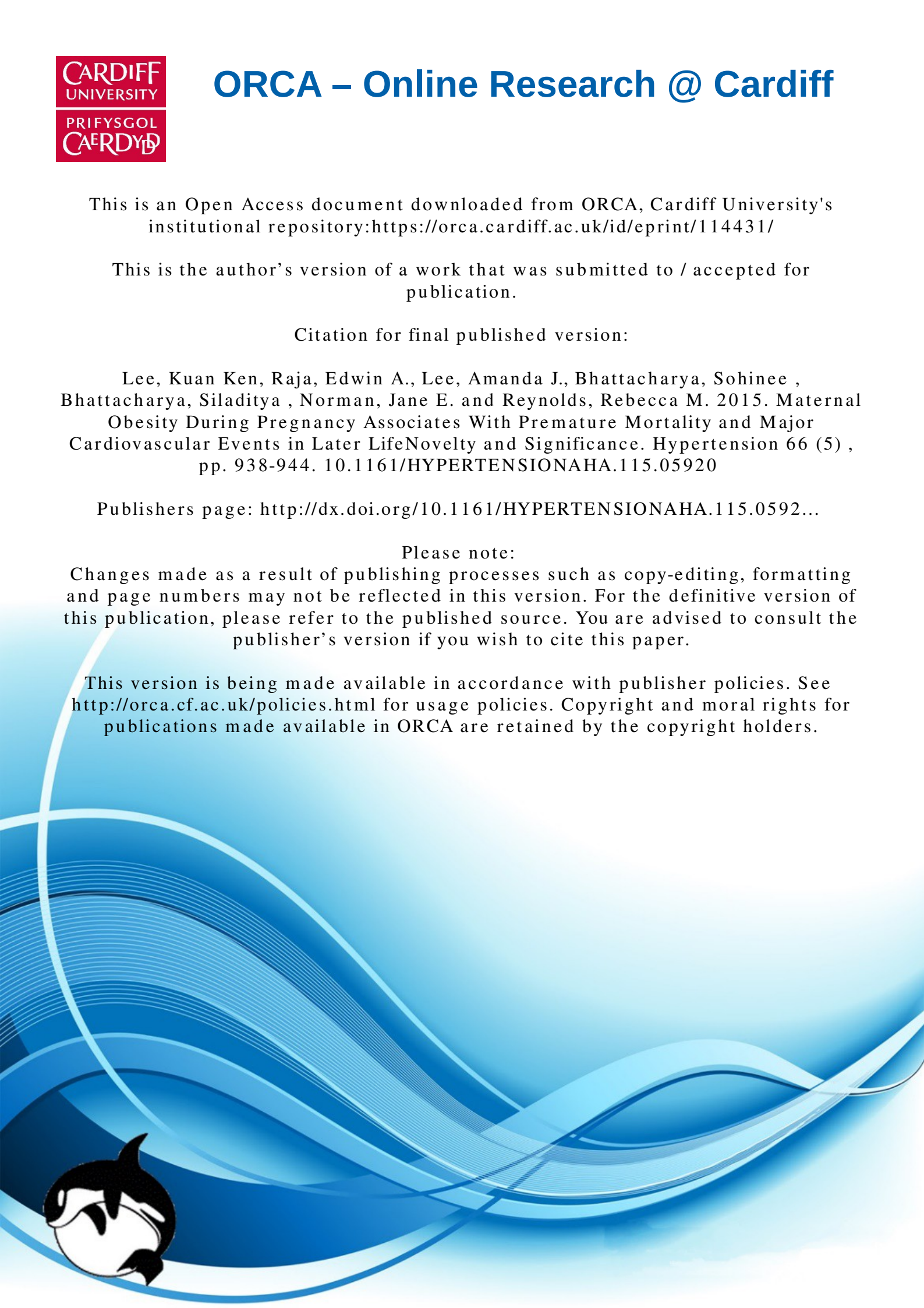

MATERNAL OBESITY DURING PREGNANCY ASSOCIATES WITH PREMATURE MORTALITY AND MAJOR CARDIOVASCULAR EVENTS IN LATER LIFE

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Abstract

One in five pregnant women is obese but the impact on later health is unknown. We aimed to determine whether maternal obesity during pregnancy associates with increased premature mortality and later life major cardiovascular events. Maternity records of women who gave birth to their first child between 1950 and 1976 (n=18,873) from the Aberdeen Maternity and Neonatal databank were linked to the National Register of Deaths, Scotland and Scottish Morbidity Record. The effect of maternal obesity at first antenatal visit on death and hospital admissions for cardiovascular events was tested using time to event analysis with Cox proportional hazard regression to compare outcomes of mothers in underweight, overweight, or obese BMI categories compared to normal BMI. Median follow-up was at 73 years. All-cause mortality was increased in women who were obese during pregnancy (BMI>30kg/m^2) compared with normal BMI after adjustment for socioeconomic status, smoking, gestation at BMI measurement, pre-eclampsia and low birthweight (hazard ratio 1.35, 95% confidence interval 1.02 to 1.77). In adjusted models, overweight and obese mothers had increased risk of hospital admission for a cardiovascular event (1.16, 1.06 to 1.27 and 1.26, 1.01 to 1.57) compared to normal BMI mothers. Adjustment for parity ~~increased~~ largely unchanged the hazard ratios (mortality: 1.43, 1.09 to 1.88; cardiovascular events overweight 1.17, 1.07 to 1.29 and obese 1.30, 1.04 to 1.62). In conclusion, maternal obesity is associated with increased risk of premature death and cardiovascular disease. Pregnancy and early post-partum could represent an opportunity for interventions to identify obesity and reduce its adverse consequences.

Key words: obesity, BMI, pregnancy, cardiovascular disease, death

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INTRODUCTION

Overweight and obesity is a growing threat to population health worldwide. (1) During the last two decades the prevalence of obesity has increased rapidly across all age groups. (2) A recent report from the American Heart Association has documented the alarmingly rapid rise in prevalence of obesity in the young (3), which is of concern as longer cumulative exposure to adiposity could potentially lead to higher risk of premature disease. (4) Prevention of obesity at an early stage could therefore lead to much greater benefit. However, whilst there is a substantial literature exploring the relationship between BMI and mortality, most of these studies included height and weight measured in middle age; few have examined the association between adiposity in early life and cardiovascular mortality and even fewer have explored this relationship in women of reproductive age.

In the United States, 64% of women of reproductive age are overweight and 35% are obese, (2) a pattern similar to Europe. (5) Although young women are increasingly recognized as an overlooked group with disproportionately high morbidity following cardiovascular events compared to older men and women, the association between their obesity and the risk of cardiovascular disease has yet to be determined. Pregnancy results in critical changes in weight at a time when women have relatively greater contact with healthcare professionals and are highly motivated to improve their health. This could

represent a window of opportunity for interventions to reduce obesity and to identify those who would benefit from primary prevention strategies for cardiovascular disease.

A recent study of 11 006 women with 37 year follow-up reported an association between self-reported BMI in pregnancy and increased coronary heart disease mortality. (6) The study included multiparous women which may have introduced bias due to cumulative weight gain with increasing parity. (7) Additionally, self-reported BMI is notoriously inaccurate. (8) We hypothesized that maternal obesity in the first pregnancy is associated with increased risk of premature death and increased cardiovascular events in later life and that increased parity would associate with greater risk. To test this hypothesis we examined hospital admissions for cardiovascular events and death rates in 18 873 women who were pregnant with their first child between 1950-1976. We used a large database of pregnancy data, the Aberdeen Maternity and Neonatal Databank (AMND), linked to national death and morbidity records with a median of 50 years' follow-up. The large size of the database allowed us to examine additional effects in women who had clinically diagnosed pre-eclampsia (9) and/or a baby with low birthweight, two pregnancy complications which are associated with maternal obesity and also potentially maternal cardiovascular disease later in life.

METHODS

Detailed description of Methods is given in the on-line only Data Supplement. Briefly, maternity records of women who gave birth to their first child between 1950 and 1976 (n=18,873) from the AMND were linked to the National Register of Deaths, Scotland and Scottish Morbidity Record. The effect of maternal obesity at first antenatal visit on death and hospital admissions for cardiovascular events was tested using time to event analysis using two Cox proportional hazard models to compare outcomes of mothers in underweight, overweight, or obese BMI categories compared to normal BMI. The first model was the standard approach in which the primary time scale was time on study (defined as time between age at delivery and 'event') with age at delivery included as a confounder. The second model used age as the primary time scale (10), and age at delivery as the year at entry in order to control for the stronger effects of age in later life. The results of this second model are reported in the paper, whilst the results of the first model were considered as a sensitivity analysis and are reported in the supplement. All analyses were done (i) for all women with the first maternal weight measured at any time during pregnancy and (ii) for the subset of women with first weight recorded before 20 weeks' gestation to avoid the additional influences of weight gain during pregnancy, which might be an independent risk factor for the outcomes of interest.

RESULTS

Table S1 shows the characteristics of the 18 873 women who delivered their first singleton baby at term between 1950 and 1976. A total of 17.3% (n=3260) were

overweight and 2.4% (n=452) were obese. Obese women were older, more likely to smoke, and of lower social class. The gestation at which weight was first measured in the pregnancy was significantly later in obese women. The characteristics of women whose weight was measured in the first half of pregnancy were otherwise similar to the complete dataset. 5,552 (29.4%) women had more than one pregnancy.

Maternal obesity and mortality

Among the 18 873 women, there were 2005 deaths from any cause. 41.9% were deaths from cardiovascular causes. Table 1 shows the hazard ratios and 95% CI for death in offspring according to maternal BMI category. There was significantly greater all-cause mortality in mothers who were obese. In the subgroup with BMI measurements taken before 20 weeks, unadjusted hazard ratios were significantly higher in both overweight and obese mothers compared with those of normal weight and remained significant for overweight women after adjustment for social class, smoking status, gestational age at which weight was measured, pre-eclampsia and low birth weight. Survival curves are displayed in Figure 1a.

Maternal obesity and cardiovascular events

At time of follow-up, 17% of women (n=3220) had been admitted to hospital with a cardiovascular event. In the complete dataset, there was a significant association between maternal overweight and obesity and increased cardiovascular events in later life (Table 2

and Figure 1b). Major cardiovascular events, (MACE) were significantly higher in mothers who were underweight, and obese. There were also significant associations between maternal overweight and peripheral arterial disease and other cardiovascular disease and maternal obesity and angina, peripheral arterial disease and other cardiovascular disease. Similar patterns were seen in the restricted dataset of women with BMI measured in early pregnancy (Table S2). All-cause mortality and MACE were significantly greater in women who had a low birthweight baby (n=120 (15.5%) vs. n=1885 (10.4%), $p<0.01$ and n=147 (18.9%) vs. 2413 (13.3%), $p<0.001$, respectively) but not in women with a history of pre-eclampsia (n=9.1 (9.3%) vs. n=1914 (10.7%), $p=0.169$ and n=118 (12.1%) vs n=2442 (13.7%), $p=0.160$, respectively). Hazard ratios for MACE remained significant after adjusting for husband/partner's social class, smoking status, gestational age at which weight was measured, pre-eclampsia and low birth weight (Tables 2 and S2).

Exploring the non-linear relationship of maternal BMI and outcomes

Figure 2a shows that the hazards of women's death (all-cause mortality) were greater among women with low BMI compared to those with BMI of 23 kg/m^2. The hazards ratio increased as the maternal BMI increased over 23 kg/m^2. It can be inferred from Figure 2a that the chances of death increased with increasing maternal BMI above 25 and the association was non-linear ($p<0.05$). A similar pattern was observed for MACE (Figure 2b).

Analyses repeated using the time scale as time-on-study (see online supplement) showed a similar pattern with significantly greater all-cause mortality in mothers who were obese (adjusted HR1.37, 95% CI 1.04 to 1.80). In the subgroup with BMI measurements taken before 20 weeks, hazard ratios were significantly higher in overweight mothers compared with those of normal weight. Likewise there was a significant association between maternal overweight and obesity and increased cardiovascular events in later life (adjusted HR1.26, 95% CI 1.15 to 1.38 and adjusted HR 1.52, 955 CI 1.22 to 1.90 respectively). Major cardiovascular events, MACE were significantly higher in women who were underweight and obese (See Tables S3, S4 and Figures S1-4).

Exploring the influence of parity and weight change between pregnancy on outcome

Additional adjustment for parity in the models largely unchanged ~~strengthened~~ the between maternal obesity and outcomes though ~~as indicated by greater~~ hazard ratios (Tables 1,2 and S2).Maternal BMI trajectories across pregnancies in the 5552 women with more than one pregnancy are shown in Figure S5. Almost all women gained some weight between pregnancies. In general, women with higher first pregnancy BMI had a steeper increase in BMI trajectory with subsequent pregnancies than women with lower first pregnancy BMI. Subsequent analyses to look at the influence of change in BMI between first and last pregnancy were underpowered but overall were consistent with a greater adverse effect of having a first pregnancy BMI overweight or obese than having a positive change in BMI between pregnancies (Table S5).

DISCUSSION

In this large cohort study, maternal overweight and obesity were strongly associated with premature death from cardiovascular disease and risk of later life major adverse cardiovascular events. While the increased adverse health risks from obesity are accepted, controversy remains about the relationship between overweight and mortality. We found mothers who were overweight at <20 weeks gestation also had a higher risk for all-cause mortality and hospitalisation for cardiovascular disease in later life.

Our results build on existing literature describing the association between BMI and cardiovascular morbidity and mortality. Consistent with other publications, we observed a J-shaped association between BMI and all-cause mortality and hospitalisation for cardiovascular events. (11-13) Most previous studies have recruited middle aged women and very few have examined the association between mortality and BMI in young adulthood. (14-16) Unlike our study which had a median follow-up period of 50 years, up to the age when cardiovascular events occur, the Nurses' Health Study (14,15) and US National Interview Survey study (16) had a relatively short period of follow-up of less than 20 years. Ending follow-up before the age of highest risk would underestimate the association between BMI and cardiovascular mortality and does not take into account other cumulative factors that may alter the trajectory of risk in later life.

Our results are consistent with the one previous smaller study examining the association between BMI in pregnancy and subsequent mortality (6). The Child Health and

Development Studies Cohort had fewer years of follow-up, relied on self-reported pre-pregnancy BMI and included a significant proportion of multiparous women. In our primary analysis we selected only those women with BMI measured at their first pregnancy. Child-bearing results in a significant accumulation of weight (17) and is strongly associated with cardiovascular disease making it difficult to avoid residual confounding. (7,18) We excluded rather than adjusted for those with prior pregnancies in order to eliminate the possibility that both maternal BMI and cardiovascular events are confounded by prior parity. Indeed, 29.4% of women in the study had subsequent pregnancies ~~and~~ but inclusion of parity in the models largely unchanged ~~increased~~ the of the associations. In addition, we were able to include adjustment for low birthweight and pre-eclampsia, two pregnancy complications that have been linked to later-life cardiovascular disease (19,20), and which themselves are increased in women with maternal obesity. Consistent with some studies (19) we found a significant association between low birth weight and adverse outcome, but unlike others (20) we found none with pre-eclampsia. This was surprising but may reflect the relatively small sample size (n=978). Inclusion of both low birthweight and pre-eclampsia in our models did not significantly alter the findings, so the effect of maternal obesity on later life MACE occurs independently of pregnancy complications.

A major strength of our study was its large size and the quality of the antenatal records. Height and weight were measured at the first antenatal visit and so calculation of BMI did not rely on self-reported values which can lead to recall bias and underestimation of BMI in overweight and obese individuals. Furthermore, linkage rates were greater than

80%. The use of collated data from the Information and Services Division enabled us to capture events among women who moved from Aberdeen to other parts of Scotland but not those occurring outside the country. The loss of information was likely unconnected to maternal weight or death therefore its effect will have been to reduce the strength of associations rather than introducing a systematic bias. In addition, although we did not record data on co-morbid disease, BMI was recorded in the women at a median age of 23 years, reflecting typical adult weight largely unaffected by pre-existing disease that may affect both weight and risk of death. Individuals are also less likely to experience adverse events early during follow-up when deaths are likely a result of pre-existing disease. This minimizes the potential for reverse causation and survivor bias.

A further strength of our study is the statistical approach that we used to examine 'time to event'. There are two choices of time scale for a Cox proportional hazards model, time on study or age (21,22). Korn et al (21) proposed the use of age as the time-scale (with or without adjustment for any cohort effect) for longitudinal studies and studies examining 'all-cause' mortality to account for the fact that the ageing process is associated with an increasingly higher risk of chronic diseases and mortality. The Framingham Heart study (23) used time on study as their time scale, whilst the Systematic Coronary Risk Evaluation (SCORE) project (24) used age. Our results, like those from the Framingham study show similar estimates from both models (25).

The main limitation of our study was its reliance on height and weight measured at a single point in time. Changes in weight during pregnancy or across the lifecourse, post pregnancy exposures and other lifestyle factors that influence cardiovascular disease were not measured. We attempted to explore the influence of change in BMI between pregnancies. Although underpowered, the data suggest that the first pregnancy BMI had a stronger impact in determining outcome than the change in BMI per se. Nevertheless, as no first trimester BMI was available for many of the women, more work is needed to further interrogate the effects of change in weight between pregnancy and gestational weight gain on outcomes. Whilst we acknowledge that the numbers of women who were obese at first pregnancy in this study were small, these findings are of major public health concern if findings are extrapolated to the much higher levels of obesity in pregnancy seen today. With a median age of 73 at the end of follow-up, our cohort was relatively young and therefore it is likely that the rate of adverse events will continue to increase over time. In particular, this is at an age before the mean age at first stroke in women (26) and may explain the small number of cerebrovascular events in the study. We also only looked at hospital admissions for cardiovascular events; therefore we only examined more severe cardiovascular disease. A further limitation is that we had no data on early adverse maternal perinatal outcomes. However, by limiting our analysis to live births we hope to have reduced the numbers of such events. We also had no information on gestational diabetes or gestational hypertension, ~~a~~ known risk factors for later cardiovascular disease.

Perspectives

To our knowledge, this is the largest study examining the association between maternal obesity at pregnancy (measured objectively) and cardiovascular mortality. More work is needed to understand the mechanisms, but it is thought that the spectrum of cardiometabolic changes observed in obese pregnancy (27-29) potentially "unmask" a vascular phenotype that may re-emerge in later life with adverse cardiovascular events. In a previous study, we demonstrated an association between maternal obesity and cardiovascular mortality in the adult offspring of overweight and obese mothers. (30) Here we find that the adverse effects of obesity in pregnancy also have an adverse impact on maternal health. With the rising rates of maternal obesity, our findings of an association between maternal overweight and obesity and premature death in later life is a major public health concern. Pregnancy and the early post-partum period are key episodes in a woman's life when critical changes to weight coincide with close contact with healthcare professionals and a strong motivation to improve her health. This could represent an important window of opportunity to identify women at risk and reduce the shift to obesity.

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Disclosures

None

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Novelty and significance

What is new?

Using maternity records of women who gave birth to their first child between 1950 and 1976 from the Aberdeen Maternity and Neonatal databank linked to the General Register of Deaths, Scotland and the Scottish Morbidity Record systems, with median follow-up of 73 years, we showed that maternal obesity in pregnancy is associated with an increased risk of premature death and cardiovascular disease in later life.

What is relevant?

Obesity in middle age is recognised as cardiovascular risk factor but few studies have examined the long-term effects of obesity in young adult women. One in five women is currently obese at antenatal booking and pregnancy could represent a window of opportunity for interventions to identify obesity and reduce its adverse consequences.

Summary

Our study shows that maternal obesity identified in the first pregnancy is associated with an increased risk of premature death and cardiovascular disease in later life.

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