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

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Summary

Using data on the national male population of 18-year old males in the Netherlands we report 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 also exposed to the longest period of in utero famine. The increased risk is limited to sons of manual workers who were born in the largest 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, and to the inclusion of individuals who were conceived during or after the famine. Further studies are needed to trace the impact of these weight changes in young adults on subsequent morbidity and mortality.

Introduction

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. (Stein, Susser et al. 1975, Lumey and Van Poppel 2013, Ekamper, Van Poppel et al. 2014, Ekamper, van Poppel et al. 2015) The severity and widespread nature of the famine have been fully documented. (Burger, Drummond et al. 1948, Stein, Susser et al. 1975, Trienekens 2000) Contemporary reports show that the famine was the most severe in the largest cities of the Western Netherlands during the last months of the war, between the end of October 1944 and Liberation. (Boerema 1947, Burger, Drummond et al. 1948, Lumey 2012) 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 journal on the relation between prenatal exposure to the Dutch famine of 1944-45 and weight among young adult men, lower obesity rates based on the weight to height ratio 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 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. (Ravelli, Stein et al. 1976)

There is a need to re-examine these findings for several reasons.

1. In the 1976 report, ‘obesity’ was defined as a weight/height ratio exceeding 120% of the population average, based on impaired health outcomes beyond that point. (Actuaries 1959, MLIC 1983) After 1976, there have been significant improvements in our understanding of the relation between body size, morbidity, and mortality. (NIH/NHLBI 1998). By the late 1990’s, a person’s Body Mass Index (BMI: weight/height^2) had been accepted worldwide as the most useful measure at the

population level not only of being overweight (BMI of 25 or over) but also of obesity (BMI of 30 or over). (WHO 2000)

2. Famine exposure was defined by place and date of birth, but some birth regions were not included. Births in selected months from the seven most affected cities in Western Netherlands were selected as 'exposed' populations and grouped according to exposure period to identify critical periods and before-and-after 'time' controls. Births in urban conglomerations outside the famine area were selected as 'place' controls. (Ravelli, Stein et al. 1976) The study population did not include births in the smaller urban conglomerations in the Western Netherlands or in rural areas across the Netherlands.

3. Famine severity has also been taken into account by mortality studies in this population that have used additional information on the weekly distributed food rations during the famine to define the period of most extreme famine in relation to the stage of gestation. (Ekamper, Van Poppel et al. 2014, Ekamper, van Poppel et al. 2015). This approach has not yet been applied to obesity studies when this population was 18 years old at military examination.

4. The steep decline in births during the famine (Stein, Susser et al. 1975), especially among the manual (vs non-manual) socio-economic classes has been attributed among other things to socio-economic gradients in food access during the famine. We will explore the potential impact of selective fertility as a potential confounder of reported famine effects as this has not yet been examined to date.

With regard to analytical methods, we quantify the long-term famine effects as interactions between place and date of birth as they relate to body size at age 18. Quantile regression approaches further clarify the impact of the famine on height and weight as continuous variables between different quantiles of the distribution. We thereby examine the robustness of the study outcomes to the use of current BMI based binary outcome of being overweight or obese.

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 use modern epidemiologic methods and also examine relations with birth order and family size that might affect our findings. Unrecognized contaminations of the study population also need correction, including individuals born outside the Netherlands and twin births.

We discuss our new findings in the light of earlier conclusions that prenatal and early postnatal nutrition determines subsequent obesity. (Ravelli 1976)

Materials and Methods

Study population

We evaluated anthropometric measures at age 18 in male conscripts born between January 1, 1944 and December 31, 1947 and examined for military service in the Netherlands. (Ravelli, Stein et al. 1976) 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.

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 (CBS 1941) 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 population dispersion characteristics. 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.

Grouping by month of birth

We compared body size at age 18 among 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. (Stein, Susser et al. 1975)

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-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 previous 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. (Ekamper, Van Poppel et al. 2014, Ekamper, van Poppel et al. 2015) 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) and or in the immediate post-natal period (births Nov 1944-March 1945). All 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. (Ravelli, Stein et al. 1976). Supplement Table 1 shows the three famine exposure classifications based on year and month of birth. (Supplement Table 1 and Supplement Figure 1)

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. (Ravelli and Belmont 1979)

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. (Ravelli, Stein et al. 1976)

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.

As the measure of a 'famine effect' we examine the cross-product coefficients of the date and place of birth main effects for study outcomes as they relate to a) births in the West famine cities or b) births in the remaining urban or rural areas in the Western Netherlands in specific birth months. The selected 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. *Presented at this point are simple cross-product differences; we will further examine the differences between the cross differences as suggested in the economic literature for non-linear models*. *(Ai and Norton 2003, Puhani 2012)*

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. (Stein, Susser et al. 1975, Ravelli, Stein et al. 1976)

In later analyses, three-way interactions were explored between birth cohort, birth region, and social class, and birth cohort, birth region, and birth order (firstborn vs later-born conscripts). We observed no three-way interactions. Analysis stratified by birth order (first vs higher order births) show no consistent relation by birth order 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) (Ravelli, Stein et al. 1976) in logistic regression models. We further examined height and body mass index as a continuous variable, using quantile regressions to examine the relation of famine exposure to BMI at age 18 across the entire range of the BMI distribution.

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.

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.

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)

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 largest 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 in1940 was 46.5% in the country as a whole but only 29.8% outside the Western Netherlands.

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.

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 however for births in the West from non-manual backgrounds or for births in the West outside the largest 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 term 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 cutpoint (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.

With regard to height, no relation is seen between any of the famine exposure trimesters and height at age 18.

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. (Ekamper, Van Poppel et al. 2014, Ekamper, van Poppel et al. 2015) Second by comparing our results with the 1976 obesity study when the cohorts were defined as ‘critical periods of famine exposure with adequate numbers’. (Ravelli, Stein et al. 1976)

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.

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 in this cohort we found a strong relation between height and education, father’s occupation, region of birth, family size and religion (Huang, van Poppel et al. 2015), as also documented by others (*refs to add*) but it appears that prenatal famine exposure in itself had no relation to height at age 18.

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 (WHO 2000) and of the accumulation of excess body 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 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 appeared to be 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 therefore appears to be subject to some residual confounding by social class of the relation between prenatal famine and overweight status at age 18. Stratification by social class in the analysis using two strata (manual vs non-manual) therefore appears to be effective in removing most but not all confounding of the relationship between famine exposure and adult weight.

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%). These dichotomized 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 BMI increase or increase in overweight prevalence 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 extreme famine exposure with a long term impact on body size was limited to births in the largest cities in the West, as previously suggested by contemporary accounts (Burger, Drummond et al. 1948) and regional mortality data (Ekamper, van Poppel et al. 2017) but not yet confirmed in individuals nationwide.

There was no BMI decrease in births with third trimester exposure. In quantile regressions, we did observe a negative association between third trimester famine exposure and BMI but this was limited to the extreme upper tail of the distribution and reached statistical significance only beyond the 98th BMI percentile. These associations do not reflect the overall impact of the famine across BMI percentiles.

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 changes among births exposed to famine in the first year of life *(by some identified a as a vulnerable group. Refs to be added).* 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 starting in the first trimester of gestation. Age-related increases of BMI and overweight in this population are not an issue as all individuals underwent their medical examination 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. (Ekamper, Van Poppel et al. 2014, Ekamper, van Poppel et al. 2015) 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'. (Ravelli, Stein et al. 1976)

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 in that they 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.

With respect to the 1976 analysis by Ravelli et al. that does address selective fertility issues other than by a graphical analysis of 'obesity' by social class (Ravelli, Stein et al. 1976), 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 by Ravelli et al. comparing famine vs control areas (2.77% vs. 1.45%).

Contrary to Ravelli et al., we found no decrease in BMI among births exposed at the end of gestation (B1). This difference can be understood by quantile regressions on the births exposed at the end of gestation. These show no impact of prenatal famine across most of the BMI distribution. A strong negative relation was seen however in the extreme upper centiles based on very small numbers.

Smaller differences with the Ravelli findings could be related to the inclusion of births in all regions in our analysis and the use of current approaches to data analysis that employ an approach incorporating month and region of birth as main effects and their interactions, father's occupation, and birth order in a single model. Such analyses go beyond the pairwise comparison of famine area and control area birth cohorts as used in the past.

On the role of birth order and family size, previously explored by Belmont and Ravelli for obesity defined by the weight/height ratio (Ravelli and Belmont 1979) 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 but could not be analyzed separately in the absence of a family identifier. Neither could brothers be identified although the numbers could be relatively limited in the four year observation window. Twins might provide a unique occasion to test for intrauterine — in addition to extra-uterine — selection effects of the famine, but given the further limitations in the data at hand (only males are included, and zygosity cannot be ascertained), we have only tested the robustness of the results to the exclusion of the 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.

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. (Ravelli, van Der Meulen et al. 1999, Stein, Kahn et al. 2007) 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. (Zhou, Zhang et al. 2018) In all 20 studies included in the review, outcomes in famine exposed individuals were compared to outcomes in individuals born after the famine however, leading to uncontrolled age differences between famine and post-famine births that could explain the BMI difference attributed to the famine. (Li and Lumey 2017)

It is possible that the 1.5 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 (Ekamper, Van Poppel et al. 2014) but no association with deaths from cancer or cardiovascular disease. (Ekamper, van Poppel et al. 2015). 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. This may improve as the cohort ages and overall mortality has further increased.

Need transition from overweight and obesity to Type 2 Diabetes Mellitus (T2DM) in later life

With respect to T2D in later life, studies from Ukraine famine of 1932-1933 (Lumey, Khalangot et al. 2015), the Dutch famine of 1944-45 (Ravelli, van der Meulen et al. 1998, Lumey, Stein et al. 2009), and three famines in 20th century Austria (Thurner, Klimek et al. 2013) show a relation with prenatal famine exposure. The timing of the famine in relation to the stage of gestation is particularly well defined in the Ukraine and

Dutch studies, the risk of adult hyperglycaemia in the Chinese study, and a large number of patients with antidiabetic medication over a long time period is included in the nationwide Austrian study. In the Ukraine study, T2DM prevalence at ages 40 and over was increased by 1.5 fold in cases registered in the national diabetes registry in Kiev who were exposed in early gestation and born in regions with the highest famine severity. Reported diabetes findings from the Chinese studies are still problematic because most current analyses have ignored differences in age at examination between famine exposed individuals and unexposed controls who were born after the famine and thereby younger. (Li and Lumey 2017)

Prenatal famine in relation to diabetes deaths will be hard to examine because a large proportion of diabetes related deaths is not ascribed to diabetes on the death certificates. *(ref to be added)* Studies also show that among non-reported diabetes deaths, deaths from cancer are the most commonly reported causes. The reporting is also biased by co-morbidities. Diabetes deaths among diabetes patients are more commonly reported in the presence of CHD co-morbidities/mortality than otherwise. CVA and cancer deaths are better reported than IHD and diabetes deaths. *(refs to be added*) These issues are common in mortality statistics and will not be easy to overcome.

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 also exposed to the longest period of in utero famine. The increased risk is limited to sons of manual workers who were born in the largest 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.

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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			
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 (%)**	**E**
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)	1
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)	4
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)	3 ((
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)	4 ((
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)	1 ((
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)	2 ((
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)	2 ((
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)	8

*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: $2^{nd}/3^{rd}$ trimester D1: 1^{st}/ 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

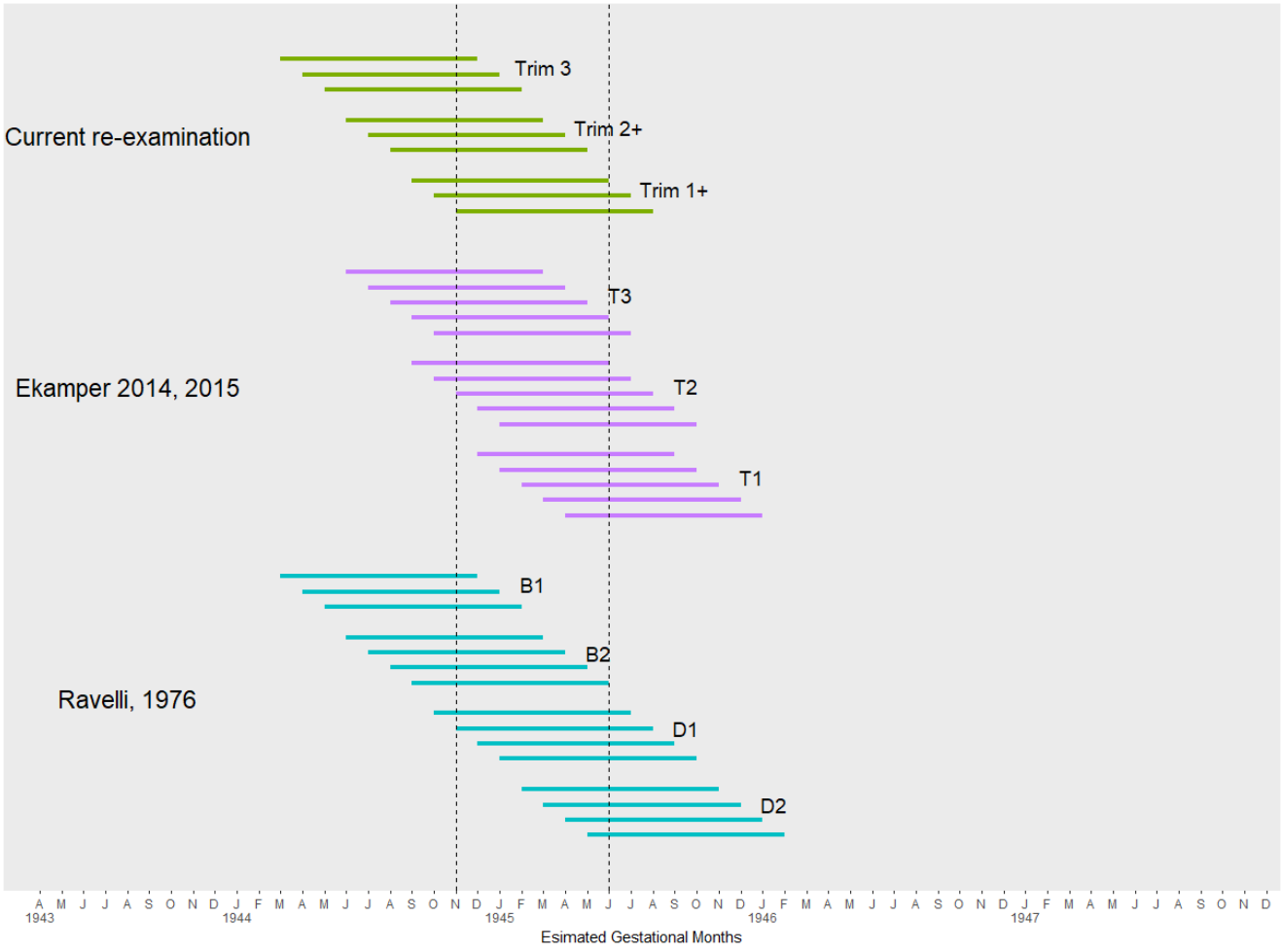
'Obese' (Ravelli 1976) prevalence after prenatal famine exposure
Dutch male conscripts born in 1944-1947
Odds Ratios (95% CI) relative to unexposed controls
(All births; n=371,100)

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

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

