Heart

Maternal gestational weight gain and offspring's risk of cardiovascular disease and mortality

Journal:	*Heart*
Manuscript ID	heartjnl-2015-308709.R2
Article Type:	Original research article
Date Submitted by the Author:	n/a
Complete List of Authors:	Bhattacharya, Sohinee; University of Aberdeen, Public Health McNeill, Geraldine; University of Aberdeen, Division of Applied Health Sciences Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics, Dept. of Public Health Allan, Keith; University of Aberdeen, Institute of Applied Health Sciences Clark, Heather; University of Aberdeen, Division of Applied Health Sciences Reynolds, Rebecca; University of Edinburgh, Endocrinology Unit Norman, Jane; University of Edinburgh, Department of Medicine Hannaford, Philip; University of Aberdeen
Keywords:	Pregnancy < Heart Disease < DISEASES, Metabolic syndrome < Cardiac risk factors and prevention < DISEASES, Obesity < Heart Disease < DISEASES
Abstract:	Objective: To examine the effect of maternal gestational weight gain (GWG) on adult offspring mortality and cardiovascular and cerebrovascular morbidity. Methods: The Aberdeen Children of the 1950s is a population-based cohort of adults born in Aberdeen, Scotland between 1950 and 1956. GWG of the mothers of cohort members was extracted from original birth records and linked to data on offspring morbidity and mortality up to 2011 obtained from Scottish national records. Hazard ratios for cardiovascular events and mortality in offspring according to maternal weight gain in pregnancy were estimated adjusting for maternal and offspring confounders using a restricted cubic spline model. Results: After exclusions, 3781 members of the original ACONF cohort were analysed. Of these, 103 (2.7%) had died, 169 (4.5%) had suffered at least one cardiovascular event and 73(1.9%) had had a hospital admission for cerebrovascular disease. Maternal weight gain of 1 kg/ week or more was associated with increased risk of cerebrovascular event in the offspring {adjusted HR 2.70 (95% CI 1.19 to 6.12)}. There was no association seen between GWG and offspring all-cause mortality or cardiovascular event. Adult offspring characteristics (smoking, BMI and diabetes) were strongly associated with each outcome. Conclusion: Maternal gestational weight gain above 0.9 kg/ week may increase the risk of cerebrovascular disease in the adult offspring, but not all cause mortality or cardiovascular disease. Health and lifestyle factors

	such as smoking, BMI and diabetes in the adult offspring had a stronger influence than maternal and birth characteristics on their mortality and morbidity.

Maternal gestational weight gain and offspring's risk of cardiovascular disease and mortality

Bhattacharya S[1], McNeill G[1,2], Raja EA[1], Allan K,[1], Clark H[1], Reynolds RM[3], Norman JE[3], Hannaford PC[1].

[1]Institute of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK
[2] Rowett Institute of Nutrition and Health, University of Aberdeen, Bucksburn, Aberdeen AB21 9SB
[3]Endocrinology Unit, Centre for Cardiovascular Science, University of Edinburgh, Queen's Medical Research Institute, Edinburgh, UK
Correspondence to:
Dr. Sohinee Bhattacharya, Dugald Baird Centre for Research on Women's Health, Aberdeen Maternity Hospital, AB25 2ZL
email sohinee.bhattacharya@abdn.ac.uk

Conflict of Interest: All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to (i) publish, reproduce, distribute, display and store the contribution, (ii) translate the contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the contribution, (iii) create any other derivative work(s) based on the contribution, (iv) to exploit all subsidiary rights in the contribution, (v) the inclusion of electronic links from the contribution to third party material where-ever it may be located; and, (vi) licence any third party to do any or all of the above.

Contributorship: SB designed the study, facilitated data extraction and wrote the first draft of the manuscript; GMcN designed the study, supervised running of the project and commented on the analysis and draft manuscript; EAR conducted the statistical analyses; KMA cleaned the data, conducted the initial analyses and commented on the draft manuscript; HC helped to extract and interpret the data from ACONF; PCH contributed to study design, study support, data interpretation and comments on manuscript; RMR and JEN helped to clinically interpret the findings and commented on the manuscript. SB is the guarantor for this paper.

Ethics: Ethical approval for the Aberdeen Children of the 1950s Study was obtained from the North of Scotland Research Ethics Service. Approval to access and link relevant data for this analysis were obtained from the Aberdeen Maternity and Neonatal Databank steering committee, the steering committee of the Aberdeen Children of the 1950s study and the Privacy Advisory Committee of the NHS National Services Scotland.

Funding: This research was supported by Chest Heart and Stroke Scotland (R10/A128)

Role of sponsors: The University of Aberdeen acted as sponsors for this research project, but the findings and their interpretation in this study are the authors' own.

Abstract

Objective: To examine the effect of maternal gestational weight gain (GWG) on adult offspring mortality and cardiovascular and cerebrovascular morbidity.

Methods: The Aberdeen Children of the 1950s is a population-based cohort of adults born in Aberdeen, Scotland between 1950 and 1956. GWG of the mothers of cohort members was extracted from original birth records and linked to data on offspring morbidity and mortality up to 2011 obtained from Scottish national records. Hazard ratios for cardiovascular events and mortality in offspring according to maternal weight gain in pregnancy were estimated adjusting for maternal and offspring confounders using a restricted cubic spline model.

Results: After exclusions, 3781 members of the original ACONF cohort were analysed. Of these, 103 (2.7%) had died, 169 (4.5%) had suffered at least one cardiovascular event and 73(1.9%) had had a hospital admission for cerebrovascular disease. Maternal weight gain of 1 kg/ week or more was associated with increased risk of cerebrovascular event in the offspring {adjusted HR 2.70 (95% CI 1.19 to 6.12)}. There was no association seen between GWG and offspring all-cause mortality or cardiovascular event. Adult offspring characteristics (smoking, BMI and diabetes) were strongly associated with each outcome.

Conclusion: Maternal gestational weight gain above 0.9 kg/ week may increase the risk of cerebrovascular disease in the adult offspring, but not all cause mortality or cardiovascular disease. Health and lifestyle factors such as smoking, BMI and diabetes in

the adult offspring had a stronger influence than maternal and birth characteristics on their mortality and morbidity.

Key words: pregnancy, gestational weight gain, cardiovascular disease, mortality

Word count 250

Key Messages:

What is already known:

Maternal pre-pregnancy BMI and total gestational weight gain has been shown to affect cardiovascular parameters such as blood pressure in the young adult offspring. None of the published studies had adequate follow up time to assess the effects on cardiovascular events and mortality.

What this paper adds:

In a cohort follow up study spanning 60 years, rate of gestational weight gain (GWG) was not found to be associated with offspring's risk of mortality or cardiovascular events. GWG of 0.9Kg/week or more was associated with increased risk of cerebrovascular events in the offspring. Adult health and lifestyle factors such as smoking, diabetes and obesity were strongly associated with offspring's risk of mortality and morbidity.

How might this impact on clinical practice?

For the first time, this large scale cohort study was able to show that adult health and lifestyle factors and not early life risk factors played the most important role in determining cardiovascular mortality and morbidity. Modifying these risk factors (obesity, smoking, diabetes) would constitute effective preventive strategy irrespective of early life risk factors.

Introduction

Excessive weight has established health risks for both the mother and baby not only during pregnancy[1], but also in the longer term, including premature mortality[2,3]. Proposed mechanisms for this long-term risk include genetic predisposition, shared environment and fetal programming of adult disease[4].

The effect of maternal weight gain during pregnancy (gestational weight gain or GWG) on adult offspring health is less clear. Many of the cohorts designed to study the effects of maternal nutrition in pregnancy on offspring health are currently relatively young and therefore can only report adverse outcomes at the time of birth, childhood or young adulthood. Most of these have focussed on offspring BMI, with high correlations found with maternal GWG. Morrison et al[5] found that maternal GWG was positively associated with insulin levels and birthweight, length and body fat in the newborn. The Jerusalem Perinatal Family Follow-up Study found that the offspring of mothers within the upper pre-pregnancy BMI quartile (BMI> 26.4 kg/m^2) had a higher BMI, and cardiometabolic traits compared to those born to mothers in the lower quartile (BMI< 21.0 kg/m^2) at 32 years of age[6]. These associations were independent of maternal GWG and other confounders.

Record linkage of a mature cohort – Aberdeen Children of the Nineteen Fifties (ACONF) to local obstetric and national vital statistics and hospital clinical datasets available in Scotland, enabled us to test the hypothesis that maternal GWG is associated with subsequent cardiovascular morbidity and premature mortality in the adult offspring,

independent of any effects of high maternal BMI early in pregnancy and offspring characteristics.

Methods:

Ethical approval: Ethical approval for the Aberdeen Children of the 1950s study was obtained from the North of Scotland Research Ethics Service. Approval to access and link relevant data for this analysis were obtained from the Aberdeen Maternity and Neonatal Databank steering committee, the steering committee of the Aberdeen Children of the 1950s study and the Privacy Advisory Committee of the NHS National Services Scotland.

Data sources: Data were obtained from four sources –

1. The ACONF study contains data on children born between 1950 and 1956 who attended school in Aberdeen city[7] and formed the basis of the current investigation. The ACONF database contains socio-demographic variables about the children, as well as their height and weight measurements taken between 1962 and 1964 as part of a school survey. Information about adult height, weight, socio-economic status and self- reported history of diabetes was obtained from a questionnaire follow-up of the cohort conducted in 2001.
2. The Aberdeen Maternity and Neonatal Databank (AMND) is an obstetric database that records all pregnancy related events occurring in Aberdeen since 1950 (www.abdn.ac.uk/amnd). From this database we obtained pregnancy and delivery

details of the mothers of children in ACONF, including their age at delivery, height and ante-natal weights recorded during each antenatal clinic visit.

3. The Scottish Morbidity Records (SMR) database contains details of all hospital admissions and discharges in Scotland since 1981 with the discharge diagnosis coded using International Classification of Diseases version 9 (ICD-9) to April 1996 and version 10 (ICD-10) thereafter.
4. The General Register Office provided date and cause of death information for the ACONF cohort.

Record linkage: The Community Health Index number, a unique identifier attributed to all individuals registered with a general practice in Scotland was utilised for deterministic linkage. In addition, probabilistic matching using surname, date of birth, gender and post code of residence, was utilised in cases where CHI number was missing. All linkages were carried out by the Data Management Team of the University of Aberdeen and the Information and Services Division of NHS Scotland. After linkage, identifying variables were removed to generate a pseudononymised dataset before transfer to the researchers for analysis.

Data cleaning and exclusions: We excluded ACONF members who did not complete the questionnaire survey in 2001, emigrated out of Scotland or did not report one or more of the adult characteristics. We also excluded all participants whose mother, did not have more than one weight recorded in pregnancy, or who had only 2 weights recorded less than 2 weeks apart (figure 1).

Study design: This was a cohort study in which the exposure was maternal GWG obtained by subtracting the first from the last recorded antenatal weight and dividing the difference by the number of weeks elapsed between the two recordings.

We considered three outcomes in the offspring: i) all-cause mortality, ii) any cardiovascular disease- mainly identified by a hospital admission due to cardiovascular disease {(ICD 10 codes I20 – I25), arterial disease (I73 – I74), other cardiovascular disease}- as recorded in the SMR database or death from cardiovascular disease without any previous hospital admission for this condition, and iii) any hospital admission or death for cerebrovascular disease {(ICD 10 codes I60 – I69)}.

Covariates were adjusted for in a stepwise manner. Maternal level variables (age at delivery, maternal early pregnancy BMI calculated from the height and weight recorded at the first antenatal clinic visit, social class according to the Registrar General's Classification of Occupations based social class of the father) were included in the adjusted model (model 2). In model 3, offspring level variables at the time of birth and childhood (gender, standardized birth weight score[8], childhood BMI Standard Deviation Score (SDS) or z-score calculated using the LMS (Lambda- Mu-Sigma) method[9] from the height and weight recorded as part of the ACONF Reading Survey were included in addition to the covariates in model 2. Offspring's adult social class (based on the participant's employment socioeconomic group)[10], adult smoking habits, adult BMI and self-reported history of diabetes mellitus, information collected as part of the ACONF

follow up survey in 2001 when participants were aged between 43 and 49 years of age, were included in the fourth and final model in addition.

The underlying time variable for the analysis was the age of the offspring at death, date of hospital discharge for the outcomes of interest or end of follow up (31st January 2012), whichever occurred earliest.

Statistical analysis: Data were analysed using Stata (StataCorp, Version 13 MP, Texas, USA). Descriptive univariate analyses of the data were done initially. Cox's proportional hazards model was used to assess the relationship between maternal GWG and the pre-specified health outcomes in their adult offspring. To allow for some children having siblings in the dataset, we adjusted for clustering on the mother using multilevel modelling. We estimated robust standard errors after adjusting for multiple offspring clustered within mothers[11]

Rate of GWG was treated as a continuous variable in order not to lose information and to model any non-linear relationships. Unadjusted Hazard Ratios (HR) and 95% confidence interval (CI) for the pre-specified outcomes by the rate of weight gain (kg/week) were calculated (Model 1), followed by three adjusted models as described above. The proportional hazard assumption was tested using Schoenfeld residuals[12] and no violations were detected. To model the non-linear relationship between rate of weight gain and offspring outcomes, a restricted cubic spline (RCS) procedure was adopted.[13,14] This uses multiple polynomial line segments within the range of rate of weight gain, the boundaries of which are called knots. Knots were placed at equally

spaced centiles of the distribution of rate of weight gain. In our analyses, five knots were considered, placed at the 0th, 25th, 50th, 75th and 100th percentiles; corresponding rates of weight gain values were 0.01, 0.32, 0.41, 0.50 and 1.35 kg/week respectively. The spline function was assumed to be significant if the p-value for the model chi-square was less than 5% and the association was assumed to be non-linear if the spline coefficients differed significantly from each other on the Wald test for linearity. A rate of weight gain of 0.4 kg/week was used as the reference value in these RCS Cox analyses as this corresponded to the 50th centile.

Missing values: Complete case analysis was done for missing data on exposure variables. Where data were missing in categorical covariates, a separate category was created for missing observations in each of the covariates and included in the relevant analyses.

Missing in continuous variables was treated as missing in the analysis.

In the modelling diagnostic, any outliers and influential data points were checked using likelihood displacement values and LMAS values[15] for the final model. A scatter plot between predicted likelihood displacement values and time to event for each of the outcomes was used to identify any observations with disproportionate influence. Similarly, predicted LMAX was used instead of likelihood displacement measure. Four observations appeared to be somewhat influential relative to others. Those four observations were excluded and the analyses were repeated for all the outcomes in the final model. The estimates of the covariates were almost same as the estimates with the observations included in the modelling.

Multiple imputation was carried out using RealcomImpute, a software for multilevel multiple imputation. The multilevel multiple imputations were carried out for variables with missing observations using complete information on other covariates for all cases and outcome. The results were compared between complete case analysis and complete + imputed dataset.

Results:

Figure 1 shows cohort follow up with exclusions. After applying all of the exclusion criteria described above, there were 3781 members of the original ACONF cohort (n=12,151) included in the analysis. Of these, 103 (2.7%) had died, 169 (4.5%) had suffered at least one cardiovascular event and 73(1.9%) had had a hospital admission or death from cerebrovascular disease. The major causes of death were neoplasms (31.5%), diseases of the circulatory system (26.0%), diseases of the digestive system (10.0%), metabolic diseases (8.3%) and injury or trauma (6.2%).

Table 1 compares the baseline characteristics of those who did and did not experience the outcomes of all-cause mortality, or cardiac or cerebrovascular event. Members of the ACONF cohort who had died, were more likely to have mothers with a higher BMI during pregnancy {mean 23.64 (SD3.64) versus 22.85 (SD 3.12), p=0.01}; higher BMI in childhood expressed as SDS {mean 0.67 (0.84) versus 0.47 (0.88), p=0.03}. As adults they were more likely to belong to a more deprived socio-economic status group (p for trend

0.03), to be current smokers (54.4% versus 24.3%, p<0.01) and suffer from diabetes (4.9% versus 1.7%, p<0.01).

Compared to those who did not have a cardiovascular event, those who did were more likely to be male (64.5% versus 47.0%, p<0.01), and as adults belong to a more deprived socio-economic status group (p for trend <0.01), currently smoke (47.3% versus 24.1%, p<0.01), have a higher BMI (p for trend <0.01) and report diabetes (7.7% versus 1.5%, p<0.01).

Those who had had a cerebrovascular event were more likely to have mothers with a higher BMI in pregnancy {mean 23.66 (SD 3.32) Kg/m^2 versus 22.86 (SD 3.13) Kg/ m^2, p=0.03}. As adults, they were more likely to be current smokers (57.5% versus 24.5%, p<0.01) and diabetic (8.2% versus 1.6%, p<0.01).

Of note, rate of maternal GWG was not associated with any of the outcomes of interest in the offspring on univariate analysis.

Figures 2, 3 and 4 show respectively the relationship between maternal GWG and the offspring's risk of all-cause mortality, hospital admission for any cardiovascular disease and hospital admission for any cerebrovascular condition, from the fully adjusted model. The HRs with 95% CIs for these outcomes at each node of GWG are presented in Table 2, with results from each model shown separately in a stepwise fashion.

Association between GWG and offspring all-cause mortality:

Neither the unadjusted nor any of the adjusted models showed a statistically significant association between maternal GWG and offspring risk of all-cause mortality (Table 2). Figure 2 is the visual representation of the fully adjusted HRs with 95% CIs for offspring mortality by maternal GWG. According to this figure, there appears to be a reduction in offspring mortality risk with increased GWG, although the association was not statistically significant.

Association between GWG and offspring cardiovascular event :

The adjusted and unadjusted HR with 95% confidence intervals of any hospital admission or death from cardiovascular disease in the offspring by maternal GWG are presented in table 2. Cardiovascular disease in the offspring did not show statistically significant association with maternal GWG in any of the unadjusted or adjusted models. Figure 3 demonstrates the relationship between maternal GWG and hospital admission for any cardiovascular event in the offspring adjusted for confounding factors. Although not statistically significant, this figure shows a U shaped relationship with higher risk of cardiovascular events at both extremes of maternal GWG.

Association between GWG and offspring cerebrovascular event:

Table 2 and figure 4 present the relationship between maternal GWG and offspring risk of any cerebrovascular event. As table 2 shows, a weight gain of 1 Kg/ week or more was associated with an increased risk of cerebrovascular event in the offspring in the unadjusted model {HR 3.19 (95% CI 1.43, 7.09)}, the model adjusted for maternal factors only {adj. HR 2.83 (95% CI 1.31, 6.12)}, the model adjusted for maternal and offspring's

birth and childhood level factors {adj. HR 3.55 (95% CI 1.60, 7.92)}, and the fully adjusted model additionally adjusting for adult offspring level factors {adj.HR 2.70 (95% CI 1.19, 6.12)}.

Table3 presents the Hazard Ratios with 95% confidence intervals for each of the variables included in the fully adjusted models, which shows that the characteristics of offspring as adults are the main drivers of risk of all-cause mortality, and cardiovascular and cerebrovascular disease. Being a current smoker when surveyed in 2001 was strongly associated with mortality {adj HR 4.10(95% CI 2.50, 6.74)}, cardiovascular disease {adj HR 3.32(95% CI 2.29, 4.81)} and cerebrovascular disease {adj HR 5.45(95% CI 2.71, 10.93)}. Being diabetic also carried a higher risk of all-cause mortality {adj HR 2.79(95% CI 1.09, 7.11)}, cardiovascular disease {adj HR 4.05(95% CI 2.23, 7.33)} and cerebrovascular disease {adj HR 6.41(95% CI 2.85, 14.42)}. Adult offspring BMI showed inconsistent associations with the outcomes of interest – while being underweight was associated with mortality {adj HR 4.16(95% CI 1.28, 13.49)}, overweight {adj HR 1.63(95% CI 1.11, 2.39)} and obesity {adj HR 2.65(95% CI 1.71, 4.11)} were associated with increased risk of cardiovascular disease but not cerebrovascular disease.

In the secondary analysis using dataset with multiple imputations, the results were comparable to the analysis with complete cases. Only for the outcome of cerebrovascular disease in the offspring, widening confidence intervals of effect estimates with increasing GWG meant there was no longer a statistically significant association seen.

Discussion:

We did not find a statistically significant relationship between maternal GWG and offspring all-cause mortality or cardiovascular events. Being overweight or obese as adults conferred a higher risk of cardiovascular events, whereas higher maternal BMI during pregnancy was associated with an increased risk of cerebrovascular but not cardiovascular events on univariate analysis.

A key strength of this study was the well-defined cohort with adequate length of follow up to detect outcomes of interest. Even so the relatively small number of outcomes may have limited our power to detect associations that really exist, especially at the extremes of maternal GWG. Another strength of the study was the high quality data used for the analysis[16]. Linkage with ISD and GRO in Scotland by first deterministic (where possible) and then probabilistic matching maximised linkages and ensured a high proportion of true linkages[17]. The availability of data at various time points during the lifecourse of the offspring allowed the examination of risk factors at the time of delivery, offspring's childhood and middle-age adulthood. We were able to take account of clustering and co-linearity within and between variables by using multilevel modelling. The cubic spline analysis enabled us to model the non-linear relationship between GWG and offspring morbidity and mortality without losing information through categorisation.

The main limitation of this study is the exclusion of a large proportion of the original cohort because of missing information on GWG (mostly due to a single weight being

recorded during pregnancy), or non-response to the ACONF follow up questionnaire. A comparison of cohort members with and without complete information showed that they differed in terms of gender, parents' marital status, social class at birth or in childhood but not in maternal GWG[18]. As the SMR database was only initiated in 1981, left truncation of the outcome data will have occurred, although the oldest cohort members would have been 31 years old in 1981, an age when cardiovascular risk is low and mainly confined to congenital or rheumatic heart diseases. Fewer women were obese in pregnancy in the 1950s, reducing generalisability of the findings to contemporary situations. As with all observational studies, residual confounding from unmeasured or poorly measured covariates may have affected our results.

It is difficult to tease out the effects of genetic predisposition, fetal programming and shared environment when studying the effects of maternal GWG on offspring morbidity and mortality later in life. Lawlor et al showed that neither maternal nor fetal adiposity-related genetic variants were associated with higher GWG[19]. Nevertheless, higher GWG signifies higher birth weight which in turn is associated with higher risk of childhood and adult obesity.[20-24]

Far less is known about the impact of maternal GWG on offspring cardiovascular health. Some studies report a modest increase in blood pressure in children[25] and young adults[26-28] associated with high GWG. The synergistic mechanisms and the differences between maternal pre-pregnancy weight per se and GWG on the offspring's cardiovascular health warrant further discussion. GWG may be about nutritional content

of the food consumed – particularly those gaining a lot of weight. The availability of adipose stores versus available fuel from food is likely to have differing effects on fetal growth and ultimately on future health in adulthood.

There is currently no agreement on whether mothers who are overweight or obese at the start of their pregnancy should limit their weight gain. In 2009 the US Institute of Medicine recommended that mothers with BMI in the range 25-30 kg/m2should gain 7-11.5kg over the whole of pregnancy and 0.23-0.33 kg/wk in the second and third trimester, with corresponding figures of 5-9kg total gain and 0.17-0.27 kg/wk in the 2nd and 3rd trimester in those with a pre-pregnancy BMI of 30 or more[29]. In the UK, the National Institute of Clinical Excellence concluded in 2010 that maternal weight should not be routinely monitored during pregnancy[30]. Our findings are broadly reassuring since maternal GWG per se was not associated with an increased risk of all-cause mortality and cardiovascular outcomes in the offspring. In comparison, risk factors measured in the offspring as adults had a stronger relationship with the outcomes. This indicates that being healthy as an adult (ie being a non-smoker, having a healthy weight and being non-diabetic) is more important than any risks acquired in utero and in childhood. Longer-term follow-up of this cohort to accumulate cardiovascular events will allow subgroup analysis of mothers with high pre-pregnancy BMI to contribute to the debate on benefits of GWG restriction in overweight and obese women.

Conclusion:

In this population-based cohort, gestational weight gain of 1 kg/ week or more was associated with an increased risk of cerebrovascular disease in the adult offspring, an effect independent of maternal and offspring BMI as a child and adult. Maternal GWG was not associated with an increased risk of cardiovascular disease or all-cause mortality in the adult offspring. Health and lifestyle factors in the adult offspring were the strongest determinants of their morbidity and mortality.

Acknowledgements

The authors wish to thank and acknowledge the scientific input of Dr Nadeem Sarwar who led the funding application to carry out this research, Ms Katie Wilde and the Data Management Team, University of Aberdeen for data extraction from the Aberdeen databases and Ms Lena Henderson from ISD Scotland for data linkage and extraction from SMR databases.

References

1. Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG: An International Journal of Obstetrics and Gynaecology* 2006;113(10):1126-33.

2. Drake AJ, Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. *Reproduction* 2010;140(3):387-98.

3. Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: Follow-up of 1 323 275 person years. *BMJ (Online)* 2013;347(7921).

4. Poston L. Maternal obesity, gestational weight gain and diet as determinants of offspring long term health. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2012;26(5):627-39.

5. Morrison KM, Anand SS, Yusuf S, Atkinson SA, Schulze KM, Rao-Melacini P, et al. Maternal and Pregnancy Related Predictors of Cardiometabolic Traits in Newborns. *PLoS ONE* 2013;8(2).

6. Hochner H, Friedlander Y, Calderon-Margalit R, Meiner V, Sagy Y, Avgil-Tsadok M, et al. Associations of maternal prepregnancy body mass index and gestational weight gain

with adult offspring cardiometabolic risk factors: The jerusalem perinatal family follow-up study. *Circulation* 2012;125(11):1381-9.

7. Leon DA, Lawlor DA, Clark H, Macintyre S. Cohort profile: The Aberdeen children of the 1950s study. *Int J Epidemiol* 2006;35(3):549-52.

8. Campbell D, Hall M, Lemon J, Carr-Hill R, Pritchard C, Samphier M. Clinical birthweight standards for a total population in the 1980s. *Br J Obstet Gynaecol* 1993;100(5):436-45.

9. Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr* 1990;44(1):45-60.

10. Elias P. Social class and the standard occupational classifications. *A Report on Phase 1 of the ESRC Review of the OPCS Social Classification* 1995;.

11. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modelling marginal distributions. Journal of the American Statistical Association 1989; 84:1065–1073.

12. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Stat Med* 1995;14(15):1707-23.

13. Dupont W. Repeated-measures analysis of variance. *Statistical Modeling for Biomedical Researchers: A Simple Introduction to the Analysis of Complex Data* 2002;.

14. Greenland S. Dose-Response and trend analysis in epidemiology: Alternatives to categorical analysis. *Epidemiology* 1995;6(4):356-65.

15. Collet D 2003. Modelling survival data in Medical research. 2nd Ed. London. Chapman & Hall/ CRC

16. Atherton IM, Lynch E, Williams AJ, Witham MD. Barriers and Solutions to Linking and Using Health and Social Care Data in Scotland. *British Journal of Social Work* 2015;45(5):1614-22.

17. Fleming M, Kirby B, Penny KI. Record linkage in Scotland and its applications to health research. *J Clin Nurs* 2012;21(19-20):2711-21.

18. Nishiwaki Y, Clark H, Morton SM, Leon DA. Early life factors, childhood cognition and postal questionnaire response rate in middle age: The Aberdeen Children of the 1950s study. *BMC Medical Research Methodology* 2005;5.

19. Lawlor DA, Fraser A, Macdonald-Wallis C, Nelson SM, Palmer TM, Smith GD, et al. Maternal and offspring adiposity-related genetic variants and gestational weight gain. *Am J Clin Nutr* 2011;94(1):149-55.

20. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. *Obstet Gynecol* 2006;195(4):1100-3.

21. Crozier SR, Inskip HM, Godfrey KM, Cooper C, Harvey NC, Cole ZA, et al. Weight gain in pregnancy and childhood body composition: Findings from the Southampton Women's Survey. *Am J Clin Nutr* 2010;91(6):1745-51.

22. Nohr EA, Vaeth M, Baker JL, Sørensen TIA, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *Am J Clin Nutr* 2008;87(6):1750-9.

23. Hull HR, Dinger MK, Knehans AW, Thompson DM, Fields DA. Impact of maternal body mass index on neonate birthweight and body composition. *Obstet Gynecol* 2008;198(4):416.e1,416.e6.

24. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J. Outcomes of maternal weight gain. Evidence Report/Technology Assessment No. 168. *AHRQ Publication no.08-E009* 2008;.

25. Oken E, Kleinman KP, Belfort MB, Hammitt JK, Gillman MW. Associations of gestational weight gain with short- and longer-term maternal and child health outcomes. *Am J Epidemiol* 2009;170(2):173-80.

26. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of ageevidence from a birth cohort study. *Circulation* 2009;119(13):1720-7.

27. Fraser A, Tilling K, MacDonald-Wallis C, Sattar N, Brion M-, Benfield L, et al. Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation* 2010;121(23):2557-64.

28. Smith GD, Steer C, Leary S, Ness A. Is there an intrauterine influence on obesity? Evidence from parent-child associations in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Arch Dis Child* 2007;92(10):876-80.

29. Institute of Medicine and National Research Council. *Weight Gain during Pregnancy: Reexamining the Guidelines* 2009;.

30. Antenatal care: Routine care for the healthy pregnant woman. *NICE Clinical Guideline 62.* 2010;.

Table1. Comparison of maternal and offspring risk factors for offspring mortality, hospital admissions for cardiovascular and cerebrovascular disease

Characteristics	No Death (n=3678)	Death (n=103)	p-value	No CVD (n=3612)	Any CVD (n=169)	p-value	No Cerebrovascular (n=3708)	Cerebrovascular (n=73)	p-value
Maternal Characteristics									

GWG rate (Kg/week)*	0.41(0.16)	0.40(0.16)	0.53	0.41 (0.16)	0.41 (0.17)	0.97	0.41 (0.16)	0.43 (0.21)	0.40
Rate of GWG									
<0.2Kg/week	266 (7.2)	9 (8.7)	0.31	258 (7.1)	17 (10.1)	0.82	271 (7.3)	4 (5.5)	0.88
0.2-0.39Kg/week	1490 (40.5)	44 (42.7)		1466 (40.6)	68 (40.2)		1498 (40.4)	36 (49.3)	
0.4-0.59Kg/wwek	1505 (40.9)	42 (40.8)		1487 (41.2)	60 (35.5)		1523 (41.1)	24 (32.9)	
0.6-0.79Kg/week	362 (9.8)	6 (5.8)		348 (9.6)	20 (11.8)		362 (9.8)	6 (8.2)	
>=0.8Kg/week	55 (1.5)	2 (1.9)		53 (1.5)	4 (2.4)		54 (1.5)	3 (4.1)	
Age at delivery *(yrs)	27.27(5.20)	27.61(5.63)	0.51	27.31 (5.22)	26.59 (4.95)	0.08	27.28 (5.21)	27.08 (5.02)	0.75
Maternal BMI*Kg/m^2	22.85(3.12)	23.64(3.64)	**0.01**	22.86 (3.11)	23.11 (3.59)	0.31	22.86 (3.13)	23.66 (3.32)	**0.03**
Maternal Social Class									
I-IIIa Non-Manual	767 (20.9)	20 (19.4)	0.84	760 (21.0)	27 (16.0)	0.23	774 (20.9)	13 (17.8)	0.56
IIIb-V Manual	2509 (68.2)	73 (70.9)		2457 (68.0)	125 (74.0)		2528 (68.2)	54 (74.0)	
Missing	402 (10.9)	10 (9.7)		395 (10.9)	17 (10.1)		406 (11.0)	6 (8.2)	
Offspring Childhood Characteristics									
Offspring Gender									
Male	1752 (47.6)	55 (53.4)	0.25	1698 (47.0)	109 (64.5)	**<0.01**	1764 (47.6)	43 (58.9)	0.06
Female	1926 (52.4)	48 (46.6)		1914 (53.0)	60 (35.5)		1944 (52.4)	30 (41.1)	
Offspring birthweight (g)*	3323.13 (477.48)	3377.12 (516.50)	0.26	3325.46 (475.49)	3306.49 (542.10)	0.62	3323.78 (477.77)	3366.81 (520.65)	0.45
Offspring SBS*	0.01(0.97)	0.14(0.99)	0.20	0.02 (0.97)	-0.02 (1.01)	0.65	0.02 (0.97)	0.01 (0.97)	0.93
Offspring BMI SDS *	0.47(0.88)	0.67(0.84)	**0.03**	0.48 (0.88)	0.55 (0.90)	0.28	0.48 (0.88)	0.60 (0.92)	0.26
Offspring Adult Characteristics									
Offspring Social class									
SEG 1.1 to 4	1029 (28.0)	23 (22.3)	**0.03**	1012 (28.0)	40 (23.7)	**<0.001**	1040 (28.1)	12 (16.4)	0.88
SEG 5.1 to 6	1542 (41.9)	40 (38.8)		1525 (42.2)	57 (33.7)		1559 (42.0)	23 (31.5)	
SEG 7 to 8	325 (8.8)	9 (8.7)		319 (8.8)	15 (8.9)		321 (8.7)	13 (17.8)	
SEG 9 to 16	782 (21.3)	31 (30.1)		756 (20.9)	57 (33.7)		788 (21.3)	25 (34.3)	
Offspring Smoking									
Current	894 (24.3)	56 (54.4)	**<0.001**	870 (24.1)	80 (47.3)	**<0.01**	908 (24.5)	42 (57.5)	**<0.01**
Ex-Smoker	943 (25.6)	21 (20.4)		923 (25.6)	41 (24.3)		945 (25.5)	19 (26.0)	
No	1841 (50.1)	26 (25.2)		1819 (50.4)	48 (28.4)		1855 (50.0)	12 (16.4)	
Offspring Adult BMI									

Underweight	21 (0.6)	4 (3.9)	0.17	23 (0.6)	2 (1.2)	**<0.01**	25 (0.7)	0 (0)	0.88
Normal	1555 (42.3)	51 (49.5)		1560 (43.2)	46 (27.2)		1567 (42.3)	39 (53.4)	
Overweight	1446 (39.3)	26 (25.2)		1401 (38.8)	71 (42.0)		1449 (39.1)	23 (31.5)	
Obese	656 (17.8)	22 (21.4)		628 (17.4)	50 (29.6)		667 (18.0)	11 (15.1)	
Diabetes									
Yes	61 (1.7)	5 (4.9)	**0.02**	53 (1.5)	13 (7.7)	**<0.01**	60 (1.6)	6 (8.2)	**<0.01**
No	3617 (98.3)	98 (95.2)		3559 (98.5)	156 (92.3)		3648 (98.4)	67 (91.8)	

Presented as number (%) unless otherwise stated
*Mean (Standard Deviation)

CVD: Cardiovascular disease
GWG: Gestational Weight Gain
SBS: Standardised Birthweight Score
SDS: Standard Deviation Score
SEG: Socioeconomic group

Table 2. Cox proportional hazards models for association between rate of GWG (Kg/week) and offspring mortality, cardiovascular or cerebrovascular disease through restricted cubic splines

	Hazard Ratios (95% Confidence Intervals)			
Rate of GWG	**Model 1 (n=3781)**	**Model 2 (n=3771)**	**Model 3 (n=3296)**	**Model 4 (n=3296)**
Offspring mortality				
0.2 Kg/week	1.13 (0.80, 1.60)	1.02 (0.72, 1.47)	1.01 (0.70, 1.48)	0.94 (0.64, 1.40)
0.4 Kg/week	1.00	1.00	1.00	1.00
0.6 Kg/week	1.02 (0.70, 1.48)	1.01 (0.70, 1.46)	0.95 (0.64, 1.41)	0.96 (0.634 1.43)
0.8 Kg/week	0.86 (0.35, 2.11)	0.82 (0.33, 2.01)	0.77 (0.32, 1.82)	0.73 (0.31, 1.73)
1.0 Kg/week	0.63 (0.08, 5.03)	0.57 (0.07, 4.48)	0.55 (0.08, 3.74)	0.47 (0.07, 3.10)
Any Cardiovascular Disease (CVD) in Offspring				
0.2 Kg/week	1.17 (0.91, 1.51)	1.16 (0.87, 1.53)	1.20 (0.90, 1.60)	1.20 (0.89, 1.61)
0.4 Kg/week	1.00	1.00	1.00	1.00
0.6 Kg/week	1.08 (0.81, 1.44)	1.05 (0.79, 1.40)	1.06 (0.78, 1.43)	1.03 (0.76, 1.40)
0.8 Kg/week	1.31 (0.83, 2.07)	1.23 (0.78, 1.94)	1.21 (0.75, 1.97)	1.16 (0.71, 1.88)
1.0 Kg/week	1.74 (0.80, 3.76)	1.54 (0.70, 3.39)	1.50 (0.66, 3.42)	1.37 (0.59, 3.18)
Any Cerebrovascular disease in Offspring				
0.2 Kg/week	1.07 (0.66, 1.74)	0.98 (0.60, 1.60)	1.10 (0.67, 1.79)	0.97 (0.59, 1.60)
0.4 Kg/week	1.00	1.00	1.00	1.00
0.6 Kg/week	0.78 (0.49, 1.25)	0.74 (0.46, 1.19)	0.81 (0.48, 1.35)	0.80 (0.47, 1.34)
0.8 Kg/week	1.21 (0.64, 2.29)	1.11 (0.59, 2.10)	1.30 (0.65, 2.61)	1.16 (0.57, 2.40)
1.0 Kg/week	**3.19 (1.43, 7.09)**	**2.83 (1.31, 6.12)**	**3.55 (1.60, 7.92)**	**2.70 (1.19, 6.12)**

Model 1: rate of GWG as continuous variable in non-linear form (cubic spline)
Model 2: Model 1 + maternal factors: age at delivery, BMI & social class
Model 3: Model 2 + Offspring factors: gender, SBS, childhood BMI SDS
Model 4: Model 3 + smoking, adult social class, adult BMI and diabetes

Statistically significant hazard ratios are shown as bold

Table 3. Factors associated with offspring mortality/ CVD/ Cerebrovascular disease using Cox proportional hazards model (fully adjusted model: Model 4)

Characteristics	Death HR (95% CI)	Any CVD HR (95% CI)	Any Cerebrovascular HR (95% CI)
Maternal Characteristics			
Rate of weight gain			
0.2 Kg/week	0.94 [0.64,1.40]	1.20(0.89, 1.61)	0.97 (0.59, 1.60)
0.6 Kg/week	0.96 [0.64,1.43]	1.03(0.76, 1.40)	0.80 (0.47, 1.34)
0.8 Kg/week	0.73 [0.31,1.73]	1.16(0.71, 1.88)	1.16 (0.57, 2.40)
1.0Kg/week	0.47 [0.07,3.10]	1.37(0.59, 3.18)	**2.70 (1.19, 6.12)**
Age at delivery	1.01(0.97, 1.05)	0.98(0.96, 1.02)	1.00(0.95, 1.04)
Maternal BMI	1.05(0.99, 1.13)	1.00(0.94, 1.06)	1.06(0.98, 1.15)
Maternal Social Class			
I-IIIa Non-Manual	1	1	1
IIIb-V Manual	1.07(0.62, 1.83)	1.15(0.74, 1.78)	0.92(0.48, 1.79)
Missing	1.07(0.47, 2.42)	1.32(0.69, 2.50)	0.54(0.15, 2.00)
Infant/ Childhood Characteristics			
Offspring Gender			
Female	1	1	1
Male	1.26(0.81, 1.97)	**1.89(1.33, 2.67)**	**1.81(1.04, 3.15)**
Offspring SBS	1.10(0.88, 1.38)	0.98(0.82, 1.16)	0.92(0.71, 1.19)
Childhood BMI SDS	1.23(0.97, 1.55)	0.95(0.80, 1.11)	1.09(0.83, 1.44)
Offspring Adult Characteristics			
Offspring Social class			
SEG 1.1 to 4	1	1	1
SEG 5.1 to 6	1.20 [0.67 2.17	1.24 [0.81 1.90]	2.02 [0.94 4.35]
SEG 7 to 8	1.19 [0.52 2.73]	1.03 [0.55 1.92]	**3.14 [1.25 7.88]**
SEG 9 to 16	1.27 [0.71 2.26]	1.46 [0.95 2.25]	**2.23 [1.03 4.86]**
Offspring Smoking			
No	1	1	1
Current	**4.10(2.50,6.74)**	**3.32(2.29, 4.81)**	**5.45(2.71, 10.93)**
Ex-Smoker	1.64(0.89, 3.04)	1.38(0.89, 2.15)	**2.37(1.08, 5.18)**
Offspring Adult BMI			
Underweight	**4.16 [1.28, 13.49)**	3.07 [0.73, 12.93]	0
Normal	1	1	1
Overweight	**0.52 [0.31, 0.87]**	**1.63 [1.11, 2.39]**	0.57 [0.32, 1.03]
Obese	0.85 [0.48, 1.50]	**2.65 [1.71, 4.11]**	0.57 [0.25. 1.33]
Diabetes			
No	1	1	1
Yes	**2.79(1.09, 7.11)**	**4.05(2.23, 7.33)**	**6.41(2.85, 14.42)**

Statistically significant hazard ratios are shown in bold

Figure 1: Flowchart of cohort follow up with exclusions

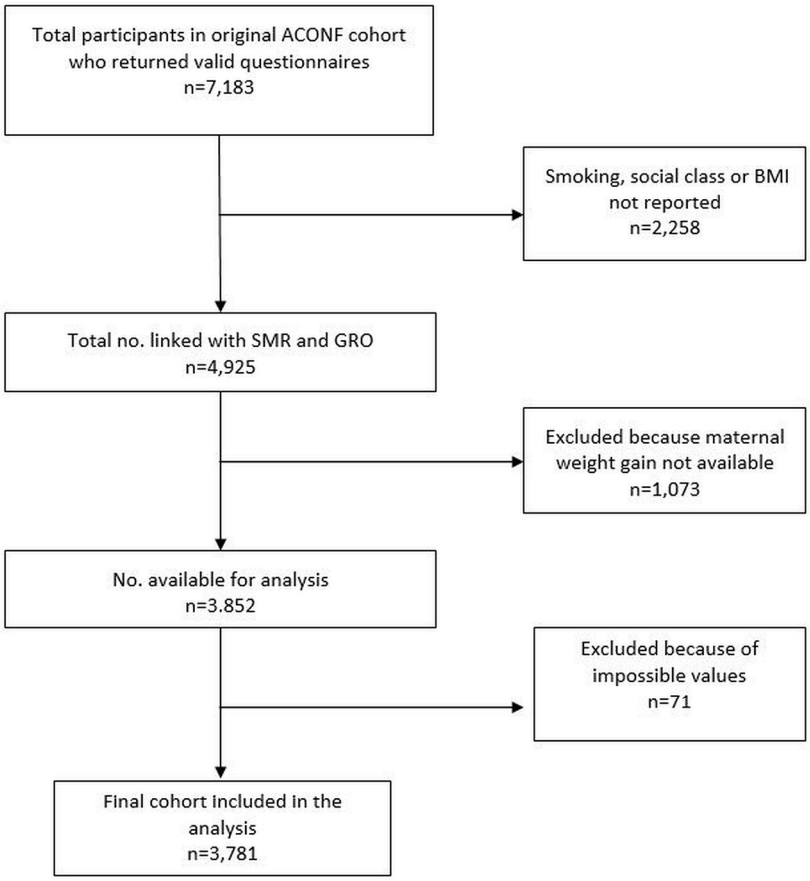

Figure 1: Flowchart of cohort follow up with exclusions
199x198mm (300 x 300 DPI)

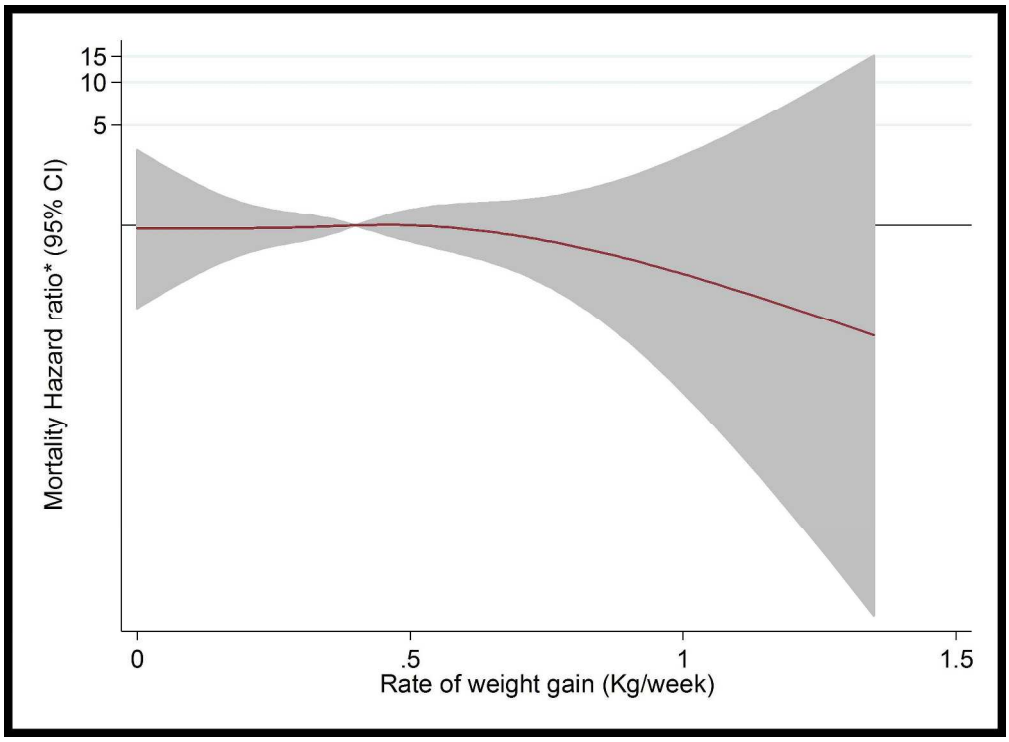

Fig. 2. Fully adjusted hazard ratios with 95% confidence intervals for offspring mortality by maternal gestational weight gain
381x278mm (300 x 300 DPI)

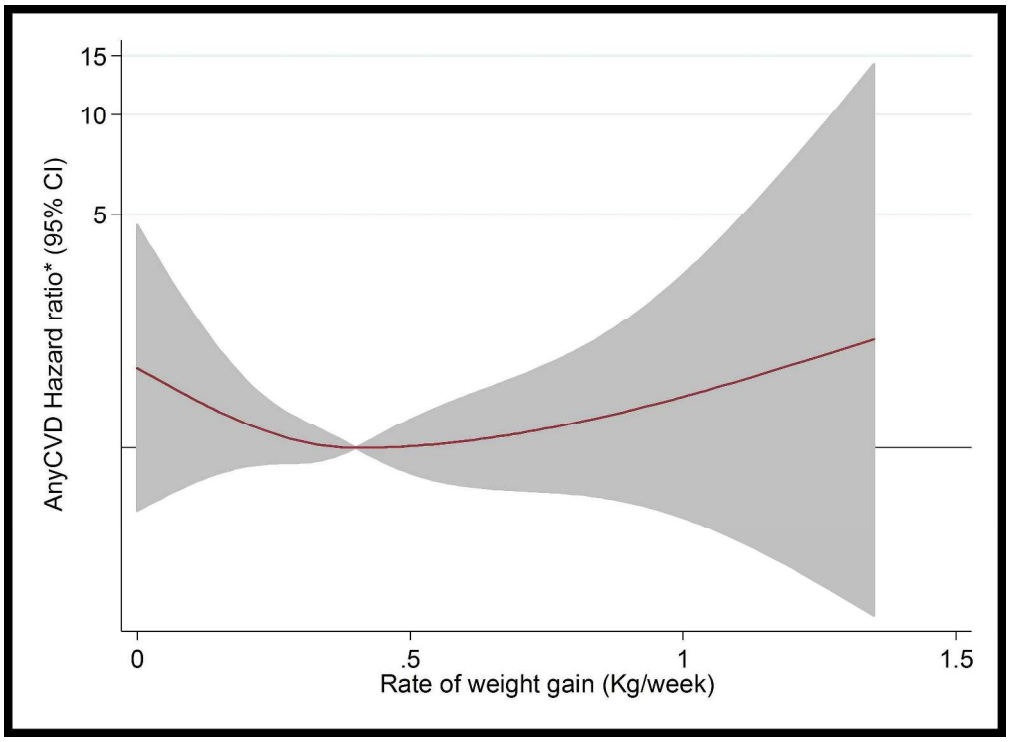

Fig 3 Adjusted Hazard Ratios with 95% confidence intervals of any cardiovascular disease event in the offspring by rate of maternal gestational weight gain

381x278mm (300 x 300 DPI)

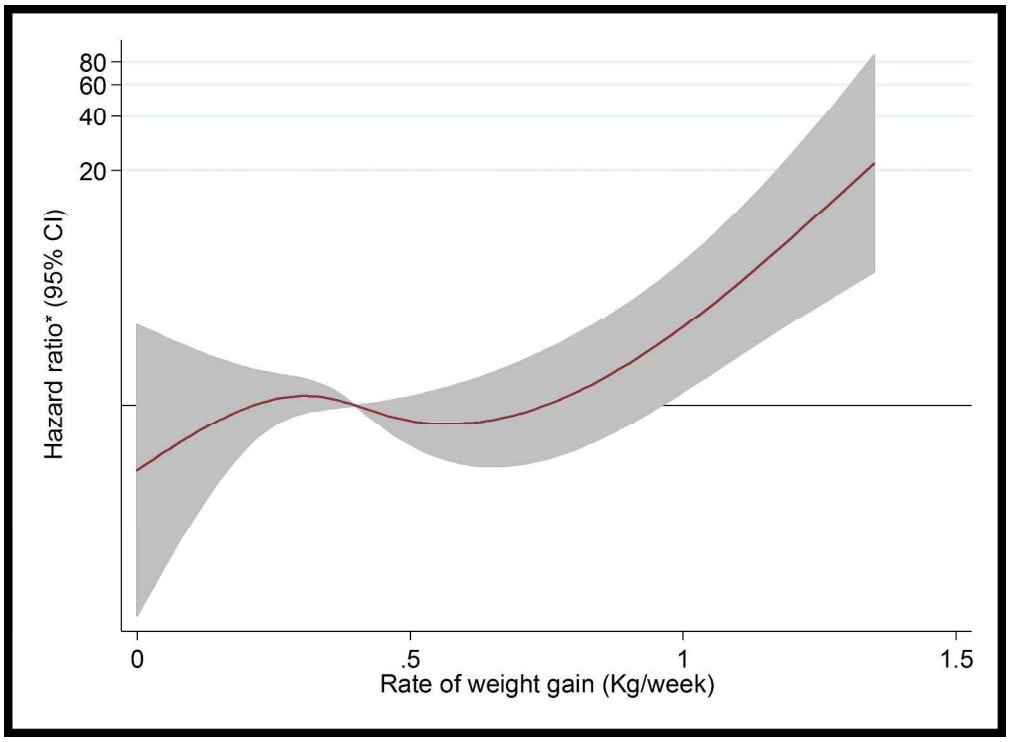

Fig.4. Adjusted hazard ratios with 95% confidence intervals for mortality due to or any cerebrovascular disease event in the offspring by maternal gestational weight gain
381x278mm (300 x 300 DPI)

Maternal and perinatal risk factors for childhood cancer
Supplemental file: STROBE Statement
Checklist of items that should be included in reports of case control studies

	Item No	Recommendation	Location within manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract: Methods Pg 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract: Methods and Results Pg 2
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction Pg 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction: last two lines Pg 5
Methods			
Study design	4	Present key elements of study design early in the paper	Methods: Pg 7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods Pg 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods Pg 5 - 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods Pg 8 -9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods; Pg 6 - 7
Bias	9	Describe any efforts to address potential sources of bias	Discussion Pg 16
Study size	10	Explain how the study size was arrived at	Results Pg 11; Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods: Pg 9 - 10

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis in methods Pg 9 - 10
		(*b*) Describe any methods used to examine subgroups and interactions	Not specified
		(*c*) Explain how missing data were addressed	Methods Pg 11
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable.
		(*e*) Describe any sensitivity analyses	Not conducted
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results Pg 11 and figure 1
		(b) Give reasons for non-participation at each stage	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 and Results Pg 11 - 12
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2, Results: Pg 12 - 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 and Table 3, figures 2, 3, 4.
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion Pg 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion Pg 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion Pg 17

Generalis-ability	21	Discuss the generalisability (external validity) of the study results	Discussion Pg 15

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page