.7	66.2 (8.5)	722
Primiparous (%)	37.2	18.8*	33.9	44.0	39.7	34.9	819
Manual (%)	80.7	75.2	68.0	58.5*	68.2	72.1	656
Birth outcomes							
Gestational age (days)	285	283	285	289*	285	285 (11)	703
Birthweight (g)	3386	3182**	3187**	3460	3439	3344 (463)	819
Adult characteristics							
Married (%)	73.9	75.0	82.5	70.3	77.5	76.1	806
Currently employed (%)	47.6	47.1	56.7	52.7	59.2	52.6	808
Socio-economic status	48	52	51	47	50	50 (14)	808
Current smoker (%)	21.3	26.8	26.4	36.0**	23.0	24.8	817
Alcohol consumption (%)	69.2	64.5	57.0**	70.7	69.6	66.8	817
Sports participation (%)	56.1	58.7	58.7	60.0	53.7	56.6	816
Body mass index (kg/m^2)	28.7	28.2	28.2	27.8	29.0	28.5 (4.9)	776
Type 2 diabetes (%)	15.0	14.5	13.2	18.7	11.6	14.0	819
Hypertension (%)	46.6	52.9	48.8	41.3	44.0	46.8	819
Coronary heart disease (%)	6.3	5.1	4.9	8.3	7.4	6.4	704

Data are given as means and standard deviations, except where given as numbers and percentages.
*Statistically significant difference ($P < 0.05$) compared to participants unexposed to famine during gestation, based on linear or logistic regression analysis; **Adjusted for gender.

Table 2. *Self-reported depression and anxiety measures according to prenatal exposure to the Dutch famine*

Exposure status	Born before famine	Exposed in late gestation	Exposed in mid gestation	Exposed in early gestation	Conceived after famine	All
N	253	138	121	75	232	819
HADS-D score	3.1	3.3	3.3	3.8	3.3	3.3 (3.1)
HADS-A score	5.3	5.4	5.8	5.9	5.5	5.5 (3.3)
HADS-D ⩾8 points (%)	9.1	10.9	12.4	12.0	11.2	10.7
HADS-A ⩾8 points (%)	18.6	21.0	26.4	32.0*	22.8	22.6
Self-reported history of professional diagnosis of depression (%)	9.5	8.7	10.7	8.1	7.8	9.0
Self-reported history of professional diagnosis of an anxiety disorder (%)	2.0	2.2	3.3	1.4	1.3	2.0

Data are given as means (S.D.) and percentages.
HADS-A, anxiety scale of the Hospital Anxiety and Depression Scale; HADS-D, depression scale of the Hospital Anxiety and Depression Scale.
*Statistically significant difference ($P < 0.05$) compared to persons unexposed to famine during gestation, based on logistic regression analysis.

Prenatal famine and self-reported depression and anxiety

Table 2 shows that there were no differences between those exposed and those unexposed to famine during gestation in the depression and anxiety measures, with the exception of a higher percentage of participants exposed to famine during early gestation with HADS-A score ⩾8 (OR = 1.8, 95% CI: 1.1–3.1). A test for interaction between exposure groups and

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sex showed a significant interaction for early exposure and sex on HADS-D score ($P = 0.02$) and the self-reported history of diagnosis of depression ($P = 0.05$) and a trend towards a statistical significant interaction on the self-reported presence of mild-to-severe anxiety (score ⩾8; $P = 0.11$). We therefore split the cohort according to sex and reanalyzed the data.

Prenatal famine and self-reported depression and anxiety in men

Table 3 shows that men exposed to famine during early gestation had a higher HADS-D score (1.4 point, 95% CI: 0.3–2.7) compared to men prenatally unexposed to famine. Self-reported presence of mild-to-severe anxiety symptoms (score ⩾8) was significantly higher for men exposed during early gestation (OR 2.7, 95% CI: 1.2–6.1). In addition, men exposed in early gestation tended to more often report a history of diagnosis of depression than unexposed men (OR 2.6, 95% CI: 0.8–8.5).

Adjusting for possible confounders or covariates did not or only minimally attenuate the associations between exposure to famine in early gestation, HADS depressive symptoms score and the presence of mild-to-severe anxiety symptoms. The effect size of the association between early exposure in men and HADS depressive symptom score changed to 1.0 point (−0.1 to 2.4) when adjusting for maternal characteristics, 1.1 point (0.1–2.3) when adjusting for birth outcomes, and 1.1 point (0.1–2.3) when adjusting for adult characteristics. A model containing all possible confounding variables associated with depressive symptom score ($P < 0.20$) yielded an effect size of 1.1 point (0.1–2.3; adjusted for birth weight, currently being employed, current SES, smoking, alcohol consumption, and sports participation). The OR of the association between early exposure in men and presence of mild-to-severe anxiety changed into an OR of 2.8 (1.1–7.2) when adjusting for maternal characteristics, to an OR of 3.8 (1.5–9.3) adjusting for birth outcomes, and to an OR of 2.5 (1.1–5.8) when adjusting for adult characteristics. A model containing all possible confounding variables associated with the presence of mild-to-severe anxiety ($P < 0.20$) yielded an OR of 2.7 (1.1–6.5; adjusted for maternal weight at the last antenatal visit, birth weight, currently being employed and alcohol consumption).

Prenatal famine and self-reported depression and anxiety in men and cardio-metabolic disease

Since diabetes and hypertension were not correlated with any of the depression and anxiety measures, there was no further purpose in testing whether these variables mediated the association between prenatal famine exposure and self-reported depression/anxiety. Adjusting for the presence of CHD minimally attenuated the size of the associations between exposure to famine in early gestation in men and HADS-D score (1.1 point, 95% CI: 0.1–2.4) and the self-reported presence of mild-to-severe anxiety symptoms (OR 2.2, 95% CI: 0.9–5.3).

Table 3. *Self-reported depression and anxiety measures in men according to prenatal exposure to the Dutch famine*

Exposure status	Born before famine	Exposed in late gestation	CI for OR	Exposed in mid gestation	CI for OR	Exposed in early gestation	CI for OR	Conceived after famine	All
N	117	61		45		31		115	369
HADS-D score	3.1	3.0		3.1		4.9*		3.6	3.4 (3.1)
HADS-A score	4.5	4.7		5.1		5.8		5.1	4.9 (3.1)
HADS-D ⩾8 points	1.0 (ref.)	0.9	0.4, 2.4	0.6	0.2, 2.2	1.7	0.6, 4.7	1.0 (ref.)	
HADS-A ⩾8 points	1.0 (ref.)	0.7	0.3, 1.7	1.1	0.4, 2.5	2.7*	1.2, 6.1	1.0 (ref.)	
Self-reported history of professional diagnosis of depression	1.0 (ref.)	1.5	0.5, 4.4	1.2	0.3, 4.4	2.6	0.8, 8.5	1.0 (ref.)	
Self-reported history of professional diagnosis of an anxiety disorder	NA**	NA**	NA**	NA**	NA**	NA**	NA**	NA**	

Data are given as means (S.D.) and ORs.
HADS-A, anxiety scale of the Hospital Anxiety and Depression Scale; HADS-D, depression scale of the Hospital Anxiety and Depression Scale.
*Statistically significant difference ($P < 0.05$) compared to men unexposed to famine during gestation, based on linear or logistic regression analysis; NA**Not applicable, only one case in all men.

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Prenatal famine and self-reported depression and anxiety in women

Table 4 shows that depression and anxiety variables did not differ for women exposed to famine during any period of gestation compared to unexposed women (all $P > 0.15$).

Discussion

The present findings provide only weak support for an association between prenatal exposure to famine and depression and anxiety. Men exposed to famine during early gestation had a higher self-reported depressive symptoms score and a higher prevalence of self-reported mild-to-severe anxiety symptoms (HADS-A score $\geqslant 8$). In addition, based upon the present results, drawing a conclusion on potential mediation of the association between prenatal famine exposure and depression and anxiety by cardiometabolic disease was difficult.

Depression and anxiety disorder are different diseases with different epidemiology and etiology, although some overlap exists. Evidence was weak, but symptoms of both seemed to be increased in men exposed to famine during early gestation. This may seem surprising; however this finding does correspond to findings from a study into the effects of prenatal exposure to DES.[1] Children of DES mothers more often suffered from depression as well as anxiety disorder in later life, suggesting that both diseases may arise from poor circumstances *in utero*. However, although it has been shown that the HADS is able to differentiate between depression and anxiety, the correlation between the two scales was quite high (but consistent with correlations reported in other studies).[21]

Brown *et al.* showed in a very large study that exposure to famine during mid and late gestation was associated with an increased risk for hospitalization for major affective disorder.[4,5] Stein *et al.* showed that self-reported symptoms of depression were highest for those who were exposed in the pre-conceptional period.[6] These studies both found increased depression (symptoms) among men and women prenatally exposed the famine, with a difference in timing of the exposure. This study findings showed weak evidence for an effect of prenatal famine exposure on depression and anxiety symptoms in men only, again with a different timing of exposure, namely early gestation. Timing is considered crucial in fetal programming, in which fetal organs and systems are thought to be especially vulnerable to the effects of a reduced supply of nutrients during periods of rapid growth and development, so-called critical periods.[24] Furthermore, boys have been suggested to be more vulnerable to nutritional deprivation during critical periods of fetal development, because they grow faster than girls.[25] This fits with our data and possibly Brown's data, which showed larger effects in men than in women, but not with the data from Stein's study.

An explanation for the differences in timing can be put forward, but this is in no way sufficient to fully explain

Table 4. *Self-reported depression and anxiety measures in women according to prenatal exposure to the Dutch famine*

Exposure status	Born before famine	Exposed in late gestation	CI for OR	Exposed in mid gestation	CI for OR	Exposed in early gestation	CI for OR	Conceived after famine	All
N	136	77		76		44		117	450
HADS-D score	3.2	3.5		3.5		3.0		3.1	3.2 (3.0)
HADS-A score	5.9	6.1		6.3		5.9		5.9	6.0 (3.4)
HADS-D $\geqslant 8$ points	1.0 (ref.)	1.2	0.5, 2.7	1.7	0.8, 3.6	0.9	0.3, 2.8	1.0 (ref.)	
HADS-A $\geqslant 8$ points	1.0 (ref.)	1.2	0.7, 2.1	1.5	0.8, 2.6	1.3	0.7, 2.7	1.0 (ref.)	
Self-reported history of professional diagnosis of depression	1.0 (ref.)	0.8	0.3, 1.8	1.2	0.5, 2.5	0.4	0.1, 1.6	1.0 (ref.)	
Self-reported history of professional diagnosis of an anxiety disorder	1.0 (ref.)	1.2	0.3, 4.8	0.8	0.2, 4.0	0.7	0.1, 5.8	1.0 (ref.)	

Data are given as means (S.D.) and ORs.
HADS-A, anxiety scale of the Hospital Anxiety and Depression Scale; HADS-D, depression scale of the Hospital Anxiety and Depression Scale.

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the divergences. Brown *et al*. studied hospitalization for major affective disorder as outcome, which is certainly not the same as self-reported depression symptoms used as outcomes in the studies by Stein *et al*. and by us. In addition, Brown studied a population much younger than the other populations (ranging from 33–51 years compared to 57–59 years). It could be that in contrast to the participants exposed to famine in Brown's study, the men exposed to famine in early gestation and the participants exposed to famine in the pre-conceptional period in Stein's study are affected by a milder form of depression with a late life onset. These different forms of depression may be programmed during different stages of gestation.

The present data do not suggest mediation of the association between prenatal famine exposure and depression and anxiety by CHD. However, investigating mediation of a potential association between prenatal famine exposure and depression and anxiety turned out to be difficult. Diabetes and hypertension were both not correlated with depression and anxiety symptoms. Given that associations between famine exposure in early gestation in men and depression and anxiety symptoms were not strong, adjusting for the presence of cardiovascular disease may be questionable. Even more so because the prevalence of CHD was higher in those exposed to famine during early gestation compared to those unexposed, but the difference in CHD prevalence was not as large as that observed at age 50 years, possibly because those affected by CVD were less likely to participate at age 58 years.

Other limitations have to be taken into account as well. We based individual prenatal exposure to famine on the date of birth of the participant and calculating whether at least 13 weeks of gestation were spent in a period where the official food rations were below 1000 calories a day. Although we do not know the actual maternal nutritional intake, the official rations rather accurately reflect the variation over time in total food available.[17,18] As 60% of eligible cohort members participated in the study, selective participation may be a source of bias. However, the birthweights of participants and non-participants did not differ. Participation rates in the group exposed to famine in early gestation were somewhat lower compared to the other groups, possibly due to poorer (mental) health, which may have led to an underestimation of the reported effects. The sample size was relatively small, the statistical power to detect differences was limited and the reported effects may be due to chance, especially since we have tested quite a large number of associations. It could be hypothesized that the associations reported in this study are a result of selective fertility among certain groups in the population. However, this is unlikely as adjusting for variables associated with fertility, such as maternal age, weight, and SES at birth, did little to change the results. The HADS questionnaire we used is a self-report instrument developed for screening of depression and anxiety. Although the HADS cannot be used to clinically diagnose depression and anxiety, several studies have shown that it performs well in assessing severity of depressive and anxiety symptoms and has a reasonable sensitivity in identifying cases of depression and anxiety.[21,26,27] Overall, mean scores on the HADS-D and HADS-A scales in this study population corresponded well with those reported in other Dutch populations.[28] Correlations between the HADS scales and history of diagnosis of depression or anxiety disorder were low. However, this may not come as a surprise as it is known that few people with psychiatric symptoms seek professional help.[29] Another disadvantage is that history of diagnosis of depression or anxiety disorder was self-reported. Finally, we cannot rule out the possibility that the reported effects are caused by prenatal exposure to stress rather than famine. However, if this were the case, we would expect to find differences between people born before the famine and those conceived after the famine, which were not found.

In conclusion, this study findings provide only weak evidence for an association between exposure to famine in early gestation and increased depression and anxiety symptoms in men. These findings do not confirm previous findings with regard to effects of prenatal famine exposure on risk for depression.

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Statement of Interest

None.

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