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RESEARCH ARTICLE

Childhood adversity and the risk of gestational diabetes: A population-based cohort study of nulliparous pregnant women

Megan Davies1 | Charlotte S. van Houten1 | Jessica Bengtsson1 | Leonie K. Elsenburg1 | Karoline Kragelund Nielsen2 | Gregers S. Andersen2 | Peter Damm3,4 | Naja H. Rod1

1Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark
2Steno Diabetes Center Copenhagen, Copenhagen University Hospital, Herlev, Denmark
3Center for Pregnant Women with Diabetes, Department of Obstetrics, Rigshospitalet, Copenhagen, Denmark
4Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence
Megan Davies, Section of Epidemiology, Department of Public Health, University of Copenhagen, 1353, Copenhagen, Denmark.
Email: megan.davies@sund.ku.dk

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Abstract

Aims: Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications, and though it may be linked to childhood adversity, the effect of different types of adversity remains unclear. Childhood adversity is linked to a younger maternal age, which may hide the overall impact of adversity on GDM risk. We therefore aimed to explore the association between different types of childhood adversity and GDM while accounting for the potential impact of maternal age.

Methods: We used Danish nation-wide register data, including 208,207 women giving birth for the first time from 2004 to 2018. Five adversity groups were used to examine the effect of childhood adversity on GDM risk: (1) low (referent group), (2) early life material deprivation, (3) persistent deprivation, (4) loss or threat of loss within the family and (5) high adversity.

Results: 5375 women were diagnosed with GDM in the study population (2.6% absolute risk). Compared to women who experienced low adversity, the other adversity groups had a higher GDM risk (absolute difference [%]) directly; early material deprivation (0.64% [95% CI 0.44; 0.84]), persistent deprivation (0.63% [0.41; 0.86]), loss or threat of loss (0.73% [0.42; 1.05]) and high adversity (0.80% [0.32; 1.27]). The indirect effect of maternal age attenuated the total effect of childhood adversity on GDM by an absolute difference of 0.25%–0.46%.

Conclusions: Experiencing childhood adversity to any extent is associated with a higher risk of GDM. Interventions aimed at preventing childhood adversity may have a positive effect in reducing GDM burden and the associated health risks.

KEYWORDS
childhood adversity, gestational diabetes, register data
1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications, with incidences predicted to continue rising globally. GDM is associated with several perinatal complications, as well as an increased risk of type 2 diabetes in later life for both mother and child. The aetiology of GDM is multifaceted, with risk factors including a higher maternal age, higher body weight, certain ethnic backgrounds, low socioeconomic status and poor mental health. Chronic stress, which causes hyperactivity in the hypothalamic pituitary adrenal region of the brain and the related release of stress hormones, increases insulin resistance and thus theoretically increases the risk of developing GDM, though this link has not fully been explored in relation to adverse life experiences.

Early childhood years are a critical period whereby the biological systems are particularly receptive to stress, and exposure to stress during this vulnerable period may form permanent effects on brain development, stress reactivity, endocrine and metabolic systems. Adverse experiences in childhood, such as living in poverty, parental divorce and grief, have previously been shown to substantially impact health across the life course and increase the risk of early mortality and morbidity in adulthood. Recent research has identified a link between childhood adversity and the risk of developing GDM, though studies are few and report mixed findings. These studies are also limited by small sample sizes, with childhood adversity measured through retrospective reporting of adversities that is prone to recall bias. Research reporting an association found that those who experienced childhood physical or sexual abuse had the greatest risk of developing GDM, with several other adversity types left unaccounted for. Other adversities occurring in childhood have previously been found to affect health outcomes including type 2 diabetes, and studies show that family and social adversity are highly entangled and cannot be understood independently of each other.

The potential relationship between childhood adversity and GDM risk is further complicated by the age that women start their families. Younger age at first pregnancy is strongly associated with early life experiences including childhood adversity. The risk of GDM, however, is positively associated with increasing maternal age, and understanding whether a relationship exists between childhood adversity and GDM is therefore difficult without also assessing whether maternal age impacts the overall effect.

Previous studies show inconsistent results on the effect of childhood adversity on GDM risk and have not taken into account the mediating effect of maternal age. It therefore remains unclear how different types of adversity are associated with GDM risk, and whether maternal age impacts this risk. Utilising full prospective life-course data, we aim to document the effect of childhood adversity on the risk of developing GDM by quantifying the direct effect of childhood adversity on GDM, the indirect effect through maternal age and the total effect of childhood adversity on GDM through both the mediating pathway of maternal age and directly from childhood adversity to GDM.

What’s new?
- In this large prospective study population, exposure to any type of adversity during childhood was found to be associated with a higher risk of GDM.
- In this study women who experienced childhood adversity had their first child at a younger age, which, particularly for those exposed to high adversity, mitigated some of the risk of GDM.
- Preventing childhood adversity could have a positive effect in reducing the burden of GDM and the associated long-term health consequences for mother and child.

2 | METHODS

We used data from the DANish LIFE course (DANLIFE) cohort, a register-based cohort created from several Danish nationwide registers, including all those born in Denmark from 1980. All Danish citizens are given a unique personal identification number at birth, enabling the linkage of registers in Denmark covering health and administrative information. For the current study, we identified women in the DANLIFE cohort born between 1980 and 2001, who were resident in Denmark until their 16th birthday and registered in the Danish Medical Birth Register as giving birth for the first time during the period 2004 until 2018 (n = 208,432) (Figure S1). We excluded women who gave birth before age 16 (n = 146) to ensure that adversities were measured throughout their entire childhood (age 0–15) and before giving birth for the first time. Including those with full information on all covariates (99.96%), we had a final study population of 208,207 women giving birth for the first time during this period.
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2.1 | Childhood adversities

The ability to link individuals to parental and sibling data through the registers allowed us to capture a multitude of adversities. DANLIFE includes twelve adversities across three dimensions; family dynamics, material deprivation and loss or threat of loss. Table S1 details the specific adversities included and the registers they were retrieved from.9 Previous modelling of DANLIFE identified five trajectory groups accounting for accumulation and duration of adversity exposure during childhood, based on the annual prevalence within each dimension and for each parent and sibling. These trajectory groups have been used in several other studies on childhood adversity and are used in the present study.8,15 The ‘low adversity’ group includes those exposed to low levels of adversity throughout childhood and adolescence. ‘Early life material deprivation’ and ‘persistent material deprivation’ capture those who experienced high annual rates of poverty and/or parental long-term unemployment in the first 4–5 years of life and throughout childhood and adolescence, respectively. ‘Loss or threat of loss’ is characterised by high annual rates of parental or sibling severe somatic illness or death within the family, and finally ‘high adversity’ captures those who experienced very high and increasing annual rates of adversity across all dimensions throughout childhood and adolescence.

2.2 | GDM

A diagnosis of GDM was identified from the Danish National Patient Register,20 using the International Classification of Diseases 10th Revision (ICD-10) code O24.4. GDM is identified through a risk-factor-based selective screening approach throughout Denmark followed by a 75 g oral glucose tolerance test.21 The recording of GDM in the National Patient Registry was inconsistent before 2004, hence we included only cases from 2004 onwards.22

2.3 | Covariates

Potential confounders of the relationship between childhood adversity and GDM included parental type 2 diabetes (yes/no) and parental country of origin (European origin/non-European origin), which also addresses confounding of the relationship between childhood adversity and maternal age (Figure 1). Parental origin was classified as non-European descent if one or both parents had a nationality from a country outside of Europe, North America, Australia and New Zealand. Parental history of type 2 diabetes was retrieved through the Danish Adult Diabetes Registry (2005–2018) (ICD8: 250/ICD10 E11) and the Danish National Patient Register (1977–2018)23 and supplemented with information on purchased prescriptions of oral anti-diabetic drugs and insulin from the Danish National Prescription Registry, based on the protocol by Carstensen et al. (2020).24 The age category of the participant’s mother at their birth (<20years/20–30years/>30years) was included as a potential confounder of the relationship between childhood adversity and maternal age.

Maternal age was defined in the Danish Medical Birth Register as age at the time of delivery and measured as a continuous variable in years. Age was included as a mediator between childhood adversity and GDM.

FIGURE 1 Direct acyclic graph (DAG) showing proposed mechanism of childhood adversity (blue) on GDM risk (purple) mediated through maternal age at first birth (yellow), with exposure-outcome confounding of parental type 2 diabetes, exposure-outcome and exposure-mediator confounding of parental origin and exposure-mediator confounding of the age of the participants’ mother at their birth (green).
Family adversity is highly linked with parental education and with being born small for gestational age (SGA), as familial adversity could affect the health of the child already in utero. These factors may be moderators or mediators on the effect of childhood adversity on GDM rather than confounders; therefore, we decided to only adjust for the effects of being born SGA (intrauterine growth below the 10th percentile of age- and sex-specific reference curves) and parental education (low <10 years/medium 10–12 years/high >12 years) in supplementary analyses among those with full information on these variables (n = 200,154 and n = 207,445, respectively) (see Table S2 and S3). Additionally, we include birth year in supplementary analysis to control for increasing GDM diagnoses over time (Table S4).

2.4 | Statistical analysis

We performed mediation analysis aimed at disentangling the direct effect of childhood adversity on GDM (adjusting for maternal age), the indirect effect of childhood adversity on GDM through maternal age and finally the total effect of childhood adversity on GDM both through the mediation of maternal age and directly from childhood adversity (indirect effect + direct effect). Mediation analysis is complex with binary outcomes, and meaningful comparisons between indirect and direct effects are problematic if the mediator and outcome are in different units. Marginal mediation analysis, which fits within the counterfactual framework, uses average marginal effects (AME) which allows for comparison between the indirect and direct effects, as AME are calculated in the original outcome units, in this case probabilities, representing the probability of the outcome changing when a variable has a one-unit increase, showing the absolute change in risk. Marginal mediation analysis additionally enables us to focus on the magnitude of the effect, rather than the significance of the indirect and direct effects.

We initially calculated the overall risk of GDM in the study population across maternal age, followed by the risk for low adversity, and finally the risk for low adversity with all covariates set to their referent categories. For the marginal mediation analysis, a logistic regression model was fitted to estimate the direct effect of childhood adversity on GDM, including maternal age, and adjusted for confounders, followed by a linear regression of childhood adversity on maternal age to estimate the indirect effect. AME were calculated post-estimation from the model estimates and data to obtain the direct, indirect and the total effect of childhood adversity on GDM. We excluded individuals with missing data on any variable and performed analyses with full information on all variables for both main and supplementary analyses. All data preparation and analysis were conducted in R, using the package lm4 for the regression models, and the Marginal Mediation package for calculating the AME of the mediation analysis. The indirect and direct effects were bootstrapped for 2000 samples to obtain 95% confidence intervals.

3 | RESULTS

A total of 5375 (2.6%) women giving birth for the first time in the period 2004–2018 were diagnosed with GDM. Table 1 presents the background characteristics of the study population across maternal age.

Figure 2 shows the probability of GDM within this study population. GDM risk was initially estimated across maternal age to calculate the overall risk for the whole study population (purple). We then predicted the risk for those women who experienced low adversity (yellow), and finally for women who experienced low adversity whilst additionally setting all other covariates to their referent category (blue): parental history of type 2 diabetes (no), parental origin (European origin), age of the participant’s mother (20–30 years). The overall risk of GDM, not including any covariates, showed a positive relationship between maternal age and GDM risk (1.23% [95% CI 1.13; 1.33] age 16 vs. 5.45% [5.04; 5.86] age 38). For women who experienced low adversity, GDM risk by maternal age was lower than the risk in the entire population, and further reduced when all other covariates were included and set to the referent category.

Figure 3 shows the results from the marginal mediation analysis, which represent the difference in absolute risk of GDM in each adversity group when compared to low adversity. Panel A shows the direct effect of childhood adversity on GDM risk, indicating there is a higher risk of GDM directly associated with childhood adversity for each trajectory group when compared to low adversity. High adversity showed the strongest direct association with risk for GDM, with a 0.80% (95% CI 0.32; 1.27) higher risk of GDM compared to the low adversity group. This corresponds to a 31% higher relative risk of GDM compared to the overall risk in the study population (2.60% overall risk increased to 3.40%). Panel B shows the indirect effect of childhood adversity on GDM risk when mediated through maternal age. The indirect effects show that through maternal age, there is a slightly lower risk of GDM for each group compared to low adversity, showing a protective effect against GDM due to younger maternal age. This lower risk was greatest for those in the high adversity group, where accounting for maternal age resulted in a reduction of the absolute risk of GDM by...
0.53% (−0.59; −0.48). Supplementary analysis showed the results were most attenuated when adjusted for parental education and SGA, with little change after adjustment for birth year (Tables S2–S4).

The total effect shows that due to a younger maternal age attenuating some of the risk of GDM, the overall absolute difference in risk of GDM for high childhood adversity compared to low adversity is not statistically significant (0.25%
Early material deprivation (0.42% [0.15; 0.71]), persistent deprivation (0.46% [0.27; 0.67]) and loss or threat of loss (0.44% [0.25; 0.63]) were associated with a higher risk of GDM, with maternal age slightly attenuating the risk directly from childhood adversity.

4 | CONCLUSIONS

In a cohort of more than 200,000 women, we found that exposure to any type of adversity during childhood was associated with a higher risk of subsequently developing GDM. In our study, women who experienced childhood adversity, and particularly high adversity, had their first child at a younger age, therefore mitigating some of the risk of GDM. Our findings suggest that, although factors such as having a genetic predisposition may have a greater impact on GDM risk, exposure to childhood adversity to any degree may carry a long-standing increased risk of disease over the life course for women and their children.

Our study indicated that high and increasing rates of adversity were associated with a higher risk of GDM than other adversity groups, though after accounting for maternal age, the total effect for this group was no longer statistically significant. The high adversity group had a mean maternal age 3 years lower than the low adversity group (24 v 27 years), reducing the absolute risk of GDM for high vs. low adversity by 0.5%. Other groups had a maternal age closer to that of the low adversity group, and thereby, their overall higher risk of GDM was less affected by maternal age. In this study, the indirect effect of maternal age had an opposite sign direction to the direct and total effects, with age therefore cancelling out some of the effect of adversity on GDM risk. Excluding age may partly explain the lack of an association reported in previous studies, demonstrating how understanding childhood adversity and GDM risk requires appropriately modelling age to understand the overall impact of childhood adversity.

Teenage pregnancy rates are very low in Denmark due to liberal abortion legislation, good accessibility to sexual health services and high rates of contraceptive use. Despite living in a welfare state with universal healthcare, 52% of women in this cohort experienced some degree of childhood adversity. Other societies with lower welfare systems might have higher rates of adversity and a different distribution of the age at which women start their families. In this study, we looked only at first births to avoid over or underestimating the effect due to differential distributions of subsequent births between groups, as high childhood adversity has been linked to a higher parity and greater likelihood of unplanned pregnancies. Women exposed to high adversity who have additional children at a later age may then have an overall higher risk of GDM than we report, which may be closer to that of the risk directly from childhood adversity not accounting for maternal age.

Several possible mechanisms may explain the link between childhood adversity and GDM. Childhood adversity is associated with an increased likelihood of depression, which may increase the risk of GDM due to disruptions of the endocrine and metabolic systems and subsequent increase of insulin resistance. Childhood adversity is also related to lower socioeconomic status in adulthood, which...
in turn increases the risk of GDM, independent of other maternal risk factors. Exposure to adversity has been found to increase overweight and obesity risk in later life, and higher BMI is strongly linked to an increased GDM risk. In this study, we aimed to establish how different types of adversities are associated with GDM risk overall, and therefore it was beyond the scope of this study to examine mechanisms that are likely on the causal pathway between childhood adversity and GDM. Future studies should explore whether childhood adversity increases the risk of GDM through specific mechanisms including BMI, depression or socioeconomic status.

There is strong mounting evidence that adverse experiences in early life have a lasting effect on health across the life course. Though introducing a systematic screening process for adversity may appear to be a solution, this would require healthcare professionals to undertake a significant degree of training, and several barriers prevent this being effectively implemented. Instead, an investment and focus on improving social determinants at a structural level should be prioritised to reduce and prevent childhood adversity. This may then subsequently reduce additional cases of GDM and associated risks, such as type 2 diabetes and overweight and diabetes in the offspring.

4.1 | Strengths and limitations

National register-based data enabled us to examine the relationship between childhood adversity and GDM risk using an unselected cohort of pregnant women. We extend previous studies using smaller sample sizes and where childhood adversity was measured through retrospective recall, which can lead to bias. We were able to objectively include several measures of adversity across different dimensions and consider the effect of frequency and duration of adversity exposure on GDM risk. In addition, we were able to account for the mediating effect of age, allowing us to better understand how adversity affects GDM risk and how this is impacted by maternal age. This study adds important new knowledge which may help develop preventive strategies with the potential to prevent the additional burden of GDM due to childhood adversity.

However, the use of register data means we were unable to include specific measures of abuse. Due to the inclusion of foster care however, we are likely to have captured the cases of those individuals exposed to severe forms of adversity and abuse within their homes. In addition, Denmark’s risk-factor-based screening protocol for GDM during pregnancy may mean that some women have been systematically missed or did not participate in screening calls, and therefore, GDM may be underestimated in the registries.

In conclusion, exposure to childhood adversity is associated with a higher risk of developing GDM during pregnancy. The extent of the effect of childhood adversity on GDM risk is somewhat masked in those exposed to high rates of adversity, as these women have a younger average maternal age. Preventing childhood adversity may be an effective strategy for reducing additional cases of GDM.

AUTHOR CONTRIBUTIONS

Megan Davies contributed to the study design and was responsible for data management, data analyses, interpretation of results and writing the first draft of the manuscript. Charlotte S. Van Houten, Jessica Bengtsson, Leonie K. Elsenburg, Karoline Kragelund Nielsen, Gregers S. Andersen, Peter Damm and Naja H. Rod contributed to the study design, interpretation of the results and reviewed and edited the manuscript. Megan Davies is the guarantor of this work and had full access to all of the data used in the study and takes responsibility for the integrity of the data and the analysis.

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CONFLICT OF INTEREST STATEMENT

J.B. is currently an employee at Novo Nordisk A/S. She contributed to this manuscript during her previous position at the University of Copenhagen and not during her current position. G.S.A. owns shares in Novo Nordisk A/S. G.S.A. is currently an employee at Novo Nordisk A/S. He contributed to this manuscript during his previous position at Steno Diabetes Center Copenhagen and not during his current position.

DATA AVAILABILITY STATEMENT

The data contain personally identifiable and sensitive information and cannot be made publicly available in accordance with the Act on Processing of Personal Data. Inquiries regarding access to the DANLIFE cohort granted by Statistics Denmark and the Danish Health Data Authorities should be directed to the PI of DANLIFE Professor Naja Hulvej Rod (nahuro@sund.ku.dk).

ORCID

Megan Davies https://orcid.org/0000-0003-0899-6386
Karoline Kragelund Nielsen https://orcid.org/0000-0002-4058-0615

REFERENCES


SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.