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Metabolic Syndrome and time to pregnancy: a retrospective study of nulliparous women

Running title: Metabolic syndrome and fertility

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Objectives: To determine 1) the association between metabolic syndrome (MetS), time to pregnancy (TTP), and infertility 2) associations between individual and increasing number of MetS components, TTP, and infertility; 3) whether these relationships differ by obesity (BMI, $<30\text{kg/m}^2$ vs. $\geq 30\text{kg/m}^2$).

Design: Retrospective cohort study.

Setting: Multi-centre (Australia, United Kingdom, New Zealand, Ireland).

Population: 5519 low-risk nulliparous pregnant women.

Methods: Data on retrospectively reported TTP (number of months to conceive) and a blood sample to assess metabolic health were collected between 14-16 weeks' gestation. MetS was defined according to the International Diabetes Federation criteria. Accelerated failure time models with log normal distribution were conducted to estimate time ratios (TR) and 95% CIs. Differences in MetS on infertility (TTP >12 months) was compared using a generalized linear model (Poisson distribution) with robust variance estimates (RR; 95% CIs). All analyses (entire cohort and split by BMI) were controlled for a range of maternal and paternal confounders.

Main Outcome Measures: TTP and infertility.

Results: Of the 5519 women included, 12.4% ($n=684$) had MetS. Compared to women without MetS, women with MetS had a longer TTP (adjusted TR 1.30; 95% CI: 1.15-1.46), which was similar in the obese and non-obese women. Marginal estimates for median TTP in women with MetS vs. without MetS was 3.1 (3.0-3.3) months vs. 4.1 (3.6-4.5) months, respectively. Women with MetS were at a 62% greater risk for infertility and were at a greater risk for infertility whether they were obese (adjusted RR 1.62; 1.15-2.29) or not (adjusted RR 1.73; 1.33-2.23). Reduced HDL-C and raised TG were the main individual components associated with risk for infertility.

Conclusions: MetS is associated with longer TTP and infertility, independent of obesity. Additional studies, pre-pregnancy, are required to support our findings and to determine the

61 applicability of which combinations of metabolic abnormalities pose greatest risk to delayed
62 fertility, or whether individual components are amenable to modification.

63

64 **Keywords:** metabolic syndrome, lipids, pregnancy, fecundity, time to pregnancy, infertility,
65 retrospective study

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67 **Tweetable abstract:** MetS associates with longer time to pregnancy and infertility,
68 independent of obesity.

69 **Introduction**

70 Metabolic health encompasses metabolic, vascular and inflammatory markers, and a clustering
71 of metabolic health abnormalities is called metabolic syndrome (MetS). While cardiometabolic
72 risk factors often cluster together and commonly associate with obesity ¹, obesity and MetS
73 can also exist independently ²⁻⁴.

74 Time to pregnancy (TTP) is a measure of how long a couple takes to conceive and
75 infertility is the failure to achieve pregnancy after 12 months or more of regular unprotected
76 sexual intercourse ⁵. Obesity is consistently associated with impaired fertility ^{6, 7}, however,
77 assessment of MetS has not been widely assessed in relation to infertility. Evidence from
78 human studies in women diagnosed with or receiving treatments for infertility, have shown
79 individual metabolic components such as raised triglycerides, total cholesterol, or low density
80 lipoprotein cholesterol, or reduced levels of high density lipoprotein cholesterol was associated
81 with infertility ⁸ or longer TTP ⁹. In couples planning a pregnancy, raised concentrations of
82 free cholesterol were associated with longer TTP ¹⁰.

83 Emerging evidence also suggests a link between infertility and cardiovascular disease
84 (CVD). A recent study demonstrated that women who reported infertility had 1.83 times higher
85 odds of having experienced a cardiovascular event compared to women who had never
86 experienced infertility ¹¹. In the adult population, the utility of MetS in predicting CVD
87 compared to its individual risk factors has been debated ¹²⁻¹⁴. However, given the reported
88 associations between individual MetS components and fertility and the recent evidence of the
89 association between infertility and CVD, the current study presents a unique opportunity to
90 investigate whether MetS associates with TTP and infertility.

91 In the adult population, the utility of MetS in predicting cardiovascular disease (CVD)
92 compared to its individual risk factors has been debated ¹²⁻¹⁴. However, given the reported

associations between individual MetS components and fertility, and CVD, the current study presents a unique opportunity to investigate whether MetS associates with TTP and infertility.

We hypothesise that MetS is associated with a longer TTP and a higher rate of infertility. The study objectives were three-fold: 1) to determine the association between MetS, TTP, and infertility 2) to examine associations between individual and increasing number of MetS components, TTP, and infertility; 3) to determine whether these relationships differ by obesity status (body mass index, $<30\text{kg/m}^2$ vs. $\geq 30\text{kg/m}^2$).

Materials and Methods

Study population

The Screening for Pregnancy Endpoints study (SCOPE) is a multi-centre prospective cohort study which recruited nulliparous women with singleton pregnancies from Adelaide (Australia), Auckland (New Zealand), Cork (Ireland), Leeds, London and Manchester (UK) (n=5628). The primary aim of SCOPE was the development of screening tests for prediction of preeclampsia, spontaneous preterm birth and small for gestational age babies. Recruitment was between November 2004 and February 2011. Included women were nulliparous with singleton pregnancies. Exclusion criteria and detailed descriptions of the SCOPE study have been published previously ¹⁵.

Ethics approval was obtained from local ethics committees [New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London, Leeds and Manchester 06/MRE01/98 and Cork ECM5 (10) 05/02/08] and all women provided written informed consent. Core outcome sets were not used, and women were not involved in the development of the research question or study outcomes. The Australian SCOPE study was funded by the Premier's Science and Research Fund, South Australian Government (<http://www.dfeest.sa.gov.au/science-research/premiers-research-and-industry-fund>). The New Zealand SCOPE study was funded

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Data collection

Data were collected by a research midwife at 14-16 weeks' gestation. Information was collected at each study centre (Adelaide, Auckland, Cork, Leeds, London, Manchester) on demographics, smoking, family, medical and gynecological history, and diet and supplement use. Weight and height (to determine BMI) were measured without shoes, or jacket, to the nearest 0.1 kg and cm, respectively. Waist circumference (WC) was measured using a tape measure, at the point half way between the top of the hip (iliac crest) and inferior margin of lowest rib. Two consecutive manual blood pressure measurements (mercury or aneroid sphygmomanometer, with a large cuff if the arm circumference ≥ 33 cm and Korotkoff V for

diastolic blood pressure) were recorded. Women reported if the current conception was associated with the use of any fertility treatments (e.g. IVF, ICSI, ovulation induction). A non-fasting blood sample was taken for measurement of HDL-C and TG at the same visit and a random whole blood glucose was measured using a glucometer, as fasting glucose samples were not available for all women in all centers. Details of immunoassay methodology for measuring lipids can be found in previous publications ^{16, 17}.

Assessment of exposure (metabolic syndrome)

MetS was defined according to the International Diabetes Federation (IDF) criteria ¹⁸. The IDF criteria cut-points are the same as the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) ¹⁹, except for glucose and WC which are both slightly lower in IDF, and in NCEP ATP III, WC is not a pre-requisite in determining MetS. The IDF criteria was chosen because the cut-point for WC aligns with the World Health Organisation guidelines ²⁰ and because WC provides a unique indicator of body fat distribution, which can identify patients who are at increased risk for obesity-related cardiometabolic disease, above and beyond the measurement of BMI ²¹. A WC ≥ 80 cm is a prerequisite risk factor, along with any 2 of the 4 variables: raised TG [≥ 1.70 mmol/L (≥ 150 mg/dl)], reduced HDL-C [< 1.29 mmol/L (< 50 mg/dL)], raised BP (i.e. systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg), or raised fasting plasma glucose (≥ 5.6 mmol/L). As this was a pregnancy cohort, a random plasma glucose sample was measured, however the same concentration cut-off was used as IDF criteria (≥ 5.6 mmol/L).

Assessment of outcome

Estimates of retrospectively reported TTP were derived from the following question “duration of sex without contraception before conception with father of baby”. Values, in months, were

recorded in a continuous fashion and used to define TTP. For this purpose of this study, infertility was defined as having a TTP of more than 12 months or use of assisted reproductive technologies. Women who conceived in their first month had a reported TTP of 1 month, with prolonged TTP censored at 12-months of attempting to conceive.

Assessment of covariates

Maternal ethnicity was self-reported and binary coded as Caucasian or other (90% were Caucasian). The socioeconomic index was developed in New Zealand and is a measure of the individual's socioeconomic position derived from a specific occupation ²². It provides a value of 10-90 with a higher score indicating higher socioeconomic position ²³. Women who had ≥ 1 of any previous miscarriage at ≤ 10 weeks' gestation or > 10 weeks' gestation were binary coded as yes/no for previous miscarriage. Retrospectively reported data at this same visit was also obtained: cigarette use and any intake of alcohol per week in the 3 months pre-pregnancy were binary coded as yes or no. Number of servings of fruit (fresh fruit and fruit juice), green leafy vegetables (vegetables high in folate such as spinach, cabbage, lettuce, broccoli), fish (with prompts of fish such as salmon, trout, sardines, shellfish and shrimp) and "fast food" (frequency of intake of burgers, fried chicken, pizza, and hot chips) have been described previously ²⁴. Paternal data, including paternal age, and paternal height and weight (to calculate BMI), was self-reported from the biological father at the first (14-16 weeks' gestation) or second (19-21 weeks' gestation) antenatal visit, or after the baby was born.

Statistical analyses

Frequencies and descriptive statistics of all women were expressed as n (%) or as means (standard deviation, SD). Median [inter-quartile range, IQR] was reported when continuous variables were not normally distributed. The impact of MetS on TTP was investigated using

accelerated failure time models²⁵ with log normal distribution to estimate time ratios (TR) and 95% CIs. Adjusted marginal estimates for median TTP according to MetS status were calculated using the STATA ‘margins’ command, together with corresponding 95% CIs. Alternative distributions were investigated but the log normal distribution was selected based on providing the lowest -2 log likelihood and Akaike information criterion value. These TRs can be interpreted as the ratios of the median values of the duration (in months) to achieve pregnancy between the compared groups. A TR above 1 implies that a given exposure is associated with longer TTP, whereas a TR below 1 indicates a shorter TTP. The impact of MetS, analysed i) a composite, ii) each metabolic component, and iii) with increasing number of MetS components above the IDF cut-point, and infertility, was compared using a generalized linear model (Poisson distribution) with robust variance estimates, with resulting relative risks (RR) and 95% CIs. The association between MetS, its individual components, and with increasing number of MetS components were assessed in the entire cohort and split by women who had a non-obese ($<30.0 \text{ kg/m}^2$) or obese ($\geq 30 \text{ kg/m}^2$) BMI.

We used causal diagrams (directed acyclic graphs) to guide selection of potential confounders for which to control, based on *a priori* selection of variables considered to be a common cause of MetS and fertility. Two separate adjusted models were used. Model 1: maternal BMI, maternal age, SEI, study centre, ethnicity (Caucasian/other), previous miscarriage (yes/no), smoking status (yes/no), alcohol intake (yes/no); Model 2: model 1 plus maternal dietary intake prior to conception, paternal age, paternal BMI. The individual MetS risk factors were not included as covariates and models for each MetS component were run individually. This was a complete case analysis.

Sensitivity analyses were performed to evaluate the robustness of the results, which were selected based on key potential sources of bias in retrospective TTP studies²⁶. Truncation bias is possible where TTP distributions or covariates are nonstationary over time and is

particularly important where exposures may vary systematically over time²⁶. The potential for truncation bias was corrected for by restricting the analysis to women with a starting time between the second year and penultimate year of participant recruitment at each site (n=3662) to account for left and right truncation bias, respectively²⁶. The exclusion of accidental or unplanned pregnancies from the analysis can introduce planning bias if the likelihood of accidental or unplanned pregnancy is associated with the exposure of interest. The potential for planning bias was corrected for by restricting the analysis to couples who reported TTP of >1 month (n=3358).

Statistical significance was defined as a two-sided p-value of <0.05. All statistical analyses were undertaken using STATA IC 14 (Stata, College Station, Texas).

Results

Participant characteristics

A total of 5519 women were included in the analysis, of which 12.4% (n=684) had MetS. Participant characteristics are reported in Table 1, and Figure S1 shows the participant flow. The median [IQR] duration of TTP in women with and without MetS was 3 [1-11] months and 2 [1-6] months, respectively, and 22.4% (n=153) and 13.7% (n=660) were infertile at 12 months ($P<0.001$). Women with MetS had a higher BMI, a lower SEI, a higher percentage smoked, but a lower percentage consumed alcohol in the one month prior to conception (Table 1).

Table 2 shows the number and type of MetS components in all women and stratified by obesity (≥ 30 kg/m² vs. <30 kg/m²). In all 5519 women, 37.0% (n=2040) had one MetS component of which high WC was most frequent (n=1295, 63.5%); 28.5% (n=1571) had two MetS components with high WC (n=1377, 87.6%) and raised glucose (n=909, 57.9%) most frequent. In the non-obese group (n=4685, <30 kg/m²), high WC was the most frequent MetS component, followed by raised glucose (n=765, 61.5%) in women with 2 components, but raised TG (n=321, 88.2%) in women with 3 MetS components. In the obese group (n=833), all women had a high WC, and in women with an additional 2, 3 or 4 MetS components, raised TG and raised glucose were most frequent.

Relationship between MetS, its individual components, and TTP

The relationship between MetS and TTP is presented in Table 3. Compared to women without MetS, women with MetS had a longer TTP, after adjustment of covariates (TR 1.30; 95% CI: 1.15-1.46). The adjusted TR for the association between MetS and TTP was similar in the non-obese and obese groups (Table 3). Marginal estimates for median TTP in women with MetS vs. without MetS was 3.1 (3.0-3.3) months vs. 4.1 (3.6-4.5) months, respectively.

In the entire cohort (Table 3), individual components of MetS such as reduced HDL-C (1.37; 1.15-1.64), raised TG (1.11; 1.02-1.21) and raised glucose (1.11; 1.02-1.20), all associated with longer TTP. Raised BP and WC were not associated with TTP. In the obese group, reduced HDL-C demonstrated the largest adjusted TR (1.70; 1.22-2.38), followed by raised TG (1.24; 1.01-1.53). Raised glucose and raised BP were not associated with TTP (Table 3).

In the entire cohort, there was a dose response relationship with increasing number of MetS and TTP (Table 3). That is, compared to no MetS components, the adjusted TR for each additional component was 0.97 (0.89-1.06) for 1 component, 1.08 (0.97-1.19) for 2 components, 1.21 (1.06-1.39) for 3 components, and 1.54 (1.16-2.04) for ≥ 4 components. There was a dose response relationship with increasing number of MetS in the non-obese and obese women, such that for ≥ 4 components, the adjusted TR was 1.45 and 2.24, respectively. Table S1 shows a mutually adjusted model (i.e. all MetS components in the one model), reporting the association between individual components of MetS and time to pregnancy or infertility in all women.

Relationship between MetS, its individual components, and infertility

MetS and risk for infertility is presented in Table 4. Women with MetS were at a 1.62 fold (1.32-1.99) greater risk for infertility, and women were at a greater risk for infertility whether they were obese (1.62; 1.15-2.29) or not (1.73; 1.33-2.23). Reduced HDL-C and raised TG were the main components associated with risk for infertility.

In all women, those with ≥ 4 MetS components had 2.06 times the risk of infertility compared to women with no MetS components (Table 4). There was a dose threshold effect with increasing number of MetS components and infertility in the non-obese women. In the obese women, those with ≥ 4 MetS components had 2.88 times the risk of infertility compared

to women with no MetS components.

Sensitivity analyses

Sensitivity analyses to evaluate possible truncation and planning bias demonstrated no remarkable difference in time ratio estimates for TTP with MetS, its individual components or with increasing number of MetS components (Table S2). In the truncated cohort, risk of infertility was slightly increased with MetS, its individual components, and with increasing number of MetS components (Table S3), and in the cohort restricted to TTP >1 month, risk ratios for infertility were slightly attenuated with increasing number of MetS components (Table S3).

Discussion

Main Findings

This is the first large, population based study to assess the association between MetS, measured in early pregnancy, and TTP and infertility. We report 12.4% (n=684) of women had MetS, and these women took approximately one month longer to get pregnant and were at a 62% greater risk for infertility, irrespective of obesity status. There is minimal published data measuring MetS in pregnancy, however a prevalence of 3.5% was reported in the mother-child cohort in Crete (n=625)²⁷, up to 36.4% (depending on glycemic status) in 136 pregnant women from Brazil²⁸, and up to 36.6% (using various MetS criteria) in 675 non-diabetic, pregnant Angolan women²⁹. The current study advances the literature assessing effects of individual metabolic health components and infertility by using established clustering of abnormalities that elicits increasing risk with increasing number of MetS components. Our results show that reduced HDL-C and raised TG appear to be major driving factors associated with delayed fertility.

Strengths and Limitations

Strengths include the large sample size, detailed collection of maternal and paternal factors, and information on method of conception. Jukic et al. highlights the strength of retrospective TTP studies in their ability to achieve a sample that is representative of the target population (i.e. women planning pregnancy) as opposed to prospective TTP studies that require recruitment of highly motivated couples, introducing the potential for response and planning bias³⁰. By definition, TTP relates only to periods of unprotected intercourse that end with conception. Sterility or subfertility bias can be introduced if the exposure of interest is associated with such severe negative impacts on fertility that women are simply not able to become pregnant. In this case, the exposure will be over-represented among women who were

able to become pregnant and the exposure may actually be observed to improve fertility (biasing results towards the null). In reality, such negative impacts on fertility are rare and this is unlikely to have influenced the results in this study. We performed a number of sensitivity analyses to test the robustness of our results demonstrating no remarkable difference in time ratio estimates for TTP or risk ratios for infertility with MetS.

Limitations include that assessment of MetS was assessed at 14-16 weeks' gestation, rather than pre-pregnancy, thus we do not know whether such measurements are reflective of those at the time of women trying to conceive. However, in a review of pregnant women without major medical problems, compared to normal laboratory reference values for non-pregnant adults, both HDL-C and TG in the first trimester demonstrated ranges that were similar to non-pregnant adults ³¹, supporting the acceptability of measuring lipids in early pregnancy. For HDL-C, there were only modest increases in the second and third trimesters whereas TG started to increase from the second trimester ³¹, similar to the elevations reported in smaller studies ^{32, 33}. It is also unlikely that measurement of WC, a pre-requisite for MetS diagnosis, would have significantly increased at the time of recruitment at 14-16 weeks' gestation ³⁴. We did not ask about menstrual cycle length which is often utilized alongside defining time to pregnancy. However, previous studies have indicated that long term recall of TTP has good agreement with prospective recall, assessed by questionnaires, even up to 25 years ^{30, 35, 36}. Thus it is unlikely that reporting of months for TTP rather than cycles leads to misclassification of TTP.

Interpretation

Metabolic syndrome in the adult population is consistently associated with cardiovascular and related diseases ³⁷⁻³⁹. We have recently shown that using the same cohort, women with MetS in pregnancy were at an increased risk for preeclampsia (RR 1.63; 95% CI: 1.23 to 2.15) and

gestational diabetes (RR 3.71; 95% CI: 2.42 to 5.67) ⁴⁰; such pregnancy complications are associated with increased risk for CVD in adulthood ^{41,42}. Our data suggest that MetS may be used to broadly identify women who are at increased risk for delayed fertility, whether they are obese or not. These women may also be susceptible to future CVD risk. The utility of diagnosing MetS pre-pregnancy to predict infertility, and the impact of MetS as a function of a combination of factors or exclusion of certain factors, require investigation in other pregnancy cohorts.

The association between obesity and infertility is well reported in previous studies ^{6, 7, 43}. However, in our study, the demonstration that MetS prolongs TTP and increases risk for infertility in non-obese women, independent of other well-known factors associated with infertility such as advanced maternal age, and cigarette use, highlights the need to consider all women in pre-pregnancy planning and antenatal care. We also found that reduced HDL-C and raised TG were the predominant factors impacting fertility, and the risk was more pronounced in the obese women.

Human mechanistic studies relating individual circulating lipoproteins and fertility is scarce ^{9, 10, 44}. However, there is extensive information characterising concentrations of lipoproteins in the oocyte ⁴⁵, revealing HDL-C is the most abundant lipoprotein in follicular fluid ⁴⁶, and appears to have the most influential role including embryo development and quality ^{45, 47, 48}. Triglycerides are found in lower amounts in follicular fluid and LDL-C is negligible ⁴⁶. Some human studies have demonstrated that increasing BMI associates with altered metabolites in the follicular fluid ^{46, 49-51}, but the evidence around an altered follicular microenvironment, oocyte quality and development, and clinical outcomes, is not strong ^{46, 50-53}. Moreover, the extent to which obesity mediates this relationship has not generally been significant ^{50, 51, 54}. Reduced HDL-C concentrations are a common feature in obese individuals ⁵⁵, whereas TG are highly variable ⁵⁶. Yet, concentrations of HDL-C measured in follicular

fluid were not different between women with lower or higher BMI, but TG in follicular fluid were reduced with increasing BMI^{50,51}. Further mechanistic examination into how circulating lipoproteins impact fertility and the ovarian microenvironment in women who are obese or not, is required. These results will be critical to support pre-conception counselling and current antenatal care.

Conclusion

MetS is associated with longer TTP and infertility, independent of obesity. Additional studies, pre-pregnancy, are required to support our results and to determine the applicability of which combinations of metabolic abnormalities pose greatest risk to delayed fertility, or whether individual components are amenable to modification. Modifications to metabolic profile may subsequently reduce risk for pregnancy complications and CVD in later life.

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Disclosure of Interest

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution of authors

LP, LMM, LCK, JM, JJW, GAD and CTR designed the SCOPE study. JAG and LEG designed the study concept, and JAG, LEG, LGS, and SYL designed the analysis plan. JAG drafted the first versions of the manuscript with subsequent contributions from LEG, LGS, PA, TBM, RJN, GAD and CTR. All authors were involved in critical discussion and all authors read and approved the final manuscript.

Details of ethics approval

Ethical approval was obtained from the relevant institutional ethic committees responsible for human experimentation and all women provided written informed consent. In New Zealand, approval for the SCOPE study was given by Northern Region Ethics Committee on 23/04/2003 reference number: AKX/02/00/364, in Australia by Central Northern Adelaide Health Service Ethics of Human Research Committee on 02/09/2005 reference number: REC 1714/5/Application number 2005082, in London, Leeds and Manchester by the NHS South East Research Ethics Committee, South East Coast Strategic Health Authority, Kent on 19/01/2007 reference number: 06/MRE01/98 and in Ireland by the University College Cork, Teaching Hospital Research Ethics Committee on 06/02/2008 reference number: ECM5(10)05/02/08.

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REFERENCES

1. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol.* 2006;26:968-76.
2. Bell LK, Edwards S, Grieger JA. The Relationship between Dietary Patterns and Metabolic Health in a Representative Sample of Adult Australians. *Nutrients.* 2015;7:6491-505.
3. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K et al. Identification and characterization of metabolically benign obesity in humans. *Archives of internal medicine.* 2008;168:1609-16.
4. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Archives of internal medicine.* 2008;168:1617-24.
5. World Health Organisation. (2015). *Sexual and reproductive health. Infertility definitions and terminology.* <http://www.who.int/reproductivehealth/topics/infertility/definitions/en/> Accessed 6th May 2017.
6. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertility and sterility.* 2017;107:840-7.
7. Zain MM, Norman RJ. Impact of obesity on female fertility and fertility treatment. *Womens Health (Lond).* 2008;4:183-94.
8. Verit FF, Yildiz Zeyrek F, Zebitay AG, Akyol H. Cardiovascular risk may be increased in women with unexplained infertility. *Clin Exp Reprod Med.* 2017;44:28-32.
9. Pugh SJ, Schisterman EF, Browne RW, Lynch AM, Mumford SL, Perkins NJ et al. Preconception maternal lipoprotein levels in relation to fecundability. *Human reproduction.* 2017;32:1055-63.
10. Schisterman EF, Mumford SL, Browne RW, Barr DB, Chen Z, Louis GM. Lipid concentrations and couple fecundity: the LIFE study. *The Journal of clinical endocrinology and metabolism.* 2014;99:2786-94.
11. Gleason JL, Shenassa ED, Thoma ME. Self-reported infertility, metabolic dysfunction, and cardiovascular events: a cross-sectional analysis among U.S. women. *Fertility and sterility.* 2018.
12. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation.* 2005;112:666-73.
13. Mozaffarian D, Kamineni A, Prineas RJ, Siscovick DS. Metabolic syndrome and mortality in older adults: the Cardiovascular Health Study. *Archives of internal medicine.* 2008;168:969-78.
14. Sundstrom J, Vallhagen E, Riserus U, Byberg L, Zethelius B, Berne C et al. Risk associated with the metabolic syndrome versus the sum of its individual components. *Diabetes care.* 2006;29:1673-4.
15. McCowan LM, Dekker GA, Chan E, Stewart A, Chappell LC, Hunter M et al. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. *Bmj.* 2009;338:b1081.
16. Fyfe EM, Rivers KS, Thompson JM, Thiagarajan KP, Groom KM, Dekker GA et al. Elevated maternal lipids in early pregnancy are not associated with risk of intrapartum caesarean in overweight and obese nulliparous women. *BMC Pregnancy Childbirth.* 2013;13:143.

- 476 17. Kenny LC, Lavender T, McNamee R, O'Neill SM, Mills T, Khashan AS. Advanced
477 maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort.
478 *PloS one*. 2013;8:e56583.
- 479 18. International Diabetes Federation. IDF Consensus Worldwide Definition of the
480 Metabolic Syndrome. The IDF consensus worldwide definition of the metabolic syndrome.
481 Available at file:///C:/Users/a1068108/Downloads/IDF_Meta_def_final.pdf. 2006.
- 482 19. NCEP. *Third Report of the National Cholesterol Education Program (NCEP) Expert*
483 *Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult*
484 *Treatment Panel III) final report*. *Circulation* 2002; 106: 3143-421.
- 485 20. World Health Organization. Waist Circumference and Waist-Hip Ratio. Report of a
486 WHO Expert Consultation. Geneva. 2008. Available at
487 [http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf;jsessionid=6](http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf;jsessionid=6A9DFE3CC9225CA5879B3DFDCC3994D6?sequence=1)
488 [A9DFE3CC9225CA5879B3DFDCC3994D6?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf;jsessionid=6A9DFE3CC9225CA5879B3DFDCC3994D6?sequence=1).
- 489 21. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C et al. Waist
490 Circumference and Cardiometabolic Risk: a Consensus Statement from Shaping America's
491 Health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity
492 Society; the American Society for Nutrition; and the American Diabetes Association.
493 *Obesity*. 2007;15:1061-7.
- 494 22. Davis P, McLeod K, Ransom M, Ongley P. *The New Zealand socio-economic index*
495 *of occupational status (NZSEI) (Research report no. 2)*. Wellington: Statistics NZ. 1997.
496 Available from:
497 [http://www2.stats.govt.nz/domino/external/web/prod_serv.nsf/874ea91c142289384c2567a80](http://www2.stats.govt.nz/domino/external/web/prod_serv.nsf/874ea91c142289384c2567a80081308e/dc0ac1758236cb28cc256cef00748da5/$FILE/NZSEI.pdf)
498 [081308e/dc0ac1758236cb28cc256cef00748da5/\\$FILE/NZSEI.pdf](http://www2.stats.govt.nz/domino/external/web/prod_serv.nsf/874ea91c142289384c2567a80081308e/dc0ac1758236cb28cc256cef00748da5/$FILE/NZSEI.pdf).
- 499 23. Galbraith C, Jenkin G, Davis P, Coope P. *New Zealand socioeconomic index 1996:*
500 *User's Guide*. Wellington (NZ): Statistics New Zealand. 1996.
- 501 24. Grieger JA, Grzeskowiak LE, Bianco-Miotto T, Jankovic-Karasoulos T, Moran LJ,
502 Wilson RL et al. Pre-pregnancy fast food and fruit intake is associated with time to
503 pregnancy. *Human reproduction*. 2018.
- 504 25. Gaskins AJ, Rich-Edwards JW, Missmer SA, Rosner B, Chavarro JE. Association of
505 Fecundity With Changes in Adult Female Weight. *Obstet Gynecol*. 2015;126:850-8.
- 506 26. Joffe M, Key J, Best N, Keiding N, Scheike T, Jensen TK. Studying time to
507 pregnancy by use of a retrospective design. *American journal of epidemiology*.
508 2005;162:115-24.
- 509 27. Chatzi L, Plana E, Daraki V, Karakosta P, Alegkakis D, Tsatsanis C et al. Metabolic
510 syndrome in early pregnancy and risk of preterm birth. *American journal of epidemiology*.
511 2009;170:829-36.
- 512 28. Negrato CA, Jovanovic L, Tambascia MA, Calderon Ide M, Geloneze B, Dias A et al.
513 Mild gestational hyperglycaemia as a risk factor for metabolic syndrome in pregnancy and
514 adverse perinatal outcomes. *Diabetes Metab Res Rev*. 2008;24:324-30.
- 515 29. Dos Prazeres Tavares H, Dos Santos DC, Abbade JF, Negrato CA, de Campos PA,
516 Calderon IM et al. Prevalence of metabolic syndrome in non-diabetic, pregnant Angolan
517 women according to four diagnostic criteria and its effects on adverse perinatal outcomes.
518 *Diabetol Metab Syndr*. 2016;8:27.
- 519 30. Jukic AM, McConaughy DR, Weinberg CR, Wilcox AJ, Baird DD. Long-term
520 Recall of Time to Pregnancy. *Epidemiology*. 2016;27:705-11.
- 521 31. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies:
522 a reference table for clinicians. *Obstet Gynecol*. 2009;114:1326-31.
- 523 32. Geraghty AA, Alberdi G, O'Sullivan EJ, O'Brien EC, Crosbie B, Twomey PJ et al.
524 Maternal Blood Lipid Profile during Pregnancy and Associations with Child Adiposity:
525 Findings from the ROLO Study. *PloS one*. 2016;11:e0161206.

- 526 33. Lippi G, Albiero A, Montagnana M, Salvagno GL, Scevarolli S, Franchi M et al.
527 Lipid and lipoprotein profile in physiological pregnancy. *Clin Lab*. 2007;53:173-7.
- 528 34. IOM. In: Rasmussen KM, Yaktine AL, editors. Institute of Medicine of the National
529 Academies Weight Gain During Pregnancy: Reexamining the Guidelines. The National
530 Academies Collection: Reports funded by National Institutes of Health: Washington (DC);
531 2009.
- 532 35. Baird DD, Weinberg CR, Rowland AS. Reporting errors in time-to-pregnancy data
533 collected with a short questionnaire. Impact on power and estimation of fecundability ratios.
534 *American journal of epidemiology*. 1991;133:1282-90.
- 535 36. Joffe M, Villard L, Li Z, Plowman R, Vessey M. Long-term recall of time-to-
536 pregnancy. *Fertility and sterility*. 1993;60:99-104.
- 537 37. Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic
538 syndrome, insulin resistance and cancer. *Proc Nutr Soc*. 2012;71:181-9.
- 539 38. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-
540 metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective
541 cohort studies. *Int J Cardiol*. 2013;168:4761-8.
- 542 39. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of
543 the evidence. *Diabetes care*. 2008;31:1898-904.
- 544 40. Grieger JA, Leemaqz SY, Dekker GA, Poston L, McCowan L, Kenny LC et al. Poor
545 metabolic health, in the absence of obesity, increases risk for gestational diabetes and
546 preeclampsia in pregnant women. *Journal of Nutrition & Intermediary Metabolism*.
547 2017;8:77-8.
- 548 41. Lewandowski AJ, Leeson P. Preeclampsia, prematurity and cardiovascular health in
549 adult life. *Early human development*. 2014;90:725-9.
- 550 42. Varner MW, Rice MM, Landon MB, Casey BM, Reddy UM, Wapner RJ et al.
551 Pregnancies After the Diagnosis of Mild Gestational Diabetes Mellitus and Risk of
552 Cardiometabolic Disorders. *Obstet Gynecol*. 2017;129:273-80.
- 553 43. Bakos HW, Mitchell M, Setchell BP, Lane M. The effect of paternal diet-induced
554 obesity on sperm function and fertilization in a mouse model. *Int J Androl*. 2011;34:402-10.
- 555 44. Verit FF, Keskin S, Omer B, Yalcinkaya S, Sakar N. Is there any relationship between
556 cardiovascular risk markers and young women with diminished ovarian reserve? *Gynecol*
557 *Endocrinol*. 2014;30:697-700.
- 558 45. Dunning KR, Russell DL, Robker RL. Lipids and oocyte developmental competence:
559 the role of fatty acids and beta-oxidation. *Reproduction*. 2014;148:R15-27.
- 560 46. Pantasri T, Wu LL, Hull ML, Sullivan TR, Barry M, Norman RJ et al. Distinct
561 localisation of lipids in the ovarian follicular environment. *Reprod Fertil Dev*. 2015;27:593-
562 601.
- 563 47. Browne RW, Shelly WB, Bloom MS, Ocque AJ, Sandler JR, Huddleston HG et al.
564 Distributions of high-density lipoprotein particle components in human follicular fluid and
565 sera and their associations with embryo morphology parameters during IVF. *Human*
566 *reproduction*. 2008;23:1884-94.
- 567 48. Kim K, Bloom MS, Browne RW, Bell EM, Yucel RM, Fujimoto VY. Associations
568 between follicular fluid high density lipoprotein particle components and embryo quality
569 among in vitro fertilization patients. *J Assist Reprod Genet*. 2017;34:1-10.
- 570 49. Robker RL. Evidence that obesity alters the quality of oocytes and embryos.
571 *Pathophysiology*. 2008;15:115-21.
- 572 50. Robker RL, Akison LK, Bennett BD, Thrupp PN, Chura LR, Russell DL et al. Obese
573 women exhibit differences in ovarian metabolites, hormones, and gene expression compared
574 with moderate-weight women. *The Journal of clinical endocrinology and metabolism*.
575 2009;94:1533-40.

51. Valckx SD, De Pauw I, De Neubourg D, Inion I, Berth M, Fransen E et al. BMI-related metabolic composition of the follicular fluid of women undergoing assisted reproductive treatment and the consequences for oocyte and embryo quality. *Human reproduction*. 2012;27:3531-9.
52. Browne RW, Bloom MS, Shelly WB, Ocque AJ, Huddleston HG, Fujimoto VY. Follicular fluid high density lipoprotein-associated micronutrient levels are associated with embryo fragmentation during IVF. *J Assist Reprod Genet*. 2009;26:557-60.
53. Wallace M, Cottell E, Gibney MJ, McAuliffe FM, Wingfield M, Brennan L. An investigation into the relationship between the metabolic profile of follicular fluid, oocyte developmental potential, and implantation outcome. *Fertility and sterility*. 2012;97:1078-84 e1-8.
54. Dechaud H, Anahory T, Reyftmann L, Loup V, Hamamah S, Hedon B. Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. *Eur J Obstet Gynecol Reprod Biol*. 2006;127:88-93.
55. Rashid S, Genest J. Effect of obesity on high-density lipoprotein metabolism. *Obesity*. 2007;15:2875-88.
56. McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. *Archives of internal medicine*. 2007;167:642-8.

596 **Supporting information**

597 **Figure S1.** Study flow chart for study of association of metabolic syndrome with time to
598 pregnancy.

599 **Table S1** The association between individual components of metabolic syndrome and time to
600 pregnancy or infertility in all women.

601 **Table S2.** Primary and sensitivity analyses for the association between metabolic syndrome
602 and its individual components and time to pregnancy.

603 **Table S3.** Primary and sensitivity analyses for the association between metabolic syndrome
604 and its individual components and risk of infertility.

605

Table 1 Characteristics of the study population.

<i>Maternal characteristics (n=5,519)</i>	Metabolic Syndrome		p-value
	No 4835	Yes 684	
n			
Age (years), mean (SD)	28.6 (5.4)	28.9 (5.9)	0.596
Body mass index (kg/m ²), mean (SD)	24.7 (4.5)	29.5 (5.7)	<0.001
Socioeconomic index, mean (SD)	42.1 (16.6)	39.4 (15.7)	<0.001
Ethnicity, n (%)			
Caucasian	4350 (90.0)	618 (90.4)	0.755
Other	485 (10.0)	66 (9.7)	
Smoker (pre-pregnancy), n (%)	1216 (25.2)	229 (33.5)	<0.001
Alcohol intake (pre-pregnancy), n (%)	3749 (77.5)	495 (72.4)	0.003
Study centre, n (%)			
Adelaide (Australia)	947 (19.6)	201 (29.4)	<0.001
Cork (Ireland)	1570 (32.5)	192 (28.1)	
Manchester (United Kingdom)	277 (5.7)	36 (5.3)	
London (United Kingdom)	173 (3.6)	6 (0.9)	
Leeds (United Kingdom)	131 (2.7)	12 (1.8)	
Auckland (New Zealand)	1737 (35.9)	237 (34.7)	
Previous miscarriage, n (%)	657 (13.6)	104 (15.2)	0.251
Food group intake			
Fast food (≥1 time per week)	2936 (77.1)	366 (70.5)	<0.001
Fruit (<3 times per day)	3714 (76.8)	573 (83.8)	<0.001
Vegetables (<1 time per day)	3063 (63.4)	453 (66.2)	0.143
Fish (<1 time per week)	2234 (46.2)	369 (54.0)	<0.001
Time to pregnancy, median (IQR)	2 (1-6)	3 (1-11)	0.001
Infertile (>12 months to conceive)	660 (13.7)	153 (22.4)	<0.001
Method of conception, n(%)			
Spontaneous	4559 (94.3)	613 (89.6)	<0.001
IVF	186 (3.9)	51 (7.5)	
Ovulation induction	90 (1.9)	20 (2.9)	
<i>Paternal characteristics (n=4,300)</i>			
Age (years), mean (SD)	31.0 (5.9)	31.1 (6.6)	0.704
Body mass index (kg/m ²), mean (SD)	26.7 (4.0)	27.7 (4.7)	<0.001
Missing (n=1,219 values)			

Table 2 Number and type of metabolic syndrome components in all women and split by obesity (≥ 30 kg/m² vs. < 30 kg/m²).

HDL-C=high density lipoprotein cholesterol

	N	Metabolic syndrome component, n (%)				
		High waist circumference	Raised glucose	Reduced HDL-C	Raised blood pressure	Raised triglycerides
All women	5519					
0	1212	0	0	0	0	0
1	2040	1295 (63.5)	454 (22.3)	24 (1.2)	7 (0.3)	260 (12.8)
2	1571	1377 (87.6)	909 (57.9)	75 (4.8)	47 (3.0)	734 (46.7)
3	586	575 (98.1)	481 (82.1)	127 (21.7)	69 (11.8)	506 (86.4)
≥ 4	109	109 (100)	104 (95.4)	84 (77.1)	37 (33.9)	109 (100)
Non-Obese	4685					
0	1212	0	0	0	0	0
1	1811	1067 (58.9)	454 (25.1)	24 (1.3)	7 (0.4)	259 (14.3)
2	1243	1049 (84.4)	765 (61.5)	61 (4.9)	27 (2.2)	584 (47.0)
3	364	353 (97.0)	306 (84.1)	75 (20.6)	37 (10.2)	321 (88.2)
≥ 4	55	55 (100)	54 (98.2)	48 (87.3)	11 (20.0)	55 (100)
Obese	833					
0	-					
1	229	228 (100)	0	0	0	0
2	328	328 (100)	144 (43.9)	14 (4.3)	20 (6.1)	151 (45.7)
3	222	222 (100)	175 (78.8)	52 (23.4)	32 (14.4)	185 (83.3)
≥ 4	54	54 (100)	50 (92.6)	36 (66.7)	26 (48.2)	54 (100)

Table 3 The association between metabolic syndrome and its individual components and time to pregnancy in all women and split by obesity (≥ 30 kg/m² vs. < 30 kg/m²).

HDL-C=high density lipoprotein cholesterol

NB: High waist circumference is a prerequisite for MetS and cannot be calculated

Model 1: maternal body mass index, maternal age, socioeconomic index, recruitment site, ethnicity, previous miscarriage, smoking status, alcohol intake

Model 2: model 1 plus maternal dietary intake prior to conception, paternal age, paternal body mass index

	Entire cohort (n=5519)				Non-Obese (n=4685)				Obese (n=834)			
	Time ratio (95% CI)				Time ratio (95% CI)				Time ratio (95% CI)			
	N	Crude n=5519	Model 1 n=5519	Model 2 n=3364	N	Crude n=4685	Model 1 n=4685	Model 2 n=2820	N	Crude n=834	Model 1 n=834	Model 2 n=544
Metabolic syndrome	684	1.27 (1.16-1.40)	1.22 (1.11-1.34)	1.30 (1.15-1.46)	408	1.25 (1.11-1.40)	1.21 (1.08-1.36)	1.29 (1.11-1.50)	276	1.30 (1.08-1.55)	1.23 (1.03-1.47)	1.35 (1.08-1.69)
Metabolic components												
Reduced HDL-C	310	1.15 (1.01-1.31)	1.30 (1.14-1.48)	1.37 (1.15-1.64)	208	1.02 (0.87-1.19)	1.17 (1.01-1.37)	1.22 (0.99-1.51)	102	1.47 (1.13-1.90)	1.66 (1.28-2.14)	1.70 (1.22-2.38)
Raised triglycerides	1609	1.15 (1.08-1.23)	1.10 (1.03-1.18)	1.11 (1.02-1.21)	1219	1.12 (1.04-1.21)	1.08 (1.01-1.17)	1.08 (0.98-1.18)	390	1.24 (1.05-1.47)	1.15 (0.98-1.36)	1.24 (1.01-1.53)
Raised glucose	1948	1.07 (1.00-1.14)	1.04 (0.98-1.11)	1.11 (1.02-1.20)	1579	1.05 (0.98-1.13)	1.03 (0.97-1.10)	1.10 (1.01-1.20)	369	1.14 (0.96-1.35)	1.08 (0.91-1.27)	1.18 (0.95-1.45)
Raised blood pressure	160	1.13 (0.94-1.35)	1.09 (0.91-1.30)	1.03 (0.82-1.30)	82	1.05 (0.82-1.35)	1.08 (0.85-1.38)	0.98 (0.71-1.34)	78	1.15 (0.86-1.54)	1.09 (0.83-1.46)	1.12 (0.78-1.63)
High waist circumference	3356	1.06 (1.00-1.13)	1.02 (0.95-1.10)	1.01 (0.92-1.11)	2524	1.04 (0.98-1.11)	1.01 (0.93-1.10)	1.05 (0.94-1.17)	834	-	-	-
Number of MetS components												
0	1212	Ref	Ref	Ref	1212	Ref	Ref	Ref	0	-	-	-
1	2040	0.98 (0.91-1.07)	0.98 (0.90-1.06)	0.97 (0.89-1.06)	1811	0.99 (0.91-1.08)	0.98 (0.90-1.07)	0.96 (0.86-1.07)	230	Ref	Ref	Ref
2	1571	1.04 (0.96-1.14)	1.04 (0.95-1.13)	1.08 (0.97-1.19)	1243	1.03 (0.94-1.12)	1.02 (0.93-1.12)	1.06 (0.94-1.20)	328	1.22 (0.99-1.50)	1.14 (0.93-1.39)	1.30 (1.01-1.68)
3	586	1.22 (1.09-1.37)	1.18 (1.05-1.33)	1.21 (1.06-1.39)	364	1.19 (1.05-1.36)	1.16 (1.01-1.33)	1.28 (1.07-1.52)	222	1.40 (1.11-1.76)	1.27 (1.02-1.60)	1.48 (1.11-1.97)
≥ 4	109	1.55 (1.24-1.95)	1.47 (1.17-1.85)	1.54 (1.16-2.04)	55	1.55 (1.13-2.11)	1.45 (1.06-1.97)	1.45 (0.95-2.21)	54	1.72 (1.19-2.48)	1.60 (1.12-2.29)	2.24 (1.34-3.75)

Table 4 The association between metabolic syndrome and its individual components and infertility in all women and split by obesity (≥ 30 kg/m² vs. < 30 kg/m²).

HDL-C=high density lipoprotein cholesterol

NB: High waist circumference is a prerequisite for MetS and cannot be calculated

Model 1: maternal body mass index, maternal age, socioeconomic index, recruitment site, ethnicity, previous miscarriage, smoking status, alcohol intake

Model 2: model 1 plus maternal dietary intake prior to conception, paternal age, paternal body mass index

	Entire cohort (n=5519)						Non-Obese (n=4685)						Obese (n=834)		
	N		Relative Risk (95% CI)			N	%	Relative Risk (95% CI)			N	%	Relative Risk (95% CI)		
			Crude n=5519	Model 1 n=5519	Model 2 n=3364			Crude n=4685	Model 1 n=4685	Model 2 n=2820			Crude n=834	Model 1 n=834	Model 2 n=544
Metabolic syndrome	684	22	1.64 (1.40-1.92)	1.43 (1.21-1.69)	1.62 (1.32-1.99)	408	21	1.58 (1.29-1.94)	1.45 (1.18-1.77)	1.73 (1.33-2.23)	276	24	1.59 (1.19-2.12)	1.39 (1.04-1.87)	1.62 (1.15-2.29)
Metabolic components															
Reduced HDL-C	310	19	1.31 (1.04-1.67)	1.49 (1.17-1.89)	1.63 (1.23-2.18)	208	14	1.02 (0.73-1.43)	1.20 (0.86-1.66)	1.36 (0.90-2.05)	102	28	1.72 (1.21-2.44)	1.97 (1.35-2.86)	1.96 (1.28-3.01)
Raised triglycerides	1609	18	1.36 (1.19-1.55)	1.22 (1.07-1.39)	1.30 (1.10-1.53)	1219	16	1.27 (1.09-1.48)	1.17 (1.01-1.36)	1.24 (1.02-1.50)	390	22	1.57 (1.17-2.11)	1.39 (1.03-1.88)	1.64 (1.14-2.35)
Raised glucose	1948	16	1.14 (1.00-1.29)	1.06 (0.93-1.20)	1.12 (0.95-1.32)	1579	15	1.09 (0.94-1.27)	1.05 (0.91-1.21)	1.12 (0.93-1.35)	369	20	1.23 (0.92-1.64)	1.09 (0.81-1.45)	1.16 (0.83-1.62)
Raised blood pressure	160	16	1.11 (0.77-1.58)	0.94 (0.67-1.33)	0.93 (0.59-1.45)	82	12	0.95 (0.54-1.65)	0.91 (0.56-1.50)	0.72 (0.30-1.69)	78	19	1.08 (0.67-1.74)	0.98 (0.61-1.57)	1.08 (0.64-1.83)
High waist circumference	3356	15	1.19 (1.04-1.36)	1.08 (0.92-1.25)	1.05 (0.86-1.27)	2524	15	1.14 (0.98-1.31)	1.09 (0.92-1.30)	1.16 (0.92-1.45)	834	18	-	-	-
Number of MetS components															
0	1212	13	Ref	Ref	Ref	1212	13	Ref	Ref	Ref	0	0			
1	2040	14	1.02 (0.85-1.22)	0.98 (0.82-1.18)	0.90 (0.72-1.13)	1811	14	1.03 (0.86-1.24)	1.00 (0.83-1.20)	0.96 (0.76-1.22)	230	13	Ref	Ref	Ref
2	1571	14	1.06 (0.88-1.28)	0.99 (0.82-1.21)	0.99 (0.78-1.26)	1243	13	1.01 (0.82-1.23)	0.97 (0.79-1.20)	1.01 (0.77-1.32)	328	17	1.32 (0.87-2.01)	1.19 (0.79-1.80)	1.42 (0.85-2.37)
3	586	21	1.57 (1.27-1.94)	1.34 (1.06-1.69)	1.47 (1.10-1.95)	364	20	1.49 (1.16-1.92)	1.37 (1.05-1.77)	1.67 (1.21-2.31)	222	23	1.78 (1.17-2.70)	1.45 (0.96-2.18)	1.87 (1.12-3.15)
≥4	109	29	2.21 (1.60-3.06)	1.77 (1.25-2.52)	2.06 (1.33-3.20)	55	29	2.19 (1.41-3.39)	1.67 (1.05-2.68)	1.84 (0.93-3.61)	54	30	2.34 (1.37-3.99)	2.01 (1.17-3.46)	2.88 (1.50-5.53)

Table S1 The association between individual components of metabolic syndrome and time to pregnancy or infertility in all women.

HDL-C=high density lipoprotein cholesterol

Model 1: maternal body mass index, maternal age, socioeconomic index, recruitment site, ethnicity, previous miscarriage, smoking status, alcohol intake

Model 2: model 1 plus maternal dietary intake prior to conception, paternal age, paternal body mass index

	Time to pregnancy				Infertility			
	Entire cohort (n=5519)							
	Time ratio (95% CI)				Relative Risk (95% CI)			
	N	Crude n=5519	Model 1 n=5519	Model 2 n=3364	N	Crude n=4685	Model 1 n=4685	Model 2 n=2820
Metabolic components								
Reduced HDL-C	310	1.09 (0.96-1.25)	1.27 (1.11-1.45)	1.33 (1.12-1.59)	310	1.17 (0.92-1.48)	1.43 (1.13-1.81)	1.53 (1.15-2.03)
Raised triglycerides	1609	1.13 (1.06-1.21)	1.08 (1.01-1.15)	1.08 (0.99-1.18)	1609	1.31 (1.15-1.49)	1.18 (1.04-1.35)	1.25 (1.06-1.48)
Raised glucose	1948	1.05 (0.99-1.12)	1.03 (0.97-1.10)	1.09 (1.01-1.19)	1948	1.09 (0.96-1.24)	1.03 (0.90-1.17)	1.09 (0.92-1.28)
Raised blood pressure	160	1.09 (0.91-1.30)	1.09 (0.91-1.30)	1.03 (0.82-1.30)	160	1.01 (0.71-1.44)	0.94 (0.67-1.32)	0.94 (0.60-1.48)
High waist circumference	3356	1.03 (0.97-1.10)	1.02 (0.95-1.10)	1.00 (0.91-1.10)	3356	1.13 (0.98-1.29)	1.07 (0.91-1.25)	1.03 (0.84-1.25)

Table S2 Primary and sensitivity analyses for the association between metabolic syndrome and its individual components and time to pregnancy.

HDL-C=high density lipoprotein cholesterol

Model 1: maternal body mass index, maternal age, socioeconomic index, recruitment site, ethnicity, previous miscarriage, smoking status, alcohol intake

Model 2: model 1 plus maternal dietary intake prior to conception, paternal age, paternal body mass index

^a Restricting the analysis to those with a reported starting time for pregnancy attempts between the second year and penultimate year of participant recruitment at each site

	Entire cohort				Truncated cohort ^a				Restricted to TTP>1 month			
	N	Time ratio (95% CI)			N	Time ratio (95% CI)			N	Time ratio (95% CI)		
		Crude n=5519	Model 1 n=5519	Model 2 n=3363		Crude n=3662	Model 1 n=3662	Model 2 n=2023		Crude n=3358	Model 1 n=3358	Model 2 n=2140
Metabolic syndrome	684	1.27 (1.16-1.40)	1.22 (1.11-1.34)	1.30 (1.15-1.46)	473	1.26 (1.13-1.40)	1.20 (1.08-1.34)	1.32 (1.14-1.54)	454	1.21 (1.11-1.33)	1.15 (1.05-1.28)	1.22 (1.08-1.37)
Metabolic components												
Reduced HDL-C	310	1.15 (1.01-1.31)	1.30 (1.14-1.48)	1.37 (1.15-1.64)	223	1.19 (1.02-1.38)	1.33 (1.14-1.55)	1.44 (1.17-1.77)	196	1.16 (1.02-1.33)	1.20 (1.04-1.37)	1.20 (1.01-1.43)
Raised triglycerides	1609	1.15 (1.08-1.23)	1.10 (1.03-1.18)	1.11 (1.02-1.21)	1049	1.15 (1.06-1.24)	1.10 (1.02-1.19)	1.14 (1.02-1.27)	1020	1.12 (1.05-1.21)	1.08 (1.01-1.17)	1.07 (0.98-1.17)
Raised glucose	1948	1.07 (1.00-1.14)	1.04 (0.98-1.11)	1.11 (1.02-1.20)	1308	1.07 (0.99-1.15)	1.04 (0.97-1.12)	1.12 (1.01-1.24)	1206	1.06 (1.00-1.14)	1.04 (0.97-1.10)	1.06 (0.98-1.15)
Raised blood pressure	160	1.13 (0.94-1.35)	1.09 (0.91-1.30)	1.03 (0.82-1.30)	118	1.17 (0.95-1.44)	1.13 (0.92-1.38)	1.07 (0.81-1.42)	104	1.06 (0.89-1.28)	0.99 (0.82-1.18)	1.00 (0.80-1.28)
High waist circumference	3356	1.06 (1.00-1.13)	1.02 (0.95-1.10)	1.01 (0.92-1.11)	2274	1.06 (0.98-1.14)	1.01 (0.93-1.11)	1.02 (0.90-1.15)	2058	1.06 (1.00-1.32)	1.01 (0.93-1.09)	1.01 (0.91-1.11)
Number of MetS components												
0	1212	Ref	Ref	Ref	760	Ref	Ref	Ref	740	Ref	Ref	Ref
1	2040	0.98 (0.91-1.07)	0.98 (0.90-1.06)	0.97 (0.89-1.06)	1375	0.98 (0.89-1.09)	0.98 (0.88-1.08)	0.91 (0.80-1.04)	1187	1.06 (0.98-1.16)	1.03 (0.95-1.13)	1.03 (0.92-1.14)
2	1571	1.04 (0.96-1.14)	1.04 (0.95-1.13)	1.08 (0.97-1.19)	1031	1.05 (0.94-1.16)	1.04 (0.94-1.17)	1.08 (0.93-1.25)	972	1.05 (0.96-1.15)	1.01 (0.92-1.11)	0.99 (0.88-1.11)
3	586	1.22 (1.09-1.37)	1.18 (1.05-1.33)	1.21 (1.06-1.39)	396	1.18 (1.03-1.36)	1.14 (0.99-1.32)	1.23 (1.01-1.49)	384	1.21 (1.08-1.35)	1.14 (1.01-1.29)	1.19 (1.02-1.39)
≥4	109	1.55 (1.24-1.95)	1.47 (1.17-1.85)	1.54 (1.16-2.04)	85	1.64 (1.27-2.11)	1.56 (1.21-2.02)	1.82 (1.26-2.63)	74	1.61 (1.28-2.03)	1.48 (1.17-1.88)	1.46 (1.07-2.00)

Table S3 Primary and sensitivity analyses for the association between metabolic syndrome and its individual components and risk of infertility.

HDL-C=high density lipoprotein cholesterol

Model 1: maternal body mass index, maternal age, socioeconomic index, recruitment site, ethnicity, previous miscarriage, smoking status, alcohol intake

Model 2: model 1 plus maternal dietary intake prior to conception, paternal age, paternal body mass index

^a Restricting the analysis to those with a reported starting time for pregnancy attempts between the second year and penultimate year of participant recruitment at each site

^b number and percentage of infertile women within each group (e.g. 33% of 454 women with MetS were considered infertile)

	Entire cohort						Truncated cohort ^a						Restricted to TTP >1 month		
	Relative Risk (95% CI)						Relative Risk (95% CI)						Relative Risk (95% CI)		
	N	%	Crude n=5519	Model 1 n=5519	Model 2 n=3364	N	%	Crude n=3662	Model 1 n=3662	Model 2 n=2023	N ^b	% ^b	Crude n=3358	Model 1 n=3358	Model 2 n=2140
Metabolic syndrome	684	22	1.64 (1.40-1.92)	1.43 (1.21-1.69)	1.62 (1.32-1.99)	477	21	1.69 (1.39-2.04)	1.44 (1.18-1.76)	1.78 (1.36-2.31)	454	33	1.48 (1.28-1.71)	1.33 (1.14-1.55)	1.50 (1.24-1.81)
Metabolic components															
Reduced HDL-C	310	19	1.31 (1.04-1.67)	1.49 (1.17-1.89)	1.63 (1.23-2.18)	224	19	1.38 (1.04-1.83)	1.55 (1.17-2.06)	1.79 (1.26-2.53)	196	30	1.26 (1.01-1.58)	1.32 (1.06-1.65)	1.42 (1.09-1.84)
Raised triglycerides	1609	18	1.36 (1.19-1.55)	1.22 (1.07-1.39)	1.30 (1.10-1.53)	1054	17	1.37 (1.17-1.62)	1.22 (1.04-1.44)	1.41 (1.13-1.76)	1020	28	1.28 (1.14-1.45)	1.18 (1.04-1.33)	1.24 (1.06-1.44)
Raised glucose	1948	16	1.14 (1.00-1.29)	1.06 (0.93-1.20)	1.12 (0.95-1.32)	1316	15	1.08 (0.92-1.28)	1.01 (0.86-1.19)	1.10 (0.89-1.36)	1206	25	1.11 (0.98-1.25)	1.04 (0.92-1.17)	1.06 (0.91-1.24)
Raised blood pressure	160	16	1.11 (0.77-1.58)	0.94 (0.67-1.33)	0.93 (0.59-1.45)	119	19	1.38 (0.94-2.00)	1.13 (0.79-1.62)	1.15 (0.71-1.86)	104	24	1.03 (0.74-1.45)	0.86 (0.62-1.19)	0.88 (0.58-1.36)
High waist circumference	3356	15	1.19 (1.04-1.36)	1.08 (0.92-1.25)	1.05 (0.86-1.27)	2286	15	1.22 (1.03-1.45)	1.07 (0.89-1.30)	1.10 (0.85-1.43)	2058	25	1.17 (1.03-1.33)	1.06 (0.91-1.22)	1.02 (0.85-1.24)
Number of MetS components															
0	1212	13	Ref	Ref	Ref	762	12	Ref	Ref	Ref	740	21	Ref	Ref	Ref
1	2040	14	1.02 (0.85-1.22)	0.98 (0.82-1.18)	0.90 (0.72-1.13)	1378	13	1.07 (0.85-1.35)	1.02 (0.81-1.28)	0.93 (0.68-1.28)	1187	23	1.07 (0.90-1.27)	1.01 (0.85-1.20)	0.97 (0.78-1.20)
2	1571	14	1.06 (0.88-1.28)	0.99 (0.82-1.21)	0.99 (0.78-1.26)	1036	13	1.03 (0.80-1.31)	0.96 (0.75-1.23)	1.04 (0.75-1.45)	972	22	1.05 (0.87-1.25)	0.96 (0.80-1.16)	0.93 (0.73-1.17)
3	586	21	1.57 (1.27-1.94)	1.34 (1.06-1.69)	1.47 (1.10-1.95)	398	19	1.58 (1.20-2.07)	1.31 (0.98-1.76)	1.60 (1.09-2.33)	384	31	1.46 (1.20-1.78)	1.25 (1.01-1.56)	1.37 (1.05-1.79)
≥4	109	29	2.21 (1.60-3.06)	1.77 (1.25-2.52)	2.06 (1.33-3.20)	87	28	2.37 (1.63-3.44)	1.84 (1.23-2.77)	2.51 (1.52-4.15)	74	42	1.99 (1.48-2.67)	1.61 (1.17-2.21)	1.72 (1.14-2.60)

Supplemental Information

Fig S1. Study flow chart for study of association of metabolic syndrome with time to pregnancy.