Temporal Trends without Seasonal Effects on Gestational Diabetes Incidence Relate to Reductions in Indices of Insulin Secretion: The Cambridge Baby Growth Study

Short title: *Increasing gestational diabetes incidence & reduced insulin secretion*

Clive J. Petry[1] (cjp1002@cam.ac.uk), Benjamin G. Fisher[1] (ben.fisher@cantab.net),

Ken K. Ong[1-3] (Ken.Ong@mrc-epid.cam.ac.uk), Ieuan A. Hughes[1] (iah1000@cam.ac.uk),

Carlo L. Acerini[1] (cla22@cam.ac.uk), David B. Dunger[1,3] (dbd25@cam.ac.uk)

[1]Department of Paediatrics, University of Cambridge, Cambridge CB2 0QQ, U.K.

[2]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge

CB2 0QQ, U.K.

[3]The Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, U.K.

Corresponding Author: Dr. Clive J. Petry, Department of Paediatrics, Box 116, Cambridge

Biomedical Campus, Hills Road, Cambridge CB2 0QQ, U.K. E-mail: cjp1002@cam.ac.uk.

Abstract word count	250
Main text word count	3,134
References	39
Figures	3
Tables	1

Abstract

Aims The incidence of gestational diabetes has been reported to have risen over the first decade of this century. Some studies have also found it to vary with seasons of the year. We therefore investigated temporal and seasonal trends on gestational diabetes incidence in a single centre cohort study from Cambridge, U.K., and attempted to explain trends using associations with risk factors.

Materials and Methods Using a cosinor model we tested whether there were both temporal and seasonal trends in gestational diabetes incidence in 1,074 women recruited to the Cambridge Baby Growth Study in 2001-2009 who underwent oral glucose tolerance tests around week 28 of pregnancy. We also undertook risk factor analyses.

Results There was a temporal increase in gestational diabetes incidence over the course of recruitment to this study ($p=2.1 \times 10^{-3}$) but no seasonal effect ($p=0.7$). HOMA B ($p=3.0 \times 10^{-3}$; $n=1,049$) and the insulin disposition index ($p=3.0 \times 10^{-3}$; $n=1,000$) showed negative temporal trends. There was no negative association with HOMA S. Risk factor analyses showed a concomitant temporal slight increase in the index of multiple deprivation ($p=4.6 \times 10^{-10}$, $n=1,068$). This index was positively associated with HOMA B ($p=6.1 \times 10^{-5}$, $n=955$) but not directly with gestational diabetes ($p=0.6$, $n=1,032$), HOMA S ($p=0.2$, $n=955$) or the insulin disposition index ($p=0.4$, $n=955$).

Conclusions In this population there were temporal but not seasonal increases in gestational diabetes incidence between the years 2001 and 2009, which appeared to be related more to reductions in insulin secretion than sensitivity. Possible mediators of this link include confounding factors related to deprivation.

Keywords: insulin sensitivity, pregnancy, deprivation, cosinor

Introduction

Gestational diabetes (GDM) is traditionally defined as carbohydrate intolerance with its onset or first recognition in pregnancy,[1] although more recent definitions explicitly exclude pre-existing type 2 diabetes.[2] It is one of the most common adverse conditions of pregnancy. Its incidence has generally been reported to be rising in most populations, usually in line with the increasing prevalence of maternal obesity.[3] Other major risk factors for GDM include having a previous history of it or having previously given birth to a macrosomic baby, a family history of GDM and/or type 2 diabetes, increased maternal age, increased gestational weight gain, genetics, multiparity and ethnic factors,[4] not all of which can explain the tempo of the rising incidence. As GDM increases the risk of short- and long-term adverse complications for both the mother and her unborn child (including macrosomia, pre-eclampsia, childhood obesity and the metabolic syndrome in the mother[5]) and may contribute to the diabetes pandemic[6], a thorough understanding of its pathogenesis is essential.

With the apparent worldwide rise in the prevalence of GDM[7] paralleling the increasing prevalence of female obesity[8] of note are the temporal and potentially mechanistic links that obesity has with global warming.[9] Therefore another factor that could explain at least part of the increased incidence of GDM is exposure to raised or rising ambient temperatures in certain populations.[10-12] Following this some studies have reported seasonal variations in the incidence of GDM[13-17], although this has not been observed in all populations or climates.[18, 19] In this study we investigated whether there were temporal and seasonal trends in GDM incidence in our single centre population from Cambridge, U.K. which recruited pregnant women between 2001 and 2009. We then investigated what may have

mediated any trends. Although relating to a decade ago this seemed reasonable given that GDM was already becoming more prevalent by this time in several different populations.[20-25]

Materials and Methods

Cambridge Baby Growth Study

The prospective, longitudinal Cambridge Baby Growth Study (CBGS) was established as an observational cohort initially covering pregnancy, birth and infancy.[26] 2,229 mothers, all over 16 years of age, were recruited when attending early pregnancy ultrasound clinics at the Rosie Maternity Hospital, Cambridge, U.K. between April 2001 and March 2009. 571 of these mothers withdrew prior to the birth of their infant. Most of the clinical characteristics of the study participants were collected either during nurse-led interviews or by questionnaire with the exception of offspring birth weight, gestational age and date of birth, which were compiled from hospital notes. In this cohort 95.3% of the offspring were white, 1.7% were Asian, 1.3% were black (African or Caribbean), and 1.7% were other ethnicities (mainly mixed race), reflective of the population served by the Rosie Maternity Hospital.

Ethics

The Cambridge Baby Growth Study was approved by the Cambridge Local Research Ethics Committee, Addenbrooke's Hospital, Cambridge, United Kingdom (00/325). All procedures followed were in accordance with the institutional guidelines. Written informed consent was obtained from all the study participants.

Oral Glucose Tolerance Test and Gestational Diabetes Diagnostic Criteria

At a median (inter-quartile range) of 28.4 (28.1–28.7) weeks gestation 1,074 of the CBGS mothers underwent a 75g oral glucose tolerance test (OGTT) after fasting overnight.[27] Venous blood was collected just prior to and 60 min. after the glucose load was administered for the measurement of plasma glucose, insulin and c-peptide concentrations. 120 min. plasma glucose concentrations were only measured from May 2007 onwards so were not used in this study to define GDM (only 7% of U.K. women with GDM receive a diagnosis based solely on the 120 min. measurement in any case[28]). The International Association of Diabetes in Pregnancy Study Groups (IADPSG) thresholds for 0 and 60 min. OGTT glucose concentrations (i.e. $\geq$ 5.1 and 10.0 mmol/L, respectively[29]) were used to define the presence of GDM.

Assays

All biochemical kit-based assays were run according to the manufacturer's instructions. Glucose concentrations were measured using a routine glucose oxidase-based method. OGTT plasma insulin concentrations were measured by ELISA (Dako UK Ltd., Ely, Cambs, U.K.). Intra-assay imprecision (CV) was 4.3% at 14 mU/L (82 pmol/L), 3.0% at 67 mU/L (402 pmol/L), and 5.7% at 151 mU/L (907 pmol/L). Equivalent inter-assay imprecision was 4.3, 5.1, and 5.4%, respectively. C-peptide concentrations were also measured by ELISA (DSL Labs., London, U.K.). Intra-assay imprecision was 2.8% at 1.3 ng/mL (0.43 nmol/L) and at 4.4 ng/mL (1.47 nmol/L), and 3.2% at 8.4 ng/mL (2.80 nmol/L). Equivalent inter-assay imprecision was 15.7%, 7.8% and 10.3%, respectively.

Calculations

The maternal body mass index (BMI) was calculated as the pre-pregnancy weight divided by the height squared. Insulin sensitivity and pancreatic β-cell function were estimated using the homeostasis model assessment (HOMA S and B, respectively), calculated using the week 28 fasting circulating glucose and insulin (or c-peptide) concentrations and the online HOMA2 calculator (available at https://www.dtu.ox.ac.uk/homacalculator/).[30] For this study HOMA values were calculated using both insulin and c-peptide concentrations separately, and where mentioned in this manuscript refer to insulin-derived values unless stated otherwise. Insulin secretion (for a given insulin sensitivity) was assessed in terms of the insulin disposition index, calculated as the change in insulin concentrations over the first hour of the OGTT divided by the change in glucose concentrations, all divided by the reciprocal of the fasting insulin concentration. An equivalent disposition index was also calculated using plasma c-peptide concentrations. The index of multiple deprivation was derived and imputed from the postcode of the participants' home addresses as described.[31]

Statistical Analysis

The present analysis was restricted to those 1,074 pregnancies where the women underwent OGTTs (thereby excluding women with pre-existing type 1 diabetes) with 0 and 60 min. plasma glucose concentrations available to us. Data were logarithmically transformed prior to analyses if their distributions were positively skewed. Temporal trends, adjusted for seasonal trends, were tested for using the cosinor regression model in R (version 3.5.2; The R Project for Statistical Computing, Vienna, Austria) deploying the package Cosinor (version 1.1, available at http://github.com/sachsmc/cosinor) which assumes a sinusoidal seasonal pattern over a longitudinal period, in this case OGTT season

and year of analysis, respectively. The season was based on the month the OGTT was performed using Northern Meteorological seasons: winter (December to February), spring (March to May), summer (June to August), autumn (fall) (September to November). Further analysis was performed by standard logistic (for binary variables) or linear (for continuous variables whose model residuals using untransformed or transformed data were normally distributed) regression. Non-parametric regression (to fit linear regression models that included the index of multiple deprivation due to the lack of normal distribution of the residuals in standard linear regression models) was performed by means of the Theil–Sen procedure (deploying the R package mblm, version 0.12.1, available at https://cran.r-project.org/web/packages/mblm/index.html). Categorical analysis was performed using the χ^2 test. Unless stated all the other statistical analyses were performed using Stata (version 13.1; Stata Corp., from Timberlake Consultants Ltd., Richmond, Surrey, U.K.). Statistical significance was assumed at p<0.05 throughout.

Results

Characteristics of the Study Population

With the exception of a slight increase in parity and a reduced proportion of smokers, those women who were included in the analysis were representative of the Cambridge Baby Growth Study as a whole (Table 1). Variables that were not detectably different included GDM prevalence, fasting glucose and insulin concentrations, pre-pregnancy BMI and maternal age.

Temporal Trends of GDM Incidence and OGTT Glucose Concentrations

The overall prevalence of GDM in this population was 10.1% (108/1,071). Cosinor analysis showed a significant temporal effect associated with the year of analysis (0.014 (0.005, 0.022) proportional increase per year, $p=2.1 \times 10^{-3}$), with a trend for the incidence of GDM increasing through the years 2001-9 (Fig. 1). This finding was confirmed by logistic regression (odds ratio (OR) 1.2 (1.1, 1.3) per year, $p=2.8 \times 10^{-3}$, n=1,049), even when the small numbers of participants collected in 2009 were excluded from the analysis (OR 1.2 (1.1, 1.3) per year, $p=3.3 \times 10^{-3}$, n=1,040). There was, however, no significant association of GDM with seasonality (amplitude: 9.8 (-14.7, 34.3), p=0.4; acrophase -0.6 (-3.0, 1.9), p=0.7) (Fig. 1). Cosinor analysis revealed no significant association of the OGTT fasting glucose concentration with the year (0.009 (-0.007, 0.025) mmol/L per year, p=0.3) or with seasonality (amplitude: 21.3 (-24.1, 66.6), p=0.4; acrophase -0.4 (-2.4, 1.6), p=0.7). Conversely there was a temporal trend with the OGTT 60 min. glucose concentrations (0.117 (0.067, 0.166) mmol/L per year, $p<1 \times 10^{-4}$) (Fig. 2), a finding which was confirmed by linear regression (β'=0.147, $p=1.3 \times 10^{-6}$, n=1,071), without a seasonal effect (amplitude: 53.7 (-84.1, 191.5), p=0.4; acrophase -0.9 (-3.4, 1.7), p=0.5).

Temporal Trends of Indices of Insulin Sensitivity and Secretion

Insulin-derived HOMA S was positively associated with the year of testing (0.016 (0.001, 0.032) per year, p=0.04) but not with the season of testing (amplitude: 21.7 (-20.8, 64.1), p=0.3; acrophase 1.3 (-0.7, 3.4), p=0.2), a finding which was confirmed by linear regression (β'=0.080, $p=9.1 \times 10^{-3}$, n=1,049). This association was still evident if adjusting for GDM ($p=3.4 \times 10^{-4}$, n=1,049) or by only including women who were classified as not having GDM

(p=1.2×10^{-3}; n=947). However the association disappeared if it were tested using c-peptide-derived HOMA S, in a smaller number of women (β'=0.014, p=0.7, n=929).

Whilst still having a lack of association with seasonality (amplitude: 20.9 (-6.4, 48.2), p=0.1; acrophase 0.6 (-0.7, 1.9), p=0.4), in contrast to the findings with HOMA S, insulin-derived HOMA B was negatively associated with year of testing (-0.015 (-0.025, -0.005) per year, p=3.0×10^{-3}). This association was confirmed by linear regression (β'=-0.104, p=7.0×10^{-4}, n=1,049). Again it was still evident if adjusting for GDM (p=1.2×10^{-3}, n=1,049) or if only including women without GDM (p=1.2×10^{-3}; n=947). This association was still present if it were tested using c-peptide-derived HOMA B, in a smaller number of women (β'=-0.073, p=0.03, n=929).

Similar to the results for HOMA B, the insulin disposition index was negatively associated with year of testing (-0.036 (-0.060, -0.013) per year, p=3.0×10^{-3}), a finding which was confirmed by linear regression (β'=-0.091, p=3.8×10^{-3}, n=1,000). This association was still evident if adjusting for GDM (p=0.03; n=1,000) or if only including women without GDM (p=0.03; n=905). The insulin disposition index was not, however, associated with season of testing (amplitude: 26.0 (-38.5, 90.5), p=0.4; acrophase 1.1 (-1.5, 3.7), p=0.4). The c-peptide disposition index was also negatively associated with year of testing (β'=-0.074, p=0.03, n=882).

Associations of the Year of Analysis with Potential Risk Factors

The year of analysis was not associated with either the maternal BMI (β'=0.006, p=0.9, n=827) or pregnancy weight gain (β'=-0.047, p=0.2, n=614). Neither was it associated with

maternal age (β'=-0.016, p=0.6, n=898) or parity (β'=0.007, p=0.8, n=1,022) in this population. There was no association between the year of analysis and the proportion of male babies (χ^2=4.9, p=0.8, n=1,024), birth weight of the babies (β'=-0.023, p=0.4, n=824; adjusted for gestational age at birth, mother's BMI, parity and sex) or the odds of a pregnancy being multifetal (OR 1.0 (0.9, 1.2), p=0.9, n=1,071). One potential confounder that year of analysis was modestly albeit highly significantly associated with, the index of multiple deprivation (p=4.6×10^{-10}, n=1,068) (Fig. 3), was itself not directly associated with GDM (OR 1.0 (1.0, 1.1) per unit increase in the index, p=0.6, n=1,032). There was still a significant relationship between the index of multiple deprivation and the year in the reduced number of 955 women for whom HOMA modelling was available (p=5.2×10^{-8}). In these women the index of multiple deprivation was significantly positively associated with HOMA B (p=6.1×10^{-5}; Fig. 3) but not with HOMA S (p=0.2) or the insulin disposition index (p=0.4).

Discussion

In this analysis there was a strong trend for the incidence of GDM increasing as recruitment to the cohort progressed between 2001 and 2009. Trends over a similar period of time have also been observed in populations in Canada[21], the U.S.A.[22, 24], Israel[23] and Germany[25]. The worldwide increased incidence at that time appeared to be independent of ethnicity[20] despite this being a major factor associated with GDM risk.[4] In our population the increased incidence of GDM was associated with reductions in HOMA B and the insulin disposition index (rather than HOMA S). Whilst a temporal trend in these factors could relate to changes in the performance of the insulin and glucose assays that were used over time, we used the same assays for these analytes throughout this time period and the performance

characteristics of the insulin assay matched those of similar assays available at the time.[32]

Given that the performance of the glucose assay did not change over this time, the fact that the associations with HOMA B and the disposition index persisted if they were calculated using c-peptide rather than insulin concentrations suggests that these associations were physiological rather than assay-related. The temporal increase in GDM incidence in our population therefore appeared to relate to reductions in insulin secretion rather than sensitivity (indeed insulin-derived HOMA S actually increased over the period of recruitment, albeit this association was not evident when c-peptide concentrations were used to calculate HOMA S in a smaller number of women).

The temporal increase in GDM incidence was clearly environmentally-mediated as its tempo was too fast for a genetic change. In investigating its potential causes and the reduced insulin secretion we could not find parallel increases in BMI, pregnancy weight gain, maternal age or smoking. There was, however, a significant temporal trend of increasing deprivation in the study (in a population that was generally less-deprived than the national average[26]) although deprivation itself was not associated with GDM. There was a modest albeit highly significant positive association between the index of multiple deprivation and insulin-derived HOMA B. This suggests that, in the absence of a direct associations with HOMA S or GDM risk, as the deprivation index went up pancreatic β-cell function might have had to increase slightly to maintain glucose homeostasis. Due to the lack of direct association between the deprivation index and GDM despite the temporal trend, it is possible however that as yet unidentified confounder(s) related to deprivation, such as factors connected with diet[33] and/or exercise[34], could have contributed to the temporal increase in GDM incidence. This would be consistent with studies where associations

between GDM and deprivation, lower socioeconomic status or lower social class were reported[25, 35, 36] although such associations have not been found in every study.[37] An alternative explanation for the temporal trend in deprivation in the present study is that it may just reflect unintentional secular patterning in study recruitment or uptake.

Although we observed a temporal trend of increasing GDM incidence as the decade progressed in this analysis we could not find a seasonal trend. This is despite seasonal trends in GDM previously have been observed in populations in Sweden[13], Australia[14, 15], Italy[16] and Greece[17]. However of the populations tested before where no such trend was observed[18, 19] one of these was also in the U.K.[19] so our lack of seasonal trend may relate to climate or other environmental factors specific to the U.K. Alternatively, whilst at least one of the studies that found a seasonal trend used a very similar analysis technique to the one that we used[15], other studies used analysis of variance or categorical/ordinal analyses which did not account for the recurring nature of the seasons or adjust for longer-term temporal trends[13, 14, 16, 17] so differences from our results may relate to this.

The strengths of our prospective study include the fact that we used cosinor analysis to adjust linear temporal trends for separate potential seasonal effects, unlike some of the other studies in this area. In addition we had third trimester OGTT data from all the study participants and so we were able to investigate whether temporal trends in GDM incidence were related to changes in insulin sensitivity or secretion. We calculated HOMAs using both insulin and c-peptide concentrations so that detectable temporal trends were less likely to have resulted from drift in assay performance. In addition to its strengths the study does have a number of limitations however. Firstly this Cambridge cohort may not fully reflect

the U.K. population as a whole particularly in relation to ethnic mix and smoking prevalence[25], although this means that there was probably less confounding due to ethnic effects. Secondly we did not record family histories of GDM and type 2 diabetes, major risk factors for GDM.[4] Thirdly although the study was fairly large given the level of detail that was collected, it was smaller than temporal studies of large surveys (e.g. [38]) and therefore our trends were estimated with less precision than is possible in that kind of study. This could partially account for the large magnitude of the increased GDM incidence over the course of the recruitment period in our study. Finally the insulin (and c-peptide) disposition index was not calculated using 30 min. OGTT glucose and insulin concentrations like usual, but using 60 min. concentrations instead. Although comparing OGTT results from our study with those more commonly from intravenous GTTs, its use has been deemed acceptable at least for the insulinogenic element of the disposition index.[39]

In conclusion we observed a temporal but not seasonal trend for an increasing incidence of GDM in Cambridge Baby Growth Study pregnancies from the years 2001-2009. This was associated with reductions in indices of insulin secretion rather than insulin sensitivity. Although we do not know what caused these changes it does not appear to relate to changes in maternal obesity or age. Factors relating to deprivation offer potential explanations.

Acknowledgments

Conflict of Interest Statement

The authors have nothing to disclose.

Author's Contribution Statement

CP conceived and designed the study, analysed some of the data and wrote the initial draft of the manuscript. BF analysed some of the data and commented on the initial draft of the manuscript. KO, IH, CA and DD designed, established and oversee the Cambridge Baby Growth Study. All authors commented on early drafts of the manuscript and approved the submission of the final draft.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Supplement 1):S62–S69.

2. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes Care 2018;41(Supplement 1): S13-S27.

3. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007;30:2070-2076.

4. Petry CJ. Gestational diabetes: risk factors and recent advances in its genetics and treatment. Br J Nutr 2010;104:775-787.

5. Salzer L, Yogev Y. Complications of gestational diabetes. In: *Gestational Diabetes: origins, complications and treatment* (ed. Petry CJ). Boca Raton: CRC Press; 2014, pp. 95-115.

6. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. Diabetologia 2016;59:1396-1399.

7. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep 2016;16:7.

8. Mitchell S, Shaw D. The worldwide epidemic of female obesity. Best Pract Res Clin Obstet Gynaecol 2015;29:289-99.

9. An R, Ji M, Zhang S. Global warming and obesity: a systematic review. Obes Rev 2018;19:150-163.

10. Schmidt MI, Matos MC, Branchtein L, Reichelt AJ, Mengue SS, Iochida LC, Duncan BB. Variation in glucose tolerance with ambient temperature. Lancet 1994;344:1054-1055.

11. Booth GL, Luo J, Park AL, Feig DS, Moineddin R, Ray JG. Influence of environmental temperature on risk of gestational diabetes. CMAJ 2017;189:E682-E689.

12. Retnakaran R, Ye C, Kramer CK, Hanley AJ, Connelly PW, Sermer M, Zinman B. Impact of daily incremental change in environmental temperature on beta cell function and the risk of gestational diabetes in pregnant women. Diabetologia 2018;61:2633-2642.

13. Katsarou A, Claesson R, Ignell C, Shaat N, Berntorp K. Seasonal pattern in the diagnosis of gestational diabetes mellitus in southern Sweden. J Diabetes Res 2016;2016:8905474.

14. Moses RG, Wong VC, Lambert K, Morris GJ, San Gil F. Seasonal changes in the prevalence of gestational diabetes mellitus. Diabetes Care 2016;39:1218-1221.

15. Verburg PE, Tucker G, Scheil W, Erwich JJ, Dekker GA, Roberts CT. Seasonality of gestational diabetes mellitus: a South Australian population study. BMJ Open Diabetes Res Care 2016;4:e000286.

16. Chiefari E, Pastore I, Puccio L, Caroleo P, Oliverio R, Vero A, Foti DP, Vero R, Brunetti A. Impact of seasonality on gestational diabetes mellitus. Endocr Metab Immune Disord Drug Targets 2017;17:246-252.

17. Vasileiou V, Kyratzoglou E, Paschou SA, Kyprianou M, Anastasiou E. The impact of environmental temperature on the diagnosis of gestational diabetes mellitus. Eur J Endocrinol 2018;178:209-214.

18. Moses R, Griffiths R. Is there a seasonal variation in the incidence of gestational diabetes? Diabet Med 1995;12:563-565.

19. Janghorbani M, Stenhouse E, Jones RB, Millward A. Gestational diabetes mellitus in Plymouth, U.K.: prevalence, seasonal variation and associated factors. J Reprod Med 2006;51:128-134.

20. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. Diabetes Care 2007;30 Suppl 2:S141-S146.

21. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996-2010. Diabetes Care 2014;37:1590-1596.

22. Khalifeh A, Breathnach F, Coulter-Smith S, Robson M, Fitzpatrick C, Malone F. Changing trends in diabetes mellitus in pregnancy. J Obstet Gynaecol 2014;34:135-137.

23. Sella T, Shalev V, Elchalal U, Chovel-Sella A, Chodick G. Screening for gestational diabetes in the 21st century: a population-based cohort study in Israel. J Matern Fetal Neonatal Med 2013;26:412-416.

24. Wang Y, Chen L, Xiao K, Horswell R, Besse J, Johnson J, Ryan DH, Hu G. Increasing incidence of gestational diabetes mellitus in Louisiana, 1997-2009. J Womens Health (Larchmt) 2012;21:319-325.

25. Huy C, Loerbroks A, Hornemann A, Röhrig S, Schneider S. Prevalence, trend and determining factors of gestational diabetes in Germany. Geburtshilfe Frauenheilkd 2012;72:311-315.

26. Prentice P, Acerini CL, Eleftheriou A, Hughes IA, Ong KK, Dunger DB. Cohort Profile: the Cambridge Baby Growth Study (CBGS). Int J Epidemiol 2016;45:35.a-g.

27. Petry CJ, Ong KK, Hughes IA, Acerini CL, Frystyk J, Dunger DB. Early pregnancy-associated plasma protein A concentrations are associated with third trimester insulin sensitivity. J Clin Endocrinol Metab 2017;102:2000-2008.

28. National Collaborating Centre for Women's and Children's Health. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. London: RCOG Press; 2015.

29. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676-682.

30. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998;21:2191-2192.

31. Lauzon-Guillain Bd, Wijndaele K, Clark M, Acerini CL, Hughes IA, Dunger DB, Wells JC, Ong KK. Breastfeeding and infant temperament at age three months. PLoS One 2012;7:e29326.

32. Manley SE, Stratton IM, Clark PM, Luzio SD. Comparison of 11 human insulin assays: implications for clinical investigation and research. Clin Chem 2007;53:922-932.

33. Haggarty P, Campbell DM, Duthie S, Andrews K, Hoad G, Piyathilake C, McNeill G. Diet and deprivation in pregnancy. Br J Nutr 2009;102:1487-1497.

34. Laraia B, Messer L, Evenson K, Kaufman JS. Neighborhood factors associated with physical activity and adequacy of weight gain during pregnancy. J Urban Health 2007;84:793-806.

35. Collier A, Abraham EC, Armstrong J, Godwin J, Monteath K, Lindsay R. Reported prevalence of gestational diabetes in Scotland: the relationship with obesity, age, socioeconomic status, smoking and macrosomia, and how many are we missing? J Diabetes Investig 2017;8:161-167.

36. Cullinan J, Gillespie P, Owens L, Avalos G, Dunne FP; ATLANTIC DIP collaborators. Is there a socioeconomic gradient in the prevalence of gestational diabetes mellitus? Ir Med J 2012;105(5 Suppl):21-23.

37. Janghorbani M, Stenhouse EA, Jones RB, Millward BA. Is neighbourhood deprivation a risk factor for gestational diabetes mellitus? Diabet Med 2006;23:313-317.

38. Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG 2017;124:804-813.

39. Tura A, Kautzky-Willer A, Pacini G. Insulinogenic indices from insulin and C-peptide: comparison of beta-cell function from OGTT and IVGTT. Diabetes Res Clin Pract 2006;72:298-301.

Table 1 Characteristics of those Cambridge Baby Growth Study participants who were included in the current analysis and those that were not.

Characteristic	Included	Not-Included	p-value
Mother's age at the birth of her baby (years)	33.4 (33.1, 33.6) (n=901)	33.8 (33.4, 34.2) (n=434)	0.06
Parity (n, of increasing parity)	489/373/122/32/6/3	228/267/93/29/2/3	1.2×10^{-4}
GDM	110 yes, 967 no	1 yes, 6 no	0.5
OGTT fasting glucose concentration (mmol/L)	4.3 (4.3, 4.4) (n=1,073)	4.2 (3.7, 4.6) (n=6)	0.5
OGTT fasting insulin concentration (pmol/L)	45.5 (44.0, 47.0) (n=1,053)	46.4 (41.3, 52.1) (n=83)	0.7
Pre-pregnancy BMI (kg/m^2)	23.4 (23.2, 23.7) (n=830)	23.3 (22.9, 23.7) (n=357)	0.6
Index of multiple deprivation	8.9 (8.7, 9.1) (n=1,068)	9.0 (8.7, 9.2) (n=585)	0.9
Maternal highest qualification (category 3/4/5)	80/133/358	33/52/134	0.9
Sex of baby (n males/females)	535/492	320/307	0.7
Baby's birth weight (kg)*	3.483 (3.454, 3.514) (n=830)	3.458 (3.412, 3.504) (n=357)	0.4

| Gestational age at birth of baby (weeks) | 39.8 (39.7, 39.9) (n=1,029) | 39.7 (39.6, 39.8) (n=628) | 0.1 |
| Reported smoking during pregnancy (n yes/no) | 40/987 | 46/582 | 2.0×10^{-3} |

*adjusted for maternal pre-pregnancy BMI, gestational age at birth, sex of baby and parity.

Data are either number of participants or mean (95% confidence interval).

Figure Legends

Fig. 1 (a) The proportion of women with GDM by the season of the year, following an OGTT around week 28 of pregnancy, adjusted for year of analysis. Data are means (95% confidence intervals). Analysing this data categorically (taking no account of the recurring order of the seasons) showed no association between GDM and season of the year (χ^2=2.2, p=0.5). (b) The proportion of women with GDM by the year of testing, following an OGTT around week 28 of pregnancy.

Fig. 2 A dot plot of OGTT 60 min. glucose concentrations by the year of OGTT testing. The bars represent the limits of the interquartile range of the values represented by the dots.

Fig. 3 Dot plots of (a) the index of multiple deprivation by year of testing and (b) HOMA B values by the index of multiple deprivation. The lines of best fit (minimising the distance between the line and median values) were calculated using the Theil–Sen procedure.
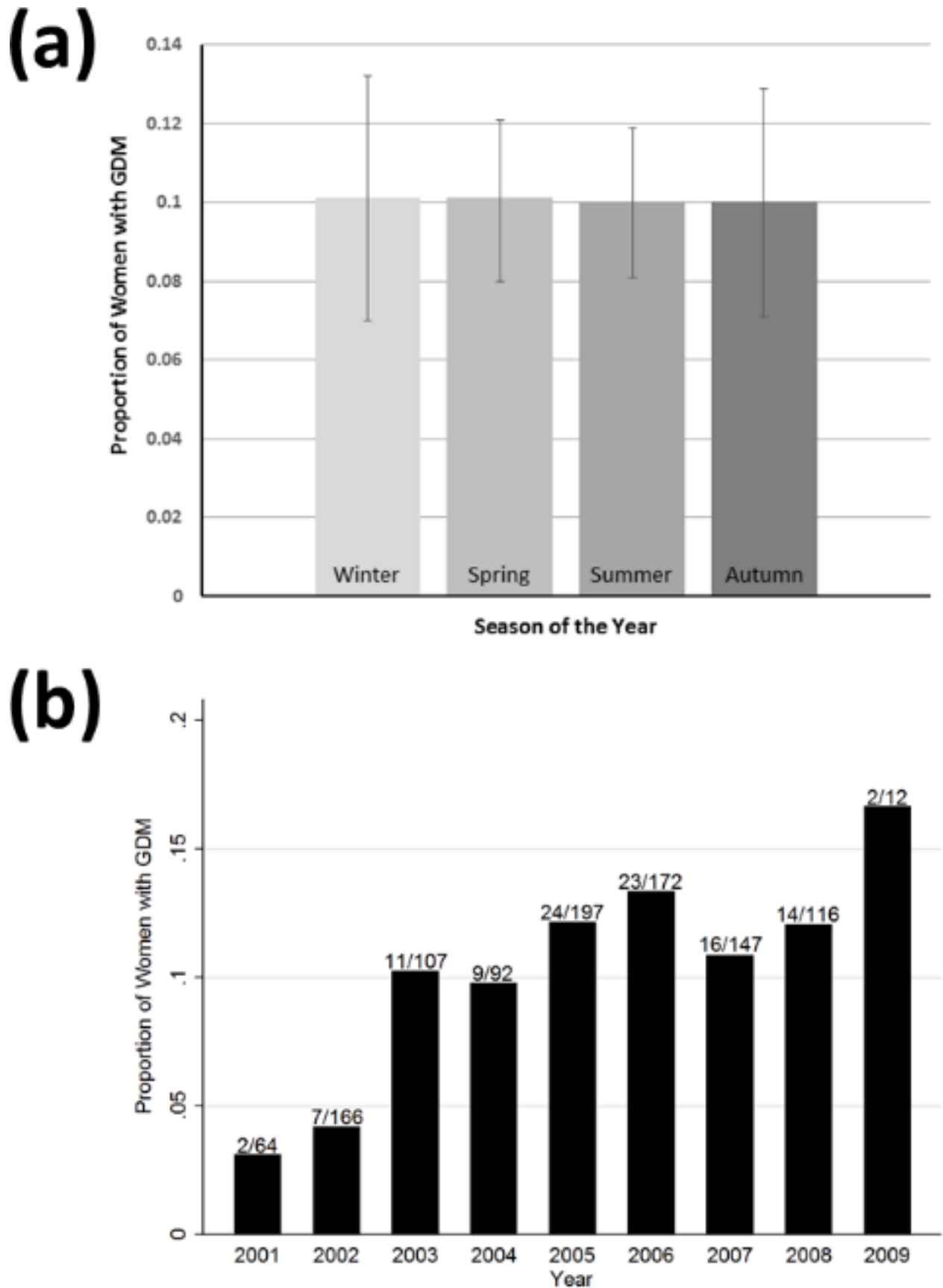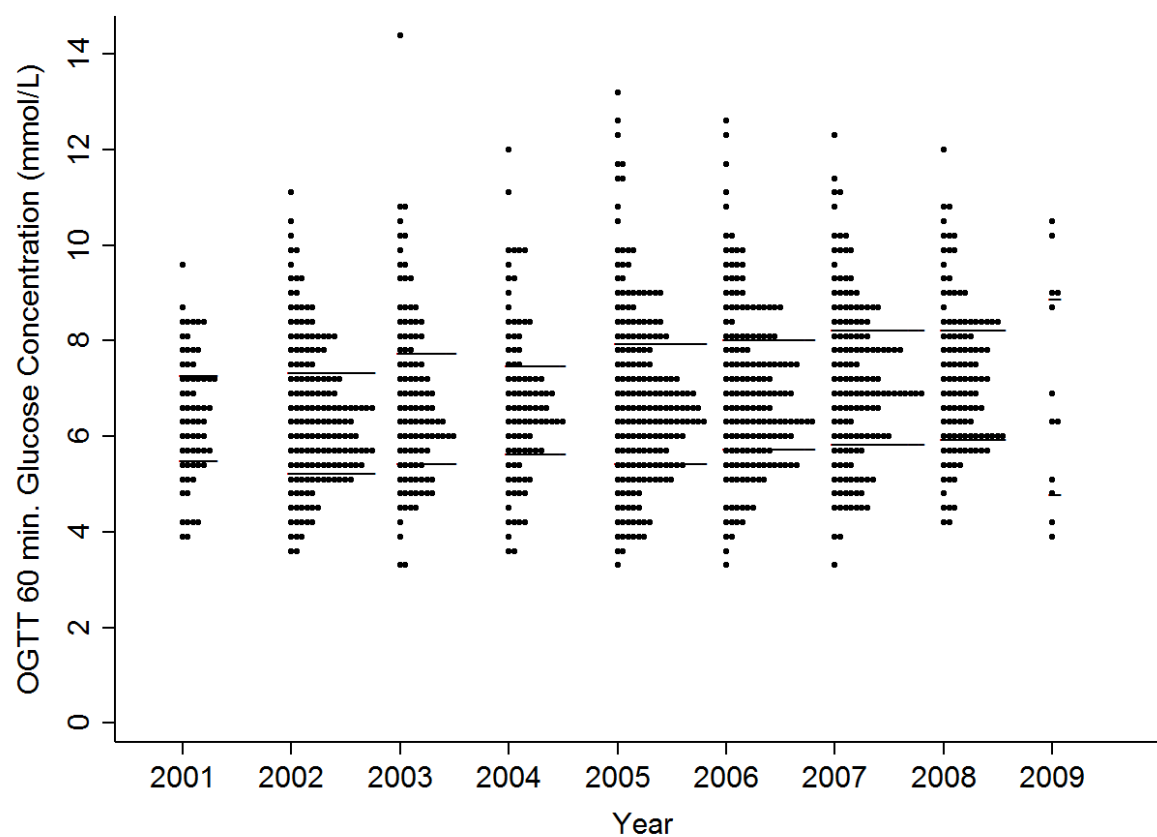
Figure 1

Figure 2

Figure 3