Overweight and obesity in young men after famine exposure in utero and early infancy: A re-examination

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Abstract

Background

In 1976, researchers reported that young men are more likely to be obese after famine exposure in utero. The findings were based on examinations at military induction of men in the Netherlands who had been exposed to the Dutch famine of 1944-1945. We had the opportunity to re-examine the relation between prenatal famine exposure and height and weight at age 18-19 with current definitions for being overweight or obese and with modern analytic methods.

Methods and findings

We used height and weight information from 408,015 men in the Netherlands born between 1943-1947 and examined for military service at age 18-19. This group includes men with and without prenatal exposure to the Dutch famine of 1944-1945. We found that the odds for being overweight at age 18 were significantly elevated (OR=1.56; CI 1.23 to 1.97) among sons of manual workers born in the famine cities. Contrary to findings in the 1976 publication, no increase was seen among sons of non-manual workers born in the famine cities. This may reflect more limited access to food by poorer populations exposed to the famine period. The increase was limited to men exposed to famine during early gestation. The risk of obesity in this group was also elevated although the prevalence of obesity (0.4%) was low.

Conclusions

We show increases in being overweight at age 18 after prenatal famine in the Netherlands among sons of manual workers. Further studies are needed to examine the impact of these weight changes as a possible mediator of famine effects on later morbidity and mortality. The underlying mechanisms of these observations need further clarification.

1. Introduction

Studies of the Ukraine famine of 1932-1933 [1], the Dutch famine of 1944-45 [2, 3], and three famines in 20th century Austria [4] show a relation between Type 2 diabetes in later life with prenatal undernutrition. Studies from the Dutch famine show a 12% increase in mortality between ages 18-62 years [5] but no increase of deaths from cancer or cardiovascular disease [6]. Obesity data on young men examined for military service in the Netherlands are available to evaluate the effect of prenatal famine exposure. These have not yet been examined to address unresolved questions on long term famine effects with modern analytic methods. .

The circumstances of the Dutch famine (Hunger Winter) of 1944-45, with civilian starvation caused by conditions of war under German occupation, offer a special opportunity to study the relation between maternal nutrition in pregnancy and adult health and later mortality in the offspring [5-8]. The severity and widespread nature of the famine have been fully documented [8-10]. Contemporary reports show that the famine was the most severe in the cities of the Western Netherlands during the last months of the war, between the end of October 1944 and Liberation [9, 11, 12]. The famine ended with the surrender of the German forces to the Allied forces in May 1945, after which food supplies were rapidly distributed across the country.

In a highly influential 1976 study in the NEJM on the relation between prenatal exposure to the Dutch famine of 1944-45 and weight among young adult men, lower obesity rates were reported after famine exposure in late gestation and the first months of life and higher obesity rates after exposure in early and mid-gestation. These findings were seen in sons of manual and non-manual workers and were based on military examination records of male conscripts in the Netherlands born between January 1, 1944 and December 31, 1947 examined for military service at age 18 [13].

There is a need to re-examine these findings for several reasons: a) In the 1976 report, ‘obesity’ was defined as a weight/height ratio exceeding 120% of the population average. Currently, a person’s Body Mass Index (BMI: weight/height^2) is used to define being overweight (BMI of 25 or over) or obese (BMI of 30 or over) [14]; b) Famine exposure was defined by place and date of birth, but births in smaller urban conglomerations in the Western Netherlands or in rural areas across the Netherlands were not included; c) Weekly distributed food rations during the famine were not taken into account to define the period of most extreme famine in relation to the stage of gestation; d) There was a steep decline in births, especially among the manual (vs non-manual) socio-economic classes but the potential impact of selective fertility as a potential confounder of study findings has not been examined to date; and e) Further insights could be gained from analytic approaches that use all available individuals in the military records and apply difference-in-difference approaches and quantile regressions.

We therefore re-examined the relation between famine exposure at different gestation periods and body size at age 18. We use current definitions of overweight and obesity and include births from 1944-1947 in all regions of the Netherlands. We compare findings from alternative definitions of famine, including distributed food rations that take famine severity into account, and examine biases associated with ignoring selective fertility during the famine as this relates to social class. Our analyses examine relations with birth order and family size that might affect the study findings. We correct unrecognized contaminations of the study population, excluding individuals born outside the Netherlands and twin births and discuss the implications of the study findings.

2. Methods

2.1 Study population

We evaluated height, weight, and BMI at age 18 in male conscripts born between January 1, 1944 and December 31, 1947 and examined for military service in the Netherlands [13]. Physical examinations included all Dutch male citizens aged 18 years in the national population registers, except those living in psychiatric hospitals, in special institutions for the blind or for the deaf-mute (0.6%). For those not examined, the military record still provides full demographic information and relevant medical diagnoses provided by the psychiatric hospitals and special institutions. We excluded from analysis all men who had been born outside the Netherlands (2.5%). These had not been identified in previous reports.

2.2 Grouping by place of birth

The men were classified as births in ‘cities’ vs. ‘rural areas’ in five regions, based on the listing of the 45 municipalities with a population size of 25,000 or over (‘cities’) in January 1940 [15] as follows: 1. births in the West famine cities Amsterdam, Delft, Den

Haag, Haarlem, Leiden, Rotterdam, Schiedam, Utrecht, Vlaardingen and Voorburg; 2. births in the other Western cities of Alkmaar, Amersfoort, Bussum, Dordrecht, Gouda, Den Helder, Hilversum, Velsen, Zaandam, and Zeist; 3. births in the West rural areas; 4. births in the North/South/Eastern cities of Almelo, Apeldoorn, Arnhem, Bergen op Zoom, Breda, Deventer, Eindhoven, Enschede, Groningen, Helmond, Hengelo, 's-Hertogenbosch, Kerkrade, Leeuwarden, Maastricht, Nijmegen, Roosendaal, Tilburg, Venlo, and Zwolle ; and 5. births in the North/South/Eastern rural areas. Births in the municipalities of Ede, Emmen, Haarlemmermeer, Heerlen, and Rheden were classified as 'rural' although their total population size exceeded 25,000 because of their extreme rural character. Our grouping by place of birth was used to define three groups of main interest: 1. Births in West famine cities; 2. Births in other cities in the West or in the rural West; 3. Births in the remainder of the Netherlands. The grouping was also used to examine the robustness of study findings to the exclusion of rural births.

2.3 Grouping by month of birth

Individuals born in different months of birth between Jan 1944 and Dec 1947, defining famine exposure in relation to specific gestation periods. These definitions assume a uniform gestation period of nine months across cohorts as the average gestation was shortened by no more than 3-4 days at the height of the famine [8].

We first examined famine exposure based on pregnancy trimesters for individuals who had already been conceived at the time of the famine, from November 1944 onwards. Births between Nov 1944 and Jan 1945 were exposed in months 7-9 of gestation (Trim

3); births between Feb-April 1945 in months 4-6 of gestation and later (Trim 2+); and births between May-July 1945 in months 1-3 and later (Trim 1+). As the extreme famine period lasted less than nine months, births exposed in the first trimester and later were not exposed throughout gestation, although the total duration of prenatal famine exposure was the longest in this group. We also examined the relation of body size with famine exposure among individuals exposed in the first year after birth but found no effects. Consistent and statistically significant findings were only observed for births between May-July 1945. (Supplement Table 1 and Supplement Figure 1) We then compared study findings with alternative definitions of famine exposure incorporating information on distributed food rations and the classification used by the 1976 obesity study.

Using distributed food rations, we had earlier quantified famine exposure during specific trimesters of pregnancy as famine rations not exceeding 900 kcal/day on average in this trimester [5, 6]. By this definition, individuals exposed in the first trimester of gestation were born in Aug-Dec 1945 (T1); those exposed in the second trimester in May-Sept 1945 (T2); and those exposed in the third trimester in Feb-Jun 1945 (T3). We also defined individuals with famine exposure in the peri-conceptional period (births Nov 1945- March 1946) or in the immediate post-natal period (births Nov 1944-March 1945). These cohorts span five months, and adjacent cohorts have two months of overlap as individuals will meet the famine definition for two trimesters of pregnancy (Supplement Table 1 and Supplement Figure 1).

In the 1976 obesity study, the recruits were grouped in cohorts by month of birth "according to the period of exposure during gestation and early postnatal life, to test for the presence of critical periods with adequate numbers" as follows: exposed in the first trimester of gestation: births Oct-Dec 1945 (D2); exposed in the first and second trimester: births Jun-Sept 1945 (D1); exposed in the second and third trimester: births Feb-May 1945 (B2); exposed in the third trimester: births Oct 1944-Jan 1945 (B1). In this classification, the birth cohorts span four months, except for cohort D2 that spans three months [13]. Supplement Table 1 shows the three famine exposure classifications based on year and month of birth (Supplement Table 1 and Supplement Figure 1).

2.4 Socio-economic and demographic characteristics Father's occupation was classified as non-manual or manual. The non-manual group includes upper professional, lower professional, managerial and clerical occupations, and the manual group includes self-employed proprietors, craftsmen and foremen, shop assistants, operatives, process workers, domestic and other service workers, mine workers, and laborers. Farm workers and farm owners were classified separately in view of their likely easier access to food supplies during the famine. Deletion of this group did not change any of the study findings however and to retain as many individuals as possible all study results are presented with farmers included. Information on birth order and family size was extracted from the examination records to further examine previously reported associations with obesity at age 18. [16]

2.5 Study outcomes

We used measured height and weight to define Body Mass Index (BMI: weight/height^2) as a continuous measure and to define overweight and obesity for men with a BMI of 25 or more (‘overweight’) or 30 or more (‘obese’), respectively. We determined which individuals had a weight/height ratio of 120% or more relative to a standard population for comparison with previous analyses [13].

2.6 Statistical analysis

We created binary variables (1 if exposed, 0 otherwise) for all groupings of the birth cohorts defined by month of birth and also dummy variables to classify the five regions of birth. With regard to analytical methods, we quantify the long-term famine effects as the time*place interaction coefficients in our statistical models that include month and year of birth, place of birth, their interaction term (Difference-in-Difference approach), and selected covariates as they relate to height, weight, and BMI outcomes at age 18. The selected birth months reflect famine exposure in selected pregnancy trimesters or in the first year of life. Births in West famine cities (Famine) and remaining births in the West (Other) are compared to births born in the North/Eastern and/or the Southern Netherlands where there had been no famine. We thereby compared systematic differences in outcomes in the famine and non-famine regions for births throughout the period 1943-1947 and any deviations from the typical pattern in selected birth months.

We stratified by social class (sons of manual vs. non-manual workers) in view of the differences in overweight by social class and the decline in births during the famine that was especially pronounced among manual workers [8, 13].

To eliminate social class as a potential confounder of the relation between famine exposure and later health, we first limited our analyses to individuals who had already been conceived when the severe famine started in November 1944. We examined the robustness of these findings to the subset of city births, excluding all rural births.

We explored three-way interactions between birth cohort, birth region, and social class. Interactions with birth order (first vs higher order births) rather than social class show no consistent relation and are not separately reported. We examined individuals meeting current definitions of being overweight or obese and of the measure of obesity as previously reported (weight/height ratio of 120% or more) [13] in logistic regression models. We further examined height and body mass index as a continuous variable in linear regression models, using quantile regressions to examine the relation of famine exposure to BMI at age 18 across the entire range of the BMI distribution. This shows if the relationship between famine exposure and BMI depends on which quantile of the distribution is being examined and if the use of BMI based binary outcomes of being overweight or obese is adequate to summarize the findings.

Ignoring the potential impact of selective fertility during the famine, we then examined the robustness of the findings to using all births between Jan 1944 and Dec 1947 with all pre-famine and post-famine births as time controls. We also examined the robustness of study findings to excluding individuals born in ‘rural’ areas across the country and also to the choice of different controls, defined as either births in the North and East only, or births in the South only, or births in the North/East and South combined. As the results did not differ, we here only report the findings using all births and combining all controls.

3. Results

The number of men included in the military examination files born between January 1944 and December 1947 is 408,015. We excluded 10,381 men (2.5%) who were born outside the Netherlands and a further 26,530 men (6.5%) because of incomplete information on height, weight, or place of birth. The remaining 371,104 men were classified as born in cities vs. rural areas based on the 1940 enumeration of municipalities with a population size of 25,000 or over. Considering births in specific regions, this results in the following categories: Births in the West famine cities (n=94,250); births in the other Western municipalities (n=17,690) or West rural areas (n=56,223) for a total of 73,913 births, and births in the North/South/Eastern cities (n=60,562) or North/South/Eastern rural areas (n=142,379) for a total of 202,941 births. (Table 1)

3.1 Demographics by region of birth

Table 1 shows selected characteristics for the study population of 371,104 men, separately for births in the famine cities in the Western Netherlands, other births in the Western Netherlands, and births outside the Western Netherlands. The mean height of the conscripts was 177.4 cm and mean Body Mass Index was 21.58. The proportion of men who at age 18 were overweight is 6.7%, of men with a weight/height index over

120% is 1.6%, and of men who were obese is 0.4%. The proportion of first-born males was higher in the famine cities of the Western Netherlands compared to the remainder of the country. The proportion of births in municipalities with a population of 25,000 or more in 1940 was 46.5% in the country as a whole but only 29.8% outside the Western Netherlands.

3.2 Overweight and obesity by month and region of birth

Table 2 shows overweight, weight/height over 120%, and obesity status for the study population by selected birth months and region of birth. Being overweight was somewhat more common (7.0%) among recruits born in the Western Netherlands famine cities compared to recruits born in other parts of the West (6.3%) or elsewhere in the Netherlands (6.7%). Variations in overweight status for births in specific months by region are hard to evaluate because of limited sample size, although a secular trend in increasing BMI is evident from the increase from 5.9% among births in 1944 to 7.3% among births in 1947 considering births in West famine cities. A similar pattern is seen for births outside the Western famine cities.

3.3 Excess overweight by date and place of birth

In Table 3 we present logistic regression results for the cross-product odds of being overweight for births in the Western famine cities (Famine) and births on the remainder of the West (Other) relative to births in the North, East, and South region combined (Control area) for the 138,962 births who had already been conceived at the time of the famine. The odds for being overweight at age 18 after famine exposure starting in the first trimester of gestation were significantly elevated (OR=1.56; CI 1.23 to 1.97) for births in Western famine cities whose fathers had manual occupations. No change was seen for births in the West from non-manual backgrounds or for births in the West outside the famine cities. These results did not change (OR=1.50; CI 1.09 to 2.05) when analyses were limited to subset of urban births in this group (n=60,489) although because of smaller number we see somewhat wider confidence intervals. (Supplement Table 2)

In Supplement Table 3, we present results for all births, ignoring the potential effects of selective fertility by social class. The odds for being overweight are somewhat smaller (OR=1.28; CI 1.07 to 1.54) than before. In all study groups, the odds for being overweight were indistinguishable from unity for births exposed to the famine in any of the other pregnancy trimesters or in the first year of life.

For obesity, famine city births exposed in the first trimester of gestation show an increase relative to controls (OR=1.62; 95% CI: 0.93 to 2.84, combining manual and non-manual births, and ignoring selective fertility). This estimate is based on only 0.4% of births however and further stratified analyses give unstable estimates for further subgroups. For the other exposure trimesters the odds for being obese at age 18 cannot be distinguished from unity. We found no increase in height in relation to prenatal famine exposure and therefore expressed all weight changes in terms of BMI.

Quantile regression results on height and BMI as continuous outcomes

In Supplement Table 4 and Supplement Figure 2 we present the quantile regression results from cross-product regressions representing the specific effects of famine exposure starting in the first trimester of gestation. Within each selected BMI quantile, the quantile regression coefficient represents the BMI change for individuals born in the Western famine cities in a specific trimester of gestation relative to unexposed controls born during the same months in the North, East, or South of the country. Coefficients for individuals born in the West of the country but outside the famine cities are not reported separately as they do not differ from unexposed controls. All analyses are adjusted for social class and birth order.

Combining all quantiles, the BMI increase at age 18 relative to controls is 0.23 BMI units (95% CI: 0.15 to 0.31) for individuals exposed to famine starting in the first trimester of gestation, There is a consistent BMI increase across all quantiles for individuals exposed in the first trimester of gestation but the largest increase is seen only beyond the 90th BMI percentile, especially beyond the 98th percentile, corresponding to the 1976 weight/height ratio over 120%, and the 99th percentile, corresponding to the obesity cut-point (extreme 0.4% tail). In our data, a weight/height ratio exceeding 120% corresponds to a BMI value between 27 and 28.

No significant BMI increases are seen after famine exposure in starting the second or third trimester of gestation. The increase was 0.06 BMI units (95% CI: -0.02 to 0.14) and 0.04 BMI units (95% CI: -0.04 to 0.12) respectively in these trimesters. After third trimester exposure, there was a consistent marginal BMI increase across the lower quantiles and BMI decrease beyond the 90th BMI percentile which reached statistical significance only beyond the 98th percentile. No relation is seen between any of the famine exposure trimesters and height at age 18.

3.4 Comparison with other exposure definitions

We evaluated the robustness of our month of birth based famine exposure definition in two ways. First by using distributed food rations during the famine to define the severity of famine exposure [5, 6]. Second by comparing our results with the 1976 obesity study when the cohorts were defined as ‘critical periods of famine exposure with adequate numbers’ [13].

Using, for convenience, the 1976 obesity definition based on weight for height, it can be seen (Supplement Table 5, ignoring selective fertility) that the ‘obesity’ increase at age 18 in West famine city births for individuals exposed to famine starting in the first trimester of gestation by our definition (Births May-July 1945; OR 1.44; CI: 1.12 to 1.85) is in close agreement with the increase for individuals exposed to famine in second trimester of gestation according to the food ration based definition (births May-Sept 1945; OR 1.40; CI 1.09 to 1.79) and with the increase for individuals exposed in the D1 cohort ‘exposed in the first and second trimester’ according to the definition based on ‘critical period with adequate numbers’ (births Jun-Sept 1945; OR 1.42 CI: 1.19 to 1.79). All definitions points towards elevated odds for BMI increases after famine exposure starting in early pregnancy (births May-Sep 1945) in the Western famine cities.

4. Discussion

We set out to re-examine and update previously reported findings of increased obesity in young men after prenatal exposure to the Dutch famine of 1944-45. We found no increase in height in relation to prenatal famine exposure and therefore expressed all weight changes in term of BMI. In a previous study of height in this cohort we found a strong relation with education, father's occupation, region of birth, family size and religion [17] but did not examine height in relation to prenatal famine.

We evaluated the impact of the famine on body weight in terms of BMI as this provides the most useful population level measure of obesity [14] and of the accumulation of excess body fat associated with long term morbidity and mortality. Unfortunately BMI does not capture specific differences in individual body fat distribution that are likely to be also important for long term health, but these measures would only provide additional rather than primary information at the population level and were not available in our study population.

We found a general increase in BMI and an increase in overweight prevalence (OR=1.56; CI: 1.23 to 1.97) for sons of manual workers born from May-July 1945 in the West famine cities, corresponding to prenatal exposure starting in the first trimester of gestation (Table 3). No overweight increase was seen in sons of non-manual workers. These findings did not change for analysis limited to city births. (Supplement Table 2)

The increase in overweight in sons of manual workers was somewhat attenuated after the inclusion of births who had been conceived during or after the famine (OR=1.28; CI; 1.07 to 1.54) (Supplement Table 3). This remaining group of births had not yet been conceived when the famine started and could be subject to residual confounding by social class of the relation between prenatal famine and overweight status at age 18. This demonstrates that stratification by social class (manual vs non-manual) appears to be effective in removing most confounding of the relationship between famine exposure and adult weight related to selective fertility.

BMI associations with prenatal famine starting in the first trimester of pregnancy were most pronounced at the extreme upper tail of the BMI distribution. This should be considered when interpreting the stronger associations between dichotomized measures of BMI at higher cut-off points, including an weight to height ratio over 120% (corresponding to a BMI value between 27-28) (overall prevalence 1.6%) and obesity (overall prevalence 0.4%). Dichotomized outcome measures should be chosen carefully with a specific purpose in mind as they do not appropriately represent the impact of famine on the overall BMI distribution.

There was no increase in BMI or overweight for births May-July 1945 in the remainder of the West. Outcomes in this group did not differ from births in the same months in the North/East or South of the country. These findings confirm that the impact of famine was most pronounced among births in the cities in the West, as previously suggested by contemporary accounts [9] and regional mortality data [18] but not yet confirmed in individuals nationwide.

Contrary to the 1976 report, we found no decrease in BMI among births exposed at the end of gestation (B1). The quantile regressions in this group show no impact of prenatal famine across most of the BMI distribution. A strong negative relation is only seen beyond the 98th BMI percentile of the distribution based on very small numbers. In this group, obesity measures do not reflect the overall lack of effect across most of the BMI distribution.

Our findings did not change when limiting controls to births before the famine (pre-famine time controls) or after the famine (post-famine controls). This reflects there were no long term BMI changes among births exposed to famine in the first year of life. The secular trend of BMI and overweight showing an increase over time for births 1944-1947 (examined for military service between 1962-1965) did not change our estimates for the impact of famine exposure of births in the Western famine cities. Age-related increases of BMI and overweight in this population generate no bias as all individuals underwent their medical examinations at the same age.

With regard to the regional characteristics of the study population, we recovered information on the births in rural areas that had not previously been used as a control population. Our stratification of municipality of birth in two groups (‘cities’ with a population of 25,000 or over vs ‘rural births’ in municipalities with smaller populations) shows that in individuals who had already been conceived at the start of the famine the increase in overweight at age 18 in sons of manual workers after famine exposure starting in the first trimester of gestation (Trim 1+) (OR=1.56; CI: 1.23 to1.97) did not change after the exclusion of rural births (OR=1.50; CI: 1.09 to 2.05).

We used additional information on the weekly distribution of food rations during the famine to define the period of most extreme famine, i.e. when average food rations did not exceed 900 kcal/day in specific pregnancy trimesters. [5, 6] We also compared our findings with the 1976 classification used by Ravelli et al. where the birth cohorts were defined by ‘critical periods of famine exposure with adequate numbers’ [13].

These comparisons show that the increase in overweight in individuals exposed to famine starting in the first trimester of gestation (births May-July 1945) correspond to the increase after second trimester (T2) exposure defined by food ration declines (births May-Sept 1945), and ‘first and second trimester’ (D1) exposure by the 1976 classification of ‘critical periods with adequate numbers’ (births Jun-Sept 1945). Supplement Table 1 shows the three famine exposure definitions by month of birth and Supplement Table 5 shows a comparison of the Ravelli obesity outcome across for all exposure definitions.

The findings of the three exposure classifications are consistent and all point towards elevated odds for overweight among sons of manual workers born in the Western famine cities who were exposed to famine from the beginning of gestation. These are also the individuals who were exposed to famine for the longest time in gestation.

Our estimate for the ‘obesity’ increase in births June-Sept 1945 in the famine area (D1 cohort) – ignoring selective fertility and social class- is somewhat more conservative (OR 1.42; CI: 1.13 to 1.79) compared to the 1.9 fold increase reported in 1976. [13]

On the role of birth order and family size [16] we found no relation of being overweight or obese by birth order. Because of the low obesity prevalence in the data (0.4%) we were not able to obtain stable estimates of the obesity risk in the separate birth cohorts for births in the Western famine cities or other Western municipalities, classified by father’s occupation and birth order.

In this analysis, possible twin births were included as they could not be distinctly labelled without a family identifier. We did however test the robustness of the results to the exclusion of 3,125 potential twin pairs in the data, based on individuals with an exact match on the following seven variables: date of birth, place of birth, family size, birth order, number of older brothers, paternal occupation and religion. The results did not change with the exclusion of these pairs.

There are several reasons why our results may differ from previous findings reported in 1976 [13]. We included all births in all regions in our analysis and employ a difference-in-difference approach, incorporating month and region of birth as main effects and their interactions, father’s occupation to classify manual and non-manual workers, and birth order in a single model. Such analyses go beyond the pairwise comparison of birth cohorts in one famine area and one control area and more effectively use all the available information in the data to reduce bias and increase precision. Our approach shows no relation between famine in early gestation and later BMI in sons of non-manual workers. In addition, we use quantile regressions to examine outcomes across the BMI distribution to understand. These show no overall decrease in BMI after famine in late gestation.

Information from other sources on overweight risk at older ages after prenatal famine exposure is scarce. In two birth cohorts from the West famine cities in the Netherlands, maternal malnutrition during early gestation was associated with a higher BMI at age 50-58 years in women, but not in men [19, 20]. The number of men in the combined studies did not exceed 750 however. In a systematic review of famine exposure and later BMI, including mostly studies of the Chinese famine of 1959-1961, a small increase was reported in being overweight (OR=1.10; CI: 1.04 to 1.16) or obese (OR=1.15; CI: 1.05 to 1.14) at ages 40-70 years [21]. In all the Chinese studies, outcomes in famine exposed individuals were compared to outcomes in individuals born after the famine. This could lead to uncontrolled age differences between famine and post-famine births and BMI differences that were mistakenly attributed to the famine [22].

The 1.6 fold increase in overweight at age 18 after prenatal famine exposure may point towards increases in mortality or morbidity in later life. In a follow-up of 5,103 deaths between ages 18-63 among 41,096 men in this study population, we found a 12% increase in mortality from all causes (CI: 1% to 24%) after prenatal famine exposure (defined by famine severity) in the first trimester of pregnancy [5] but no association with deaths from cancer or cardiovascular disease [6]. There was also some increase in deaths from other natural causes (Hazard Ratio=1.24; CI: 1.03 to 1.49) or external causes (Hazard Ratio=1.46; CI: 1.09 to 1.97) but mortality in the smaller categories of death is still too limited for meaningful interpretations. Further studies will be needed to examine the impact of weight changes at age 18 as a possible mediator of famine effects on later morbidity and mortality. This will be increasingly possible as the cohort ages and overall mortality has further increased. In other famine cohorts in the Netherlands with a clinical follow-up in late middle age, DNA methylation was demonstrated to be a mediator of the impact of early famine on BMI at age 58 years [23].

We speculate on other mechanisms that may underlie our study findings. Early life conditions have been associated with later life health as early as 1934 by ecological studies [24, 25]. David Barker interpreted these patterns as reflecting that poor nutrition at critical or sensitive time periods can change fetal development with life-long consequences [26]. The mismatch between prenatal and postnatal nutrition could then lead to later health problems, especially for the risk of developing cardiovascular disease ('predictive adaptive response' hypothesis). This theory was examined in a small study of sheep with apparent positive results [27] but larger studies of coronary artery disease in adults who were exposed to the Dutch famine during gestation show conflicting findings [28, 29]. DNA methylation studies of adults exposed to the famine also suggest that selective embryo survival is a more plausible explanation for the observed genome wide methylation patterns in adulthood than a predictive adaptive response [30].

5. Conclusions

In summary, using data on the national male population of 18-year old males in the Netherlands we report new findings of a 1.6 fold risk increase for being overweight at age 18 after prenatal famine exposure starting early in pregnancy. These births were exposed to the longest period of in utero famine. The increased risk is limited to sons of manual workers who were born in the famine cities in the West of the country, suggesting differences in food availability by social class. Our findings are confirmed by the use of three exposure definitions for prenatal famine based on date of birth, robust to modifications of the regions selected as controls. They are robust to the exclusion of individuals who were conceived during the famine. Further studies are needed to trace the impact of these weight changes in young adults on subsequent morbidity and mortality. The underlying mechanisms of these observations need further clarification.

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Funding acquisition: Lumey;

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All authors participated in conceptualization of the study outline, manuscript development and approved of the final paper.

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Competing interests

The authors have declared that no competing interests exist.

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Table 1

Selected characteristics for Dutch male conscripts born 1944-1947 and examined at age 18, by place of birth

Birth place	Western Netherlands Famine cities	Western Netherlands other cities and rural	Other Netherlands cities and rural	All
Number of subjects	94,250	73,913	202,941	371,104
Height (cm) **(sd)**	177.9 6.4	178.2 6.4	176.9 6.4	177.4 6.4
Body Mass Index (weight/ht2) (sd)	21.56 2.26	21.60 2.15	21.59 2.22	21.58 2.22
BMI ge 25 **(%)**	6,568 7.0	4,631 6.3	13,551 6.7	24,750 6.7
Obese (weight/height ge 120% of 1976 standard) (%)	1,689 1.8	1,045 1.4	3,242 1.6	5,976 1.6
BMI ge 30 **(%)**	441 0.5	250 0.3	859 0.4	1550 0.4
Father Manual Occupation **(%)**	45,323 48.1%	35,477 48.0%	106,456 52.5%	187,256 50.5%
First born **(%)**	35,219 37.4%	22,003 29.8%	60,335 29.7	117,557 31.7%
Births in municipalities with 25,000 population or over (%)	94,250 100%	17,690 23.9%	60,562 29.8%	172,502 46.5%

Table 2
Overweight and Obesity status by year and month and place of birth, Dutch male conscripts born 1944-1947 and examined at age 18

	Western Netherlands Famine cities				Western Netherlands other cities and rural				Other Netherlands cities and rural				All
Birth year and month	**Total births**	**BMI >=25 (%)**	**'Obese' Ravelli 1976 (%)**	**BMI >=30 (%)**	**Total births**	**BMI >=25 (%)**	**'Obese' Ravelli 1976 (%)**	**BMI >=30 (%)**	**Total births**	**BMI >=25 (%)**	**'Obese' Ravelli 1976 (%)**	**BMI >=30 (%)**	**Total births**
Jan-Oct 1944 Exposed to famine after birth	17596	1041 (5.9)	251 (1.4)	60 (0.3)	15306	851 (5.6)	169 (1.1)	38 (0.2)	40825	2373 (5.8)	524 (1.3)	133 (0.3)	73727
Nov1944-Jan1945 Trim 3 exposed	5023	266 (5.3)	50 (1.0)	11 (0.2)	4370	231 (5.3)	58 (1.3)	10 (0.2)	11171	659 (5.9)	131 (1.2)	42 (0.4)	6580
Feb-Apr 1945 Trim 2 and 3 exposed	5193	344 (6.6)	87 (1.7)	22 (0.4)	4884	300 (6.1)	58 (1.2)	10 (0.2)	13265	937 (7.1)	195 (1.5)	39 (0.3)	6788
May-Jul 1945 Trim 1,2 and early 3rd exposed	4683	361 (7.5)	105 (2.2)	29 (0.6)	4487	265 (5.9)	52 (1.2)	15 (0.3)	12159	780 (6.4)	173 (1.4)	45 (0.4)	7196
Aug1945-Jan 1946 Conceived during famine	5894	430 (7.3)	105 (1.8)	32 (0.5)	6309	392 (6.2)	87 (1.4)	22 (0.3)	24124	1644 (6.8)	416 (1.7)	120 (0.5)	7129
Feb-Dec 1946 Conceived and born after famine	31430	2357 (7.5)	607 (1.9)	158 (0.5)	21476	1457 (6.8)	350 (1.6)	91 (0.4)	54392	3776 (6.9)	968 (1.8)	265 (0.5)	8234
1947 Conceived and born after famine	24430	1779 (7.3)	484 (2.0)	129 (0.5)	17081	1135 (6.6)	271 (1.6)	64 (0.4)	47002	3382 (7.2)	835 (1.8)	215 (0.5)	7979
All births	94249*	6568 (7.0)	1689 (1.8)	441 (0.5)	73913	4631 (6.3)	1045 (1.4)	250 (0.3)	202938*	13551 (6.7)	3242 (1.6)	859 (0.4)	371100*

*One subject with unknown month of birth from Western Netherlands Famine cities and three from Other Netherlands.

Table 3
Overweight (BMI >=25) prevalence after prenatal famine exposure
Dutch male conscripts born in 1944-1947 in Dutch cities
Births already conceived at the time of the famine
Odds Ratios (95% CI) for births in Western Netherlands (Famine cities vs. Other West cities relative to unexposed controls by father's occupation(n=138,962)

Month of Birth	Father's Occupation	
	Manual	Non-Manual
	N=71,205	N=67,757
May-July 1945	Trim1+ Famine: 1.56 (1.23, 1.97) Other: 1.15 (0.88, 1.49)	Trim 1+ Famine: 1.18 (0.90, 1.54) Other: 0.90 (0.68, 1.18)

Famine: Western Netherlands famine cities; Other: Western Netherlands other cities and rural.
*Unexposed controls: Other Netherlands cities and rural births 1944-1947.

Supplement Table 1

Prenatal exposure to the Dutch famine
Alternative classifications based on month of birth

Classification criterion	Authors' designation of prenatal exposure period	Month of Birth	Outcome studied	Reference
Famine exposure during specific trimesters of pregnancy defined by stage of pregnancy in relation to Nov 1, 1944	Trim 3: early 3rd trimester Trim 2+: 2nd trimester and later Trim 1+: 1st trimester and later	Nov 1944 – Jan 1945 Feb 1945 – Apr 1945 May 1945 – Jul 1945	- Overweight (BMI ge 25) - 'Obese' (weight/height over 120%) - Obesity (BMI ge 30)	This study
Famine exposure during specific trimesters of pregnancy defined by average of food rations not exceeding 900 kcal/day in that trimester	T3: 3rd trimester T2: 2nd trimester T1: 1st trimester	Feb 1945 - Jun 1945 May 1945 – Sep 1945 Aug 1945 – Dec 1945	- Survival age 18-63 years, - Cause of death	Ekamper 2014, Ekamper 2015
Individuals grouped by month of birth to test for the presence of critical periods of famine exposure "with adequate numbers"	B1: 3rd trimester B2: 2nd/3rd trimester D1: 1st/ 2nd trimester D2: 1st trimester	Nov 1944 – Jan 1945 Feb 1945 - May 1945 Jun 1945 - Sep 1945 Oct 1945 - Jan 1946	- 'Obese' (weight/height over 120%)	Ravelli 1976

Supplement Table 2

Overweight (BMI >=25) prevalence after prenatal famine exposure
Dutch male conscripts born in 1944-1947 in Dutch cities
Births already conceived at the time of the famine
Odds Ratios (95% CI) for births in Western Netherlands (Famine cities vs. Other West cities relative to unexposed controls*
by father's occupation
(n=60,489)

Month of Birth	Father's Occupation	
	Manual	**Non-Manual**
	N=31,291	**N=29,198**
May-July 1945	Trim1+ Famine: 1.50 (1.09, 2.05) Other: 0.98 (0.57, 1.69)	Trim 1+ Famine: 1.37 (0.96, 1.96) Other: 0.87 (0.47, 1.62)

Famine: Western Netherlands famine cities; Other: Western Netherlands other cities.
*Unexposed controls: Other Netherlands cities

Supplement Table 3

Overweight (BMI >=25) prevalence after prenatal famine exposure
Dutch male conscripts born in 1944-1947
Odds Ratios (95% CI) for births in Western Netherlands (Famine cities vs. Other cities and rural) relative to unexposed controls* by father's occupation
All births, ignoring selective fertility
(n=371,104)

Month of Birth	Father's Occupation	
	Manual	**Non-Manual**
	N=187,256	**N=183,848**
May-July 1945	Trim1+ Famine: 1.28 (1.07, 1.54) Other: 1.05 (0.86, 1.24)	Trim 1+ Famine: 0.97 (0.79, 1.19) Other: 0.90 (0.72, 1.12)

Supplement Table 4

Quantile, linear and logistic regression BMI changes in Trim 1 exposed cohorts relative to unexposed controls Births Jan 1944 - Jul 1945

	Quantile regression				Logistic regression				
Quantile	**BMI change relative to controls**				**Cut-point**	**Odds for selected BMI grouping relative to controls**			
	kg/m^2	**95% CI**		**P-value**		**Odds ratio**	**95% CI**		**P-value**
0.01	0.21	0.00	0.43	0.06					
0.02	0.19	0.00	0.38	0.06					
0.03	0.17	0.01	0.32	0.04					
0.04	0.18	0.00	0.37	0.05					
0.05	0.26	0.10	0.42	0.00					
0.06	0.21	0.06	0.35	0.01					
0.07	0.16	0.05	0.26	0.05					
0.08	0.13	0.03	0.23	0.05					
0.09	0.15	0.02	0.28	0.02					
0.10	0.17	0.05	0.28	0.01					
0.25	0.25	0.14	0.37	0.00					
0.50	0.21	0.11	0.31	0.00					
0.75	0.20	0.08	0.31	0.00					
0.90	0.19	0.05	0.32	0.04					
0.91	0.22	0.07	0.38	0.01					
0.92	0.23	0.02	0.44	0.03					
0.93	0.30	0.04	0.55	0.02	**Overweight BMI ge 25**	1.17	1.01	1.36	0.05
0.94	0.34	0.09	0.59	0.01					
0.95	0.38	0.04	0.71	0.03					
0.96	0.45	0.07	0.82	0.02					
0.97	0.43	0.00	0.87	0.05					
0.98	0.44	0.04	0.84	0.03	**Obese Ravelli 1976**	1.45	1.09	1.94	0.04
0.99	0.56	-0.38	1.50	0.25	**Obesity BMI ge 30**	1.62	0.93	2.84	0.10
Linear regression	0.23	0.15	0.31	0.00					

Supplement Table 5

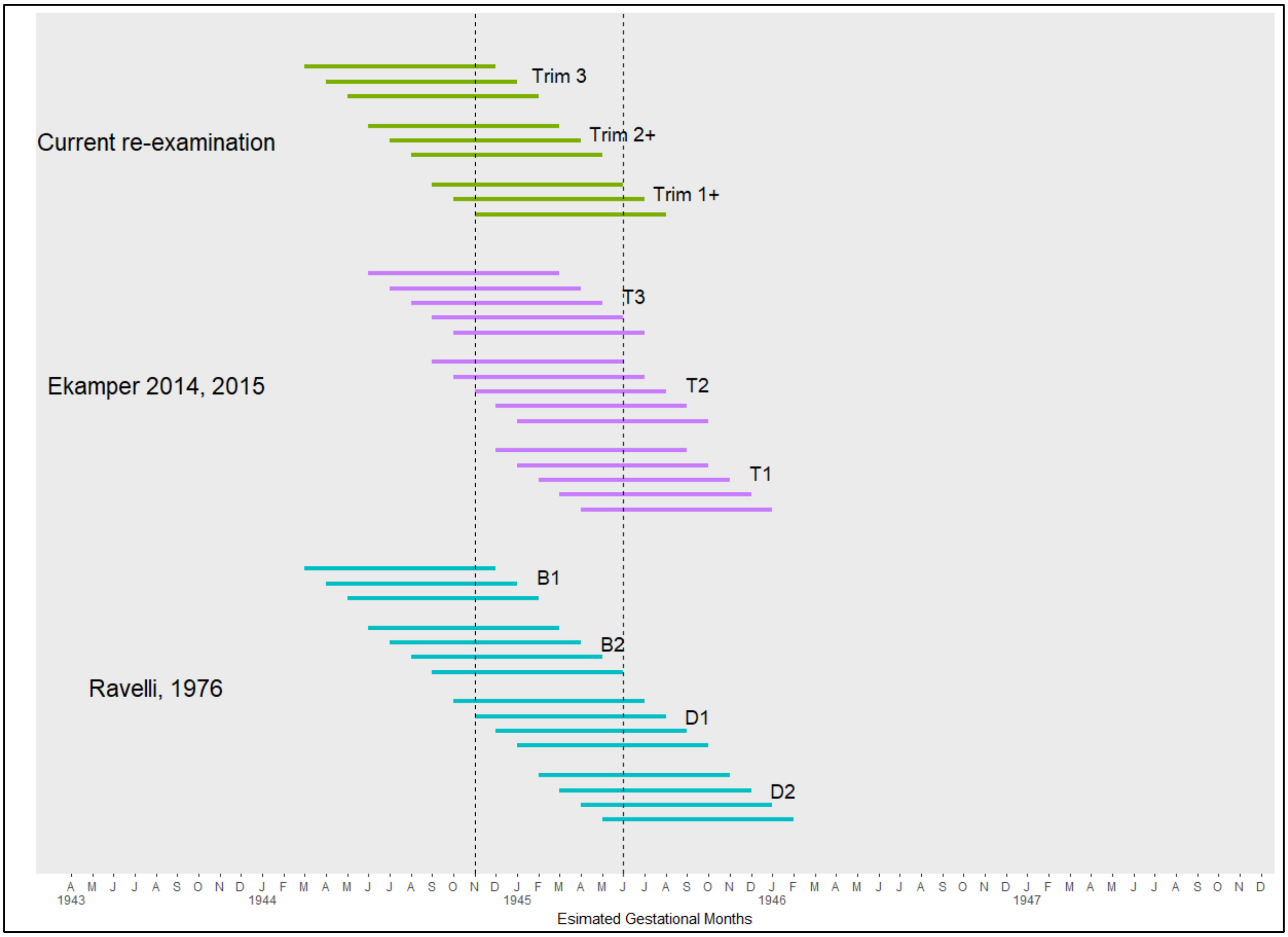
‘Obese’ (Ravelli 1976) prevalence after prenatal famine exposure
Dutch male conscripts born in 1944-1947
Odds Ratios (95% CI) relative to unexposed controls
(All births; n=371,100)

Month of Birth	**Famine exposure classification**			
	This study	**Ekamper 2014, 2015**		**Ravelli 1976**
1944/11	Trim 3 Famine: 0.76 (0.54, 1.06) Other: 1.28 (0.93, 1.76)			Cohort B1 Famine: 0.76 (0.54, 1.06) Other: 1.27 (0.92, 1.76)
12				
1945/1				
2	Trim 2+ Famine: 1.04 (0.80, 1.35) Other: 0.91 (0.67, 1.24)	T3 Famine: 1.03 (0.82, 1.29) Other: 0.94 (0.72, 1.22)		Cohort B2 Famine: 1.06 (0.85, 1.34) Other: 0.96 (0.74, 1.25)
3				
4				
5	Trim 1+ Famine: 1.44 (1.12, 1.85) Other: 0.93 (0.67, 1.28)		T2 Famine: 1.40 (1.09, 1.79) Other: 0.95 (0.71, 1.27)	
6				Cohort D1 Famine: 1.42 (1.13, 1.79) Other: 0.86 (0.64, 1.15)
7				
8		T1 Famine: 0.90 (0.68, 1.19) Other: 0.95 (0.70, 1.29)		
9				
10				Cohort D2 Famine: 0.90 (0.62, 1.30) Other: 0.96 (0.66, 1.39)
11				
12				
1946/1				

Famine: Western Netherlands famine cities; Other: Western Netherlands other cities and rural.
*Unexposed controls: Other Netherlands cities and rural births 1944-1947.

Supplement Figure 1

Prenatal exposure to the Dutch famine
Alternative classifications based on month of birth



Supplement Figure 2

BMI changes among Trim 1 exposed cohorts relative to unexposed controls by BMI quantile, point estimates and 95% CI Births Jan 1944 - Jul 1945