Danish Diabetes Birth Registry 2

a study protocol of a national prospective cohort study to monitor outcomes of pregnancies of women with pre-existing diabetes

Knorr, Sine; Aalders, Jori; Overgaard, Martin; Støvring, Henrik; Mathiesen, Elisabeth R; Damm, Peter; Clausen, Tine D; Bjerre-Christensen, Ulla; Andersen, Lise Lotte T; Vinter, Christina; Kofoed-Enevoldsen, Allan; Lauenborg, Jeannet; Kampmann, Ulla; Fuglsang, Jens; Ovesen, Per G; Christensen, Trine T; Sørensen, Anne; Ringholm, Lene; Jensen, Dorte M

Published in:
BMJ Open

DOI:
10.1136/bmjopen-2023-082237

Publication date:
2024

Document version:
Final published version

BMJ Open

Danish Diabetes Birth Registry 2: a study protocol of a national prospective cohort study to monitor outcomes of pregnancies of women with pre-existing diabetes

Sine Knorr ,[1,2] Jori Aalders,[3,4] Martin Overgaard,[4,5] Henrik Støvring,[1] Elisabeth R Mathiesen,[6,7] Peter Damm,[7,8] Tine D Clausen,[8] Ulla Bjerre-Christensen,[9] Lise Lotte T Andersen,[10] Christina Vinter,[3,4,10] Allan Kofoed-Enevoldsen,[11] Jeannet Lauenborg,[12] Ulla Kampmann,[1,2] Jens Fuglsang,[1,2,13] Per G Ovesen,[1,2,13] Trine T Christensen,[14] Anne Sørensen,[15,16] Lene Ringholm,[6,7] Dorte M Jensen[3,4]

To cite: Knorr S, Aalders J, Overgaard M, *et al*. Danish Diabetes Birth Registry 2: a study protocol of a national prospective cohort study to monitor outcomes of pregnancies of women with pre-existing diabetes. *BMJ Open* 2024;**14**:e082237. doi:10.1136/bmjopen-2023-082237

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-082237).

Received 17 November 2023
Accepted 28 March 2024

For numbered affiliations see end of article.

Correspondence to
Dr Sine Knorr;
sine.knorr@clin.au.dk

ABSTRACT

Introduction Despite technological developments and intensified care, pregnancies in women with pre-existing diabetes are still considered high-risk pregnancies. The rate of adverse outcomes in pregnancies affected by diabetes in Denmark is currently unknown, and there is a limited understanding of mechanisms contributing to this elevated risk. To address these gaps, the Danish Diabetes Birth Registry 2 (DDBR2) was established. The aims of this registry are to evaluate maternal and fetal-neonatal outcomes based on 5 years cohort data, and to identify pathophysiology and risk factors associated with short-term and long-term outcomes of pregnancies in women with pre-existing diabetes.

Methods and analysis The DDBR2 registry is a nationwide 5-year prospective cohort with an inclusion period from February 2023 to February 2028 of pregnancies in women with all types of pre-existing diabetes and includes registry, clinical and questionnaire data and biological samples of mother–partner–child trios. Eligible families (parents age ≥18 years and sufficient proficiency in Danish or English) can participate by either (1) basic level data obtained from medical records (mother and child) and questionnaires (partner) or (2) basic level data and additional data which includes questionnaires (mother and partner) and blood samples (all). The primary maternal outcome is Hemoglobin A1c (HbA1c) levels at the end of pregnancy and the primary offspring endpoint is the birth weight SD score. The DDBR2 registry will be complemented by genetic, epigenetic and metabolomic data as well as a biobank for future research, and the cohort will be followed through data from national databases to illuminate possible mechanisms that link maternal diabetes and other parental factors to a possible increased risk of adverse long-term child outcomes.

Ethics and dissemination Approval from the Ethical Committee is obtained (S-20220039). Findings will be sought published in international scientific journals and shared among the participating hospitals and policymakers.

Trial registration number NCT05678543.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Danish Diabetes Birth Registry 2 (DDBR2) is a national prospective cohort study of Danish pregnant women with pre-existing diabetes, their partners and children.
⇒ All pregnant women with pre-existing diabetes in Denmark are asked for participation in the DDBR2 registry if fulfilling the inclusion criteria.
⇒ The DDBR2 registry includes clinical data, questionnaire data and biological samples throughout pregnancy that will be combined with data from Danish national databases.
⇒ The DDBR2 enables examination of the pathophysiology, prevalence of and risk factors for adverse short-term and long-term outcomes.
⇒ The volume of the data collection is considered to be sufficient to consider the risk of rare neonatal outcomes as congenital malformations overall, but not its association with various risk factors.

INTRODUCTION

In Denmark, approximately 400 pregnancies are complicated by pre-existing diabetes every year, of which 250 are in women with type 1 diabetes (T1D), 150 in type 2 diabetes (T2D) and a few are in other diabetes types such as maturity-onset diabetes of the young (MODY), post pancreatitis diabetes or cystic fibrosis-related diabetes. Pregnancies in women with pre-existing diabetes are considered as 'high risk' pregnancies as obstetrical

and neonatal complications are two to four times more frequent compared with the background population. Among women with pre-existing diabetes, up to 50% of the offspring are large for gestational age (LGA) at delivery, one out of five are delivered preterm and offspring risk of metabolic disease later in life is increased.[1–22] During pregnancy, minimising hypoglycaemia and hyperglycaemia, achieving appropriate gestational weight gain and close monitoring of existing diabetes complications, are considered important to prevent adverse outcomes.[23] However, a large proportion of women with pre-existing diabetes do not reach the goals for glycaemic control (only 16–42% for T1D and 37–74% for T2D[1]) and/or weight gain during pregnancy.[1] To further improve outcomes, clinical care and support for pregnant women with diabetes and their families, a number of gaps need to be addressed.

Lack of national data on short-term and long-term adverse outcomes and patient-reported experiences and outcomes

Although regional Danish projects suggest improved maternal and fetal outcomes over the past years, up-to-date data on a national level regarding outcomes of pregnancies affected by pre-existing diabetes and to what extent treatment goals are met, is lacking in Denmark.[24 25] The only national study evaluating maternal and fetal outcomes, the Danish Diabetes Birth Registry, ran from 1992 to 2000 and only included women with T1D.[12] In Eastern Denmark, 38% of pregnant women with pre-existing diabetes have T2D, whereas the numbers are up to 60% in other European countries.[1 24 26] Insight into the national prevalence of pregnancy complications and comorbidities among women with pre-existing diabetes and the number of women meeting treatment goals regarding Hemoglobin A1c (HbA1c) and gestational weight gain would facilitate evaluations of current care and knowledge exchange between hospitals/regions. Moreover, in addition to biomedical outcomes, patient-reported experiences, patient-reported outcomes and overall well-being should be monitored to evaluate and further improve clinical care and to inform women with diabetes better about the expected course of pregnancy.

The unexplored role of parental factors beyond maternal glycaemic control in relation to adverse short-term outcomes

Beyond glycaemic control, other factors seem to contribute to adverse short-term outcomes; in a 5-year study from the national UK cohort, including more than 17 000 pregnancies complicated by pre-existing diabetes, HbA_{1c} >48 mmol/mol in the third trimester was the dominating risk factor for perinatal death and LGA infants (defined as birth weight centile above the 90th percentile).[1] However, the study found a steady increase in children being born LGA over the years, despite no overall deterioration in maternal glycaemic control, which suggests that other factors than HbA_{1c} contribute to fetal overgrowth.[27 28]

While maternal socio-demographic characteristics and partner health have been associated with pregnancy outcomes in women without pre-existing diabetes,[29 30] detailed data on the impact of these characteristics on pregnancy outcomes in women with pre-existing diabetes is lacking. Knowledge of how and which of these characteristics are associated with adverse short-term outcomes could facilitate the identification of women at risk and target groups for future interventions.

Moreover, among pregnant women without diabetes and non-pregnant people with diabetes, modifiable characteristics such as health behaviours (eg, comfort eating, sedentary behaviour, smoking, alcohol use, poor sleep, limited self-monitoring) and psychological distress, particularly pregnancy-related and diabetes-related distress, have been linked to adverse pregnancy and diabetes outcomes.[31–34] However, few studies in pregnant women with pre-existing diabetes have examined the role of health behaviours and psychological distress in relation to adverse outcomes.[35–41] Moreover, potential mechanisms and the role of partner support have not been explored in this group. Insight into whether these modifiable characteristics are linked to adverse outcomes, and possible mediators/moderators, could stimulate new ideas regarding prevention strategies and intervention strategies.

The optimal use of diabetes technology?

In the landmark study CONCEPTT, women with T1D, of which 50% used insulin pumps, were randomised to continued use of continuous glucose monitoring (CGM) from early pregnancy until delivery or to routine care. Overall, continued use of CGM improved neonatal outcomes.[42] In contrast, the overall use of insulin pumps has not been demonstrated to result in improved pregnancy outcomes and the risk of fetal overgrowth is still high among women using insulin pumps.[42–47] However, recent data suggests hybrid closed-loop therapy in women with T1D with HbA_{1c} 48–86 mmol/mol in early pregnancy improves maternal glycaemic control in pregnancy,[48] but no study using hybrid closed-loop during pregnancy is powered for fetal outcomes.[48] Obtaining detailed information on technology use during pregnancy and examining associations with maternal and neonatal outcomes, could give helpful insight into which women benefit from diabetes technology during pregnancy.

Limited understanding of mechanisms involved in increased offspring risk of future metabolic disease

For T1D, previous studies showed that the offspring of women with T1D have a higher T1D risk compared with the background population, but a lower risk compared with the offspring of fathers with T1D.[49–51] This suggests that either differences in heritability of maternal versus paternal susceptibility genes, maternal imprinting or maternal diabetes (ie, the intrauterine environment) modify a child's inherited risk of developing T1D. The development of T1D is preceded by a preclinical period

displaying autoimmunity. Therefore the use of genetic screening of single-nucleotide polymorphisms possibly involved in the autoimmune response prior to developing T1D has been proposed.[52]

For T2D, genome-wide association studies have described approximately 250 loci associated with this condition.[53] However, the genetic composition of T2D is dominated by common alleles with a small impact on the risk of disease.[53] As opposed to T1D, the risk of T2D is higher in the offspring if the mother has T2D in comparison to when the father has T2D.[54] Genetically, this finding can be explained by a unique parent-of-origin transmission of the risk alleles and relates to genetic programming during the intrauterine period.

Later in life, the offspring of women with T1D and T2D have an increased risk of developing obesity, prediabetes and T2D, beyond what can be explained by the DNA sequence.[20–22 55] It is speculated, that the suboptimal intrauterine environment associated with diabetes in pregnancy, may lead to epigenetic changes of the fetal DNA.[56] Epigenetics can regulate gene expression and activity, by closing or opening regions of the genome, thereby allowing for transcription.[57] Such 'fetal programming of adult disease' could provide a pathogenic explanation of why some children of mothers with T1D and T2D diabetes develop long-term adverse outcomes while others do not.

Inflammatory and metabolic markers of the intrauterine environment could provide more insight into the long-term risk of adverse outcomes among offspring, as studies have found them to potentially be altered among adolescent offspring born to women with diabetes.[58 59] The capacity of the placenta to adequately transfer oxygen and nutrients to the fetus, is also important for the developing fetus.[60] Especially, the link between placental growth factors, pre-eclampsia and fetal size and the role of exosomes in placental homeostasis, serves as an area of interest in pregnancies complicated by maternal diabetes.[60 61]

To enable national surveillance of pregnancies in women with pre-existing diabetes in Denmark and address the outlined gaps in the literature, a nationwide cohort of pregnancies in women with pre-existing diabetes, the Danish Diabetes Birth Registry 2 (DDBR2) was established. By establishing a detailed, national prospective registry focusing on a broad range of risk factors and combining this prospective registry with an accompanying biobank with available samples from both women, partners and children as well as detailed information on diabetes technology usage, partner and pre-pregnancy characteristics, health behaviours and psychological distress, a better insight can potentially be gained into the course and consequences of pregnancies in women with pre-existing diabetes.

We expect the DDBR2 to enable the identification of risk factors of pregnancy complications and comorbidities during pregnancy and early post partum and identify barriers to obtaining optimal glycaemic control and an appropriate gestational weight gain in women with pre-existing diabetes.

In addition, the inclusion of biological samples from both women, partners and children in DDBR2 in combination with detailed data on health, family history of diabetes, pregnancy outcomes and socioeconomic background, could help identify offspring at increased risk of diabetes or metabolic disease in the future.

OBJECTIVES

The aim of the DDBR2 registry is to: (1) evaluate maternal and fetal-neonatal complications in pregnancies complicated by maternal pre-existing diabetes based on 5 years cohort data, (2) evaluate the incidence of short-term and long-term adverse outcomes in pregnancies affected by pre-existing diabetes and (3) to identify pathophysiology and risk factors of adverse short-term and long-term outcomes.

Regarding short-term outcomes, we hypothesise that:

- The risk of maternal and neonatal complications following a pregnancy complicated by pre-existing diabetes has decreased since the previous national registry (DDBR) 1992–2000.[12]
- The use of diabetes technology leads to improved glycaemic control and fewer pregnancy and neonatal complications compared with data from DDBR.[12]
- Measures of glucose obtained from CGM are superior to HbA_{1c} measurements as predictors of adverse perinatal outcomes.
- Women with a lower socioeconomic status have a higher risk of adverse outcomes compared with women with a higher socioeconomic background.
- Partner health and socioeconomic background influence pregnancy outcomes.

Regarding long-term outcomes, we expect that:

- Epigenetic alterations in offspring cord blood reflect the intrauterine environment and can be used as markers for later offspring life health.
- Genetic risk scores for T1D and T2D can be used to predict offspring risk for later life disease.
- Low-grade inflammation during pregnancy negatively influences the glucose tolerance of the mother and perinatal outcomes.

Methods and analysis

DDBR2 is a 5-year prospective cohort study with an inclusion period from February 2023 to February 2028 including pregnant women with all types of pre-existing diabetes (T1D, T2D, MODY and other diabetes types), their offspring, and partners. Women and partners are eligible if they are over 18 years of age and have sufficient proficiency in Danish or English to understand oral and written information. During the study period, all women referred to their local centre for pregnant women with diabetes (ie, Odense University Hospital, Aarhus University Hospital, Aalborg University Hospital, Rigshospitalet Copenhagen University Hospital) will be screened for

eligibility. Eligible women and their partners will be invited to participate in this study by trained research personnel. Women and partners can participate at two levels, (1) by providing basic information only (interview and medical records (women) or a questionnaire (partners)) or (2) by providing basic information and additional information (questionnaires and blood samples) (tables 1–4 and figure 1). For women, background information will be collected through an interview conducted by a study nurse at inclusion. Additionally, throughout pregnancy and 1 month after delivery relevant information will be extracted from medical records or during patient contacts. For partners, background information will be collected through a short online questionnaire that will be sent out in early pregnancy. For women and partners who agree to provide additional information, additional blood samples will be drawn and additional questionnaires will be sent out at fixed time points. Offspring participation is also on a two-level basis (basic information vs basic and additional information). Basic information will be extracted from the child's medical record at birth and 1 month after delivery. For participation with additional information, offspring cord or heel blood samples will be collected at birth. Offspring participation depends on informed consent from custody holders. The set-up of the DDBR2 registry enables ongoing clinical evaluation of the data (eg, regional differences and data on women using hybrid closed-loop systems) throughout the study period.

Sample size

In the previous Danish Diabetes Birth Registry, a participation rate of 75–93% across inclusion sites was obtained.[12] By offering participation at two levels (ie, basic information vs basic and additional information), a participation rate of 80% is expected.[12] We therefore expect to include approximately 400 pregnant women each year (T1D: n=250; T2D: n=150; other types: n=5–10), resulting in an estimated sample size of 2000 mother–partner–child trios by the end of the 5-year inclusion period. The recruitment started on the 22 February 2023 and will end on 21 February 2028.

Measures

An extended overview of data and biological samples that will be collected is provided in tables 1–4. The primary maternal outcome is HbA_{1c} levels at the end of pregnancy and the primary offspring endpoint is the birth weight SD score. The extended collection of data in the DDBR2 enables reporting of a range of maternal and fetal-neonatal outcomes. As secondary outcomes, the following will be included in the study:

- HbA_{1c} levels during pregnancy at inclusion, 21, 33 and 35 weeks.
- The average glucose level and percentage of time spent in the CGM target range in pregnancy 3.5–7.8 mmol/L, below the target range in pregnancy (glucose <3.5 mmol/L) or above the target range in pregnancy (glucose >7.8 mmol/L). The levels will be evaluated at night-time (00:00 to 06:00) and over 24 hours, respectively, in pregnancy, during delivery and in the 1-month period after delivery.
- The incidence of severe hypoglycaemia in the year preceding pregnancy, during pregnancy and in the 1-month period after delivery.
- Maternal gestational weight gain and weight retention 1 month after delivery.
- In women on insulin pump therapy: insulin pump settings (mainly basal rates, carbohydrate ratio and sensitivity) in pregnancy, around delivery and in the 1-month period after delivery.
- The prevalence of fetal overgrowth, defined as the offspring's birth weight SD score >90th percentile.
- Pregnancy complications: prevalence of induced abortion (including indication for abortion), miscarriage, gestational hypertension, pre-eclampsia, need for maternal corticosteroid treatment for fetal lung maturation, diabetic ketoacidosis, urinary tract infection, early preterm delivery (before 34 completed weeks), preterm delivery (before 37 completed weeks), preterm prelabour rupture of the membranes.
- Birth complications: shoulder dystocia, birth canal trauma, mode of delivery (vaginal, caesarean section, instrumental delivery), postpartum haemorrhage, maternal death, antihypertensive treatment given 1 month after delivery.
- Neonatal morbidity (neonatal hypoglycaemia, jaundice, respiratory distress, transient tachypnoea, duration of stay in neonatal intensive care unit, total number of admission days), cord blood pH, stillbirths, infant death within 1 month.
- Major congenital malformations (International Classification of Diseases 10th Revision (ICD-10) Q00-Q99 or requiring medical or surgical treatment).
- Infant growth and health at 1 month of age.
- Maternal and partner quality of life in pregnancy and 1 month after delivery.
- Maternal mental health in pregnancy and 1 month after delivery.
- Average glucose level and the percentage of time in the first 1-month period after delivery spent in the CGM target range 3.9–10.0 mmol/L, below target range (glucose <3.9 mmol/L) or above target range (glucose >10.0 mmol/L) at night-time (00:00 to 06:00) and over 24 hours, respectively.

After the study period, the participants will be identified through Statistics Denmark providing prolonged follow-up using relevant Danish registries.[62] This enables the inclusion of data related to morbidity (eg, hospital admissions, prescribed medication), mortality beyond the neonatal period, socioeconomic status (eg, level of education, job and unemployment status, yearly household income), offspring health (eg, data collected by specialised health nurses in The National Child Health Register, offspring growth up until the age of 6–7 years) and grades when finishing primary school.[62 63] Using data from Statistics Denmark we will

Table 1 Measures in the Danish Diabetes Birth Registry-2 for women during pregnancy

Timing	Level of participation	
	Basic information	Additional information
During pregnancy		
Women	Interview and data from medical records at 8–12 weeks: *Pre-pregnancy information:* *History of disease:* Type of diabetes, diabetes duration, presence of diabetes-related comorbidities, history of gastric bypass/sleeve, other comorbidities, number of hypoglycaemic events that required assistance from others during the past year, hypoglycaemia awareness status. *Prior pregnancies:* Number of prior pregnancies, number of abortions, type and timing of abortions, year of delivery/abortion, term of prior pregnancies, birth weight of offspring, complications during prior pregnancies, mode of delivery prior pregnancies. *Pre-pregnancy use of insulin, diabetes technology and other medication:* Use of continuous glucose monitoring (CGM), type of sensor and upload platform in case of sensor use before or during pregnancy bolus advisor system use, insulin use, other medication, folic acid supplementation. Insulin pump use before pregnancy, type and dose of insulin before pregnancy, carbohydrate ratio and sensitivity before pregnancy, type of insulin pump if used before pregnancy. *Pregnancy planning:* Data of stopping contraceptives, time of intending to get pregnant and getting pregnant, fertility treatment, pre-pregnancy counselling. *Pre-pregnancy information:* Pre-pregnancy height, pre-pregnancy weight, last HbA_{1c} before pregnancy and date of assessment, last TSH, last vitamin D. *Background information:* Ethnicity, country of birth, household composition, level of education, employment status, alcohol use, smoking status, reading and/or writing problems, family history of diabetes. Medical record—each pregnancy visits to the clinic: Date of visit, HbA_{1c}, current weight, blood pressure, urine ketone, urine albumin-creatinine ratio current use of insulin/sensor or bolus calculator, hypoglycaemic events (mild/severe), ketoacidosis, current use of other anti-glycaemic medication, eye examination. *Diabetes treatment:* Current insulin dose, insulin pump specifications and settings, number of finger pricks, CGM information (including uploads, mean glucose, time above range (>7.8 mmol/L), time in range (3.5–7.8 mmol/L), time below range (<3.5 mmol/L) in pregnancy. *Pregnancy complications:* Abortion and type, current comorbidities/treatments and date of onset (including hypertension, pre-eclampsia), use of lung maturing medication, premature rupture of membranes (including timing and result). Ultrasound scans: Crown-Rump-Length, head circumference (mm and z-score), abdominal circumference (mm and z-score), femur length (mm and z-score), estimated fetal weight (in grams based on Hadlock's formula, z-score and in percentage deviation from expected for gestational age), amniotic fluid index and 'deepest pocket' in cm, uterine artery pulsatility (mean and z-score), umbilical artery pulsatility index (including z-score).	Biological samples at 12 and 28 weeks: Genetic risk score, epigenetic markers, small RNAs, inflammatory cytokines, metabolic markers, placental markers, proteomics, serum and plasma for future biobank. Questionnaire around 12 weeks of pregnancy: Health status (SF-12, V.2),[68] pregnancy symptoms hampering physical activity (SSQ), physical activity (PPAQ-DK),[69 70] eating habits,[71] diet (FFQ), changes in diet since pregnancy and supplement use (Danish national birth cohort),[72] binge drinking episodes during pregnancy (Copenhagen Pregnancy Cohort),[73] sleep (PSQI),[74] history of psychopathology and psychotropic medication use (SSQs), history of contact with a psychologist/psychiatrist (SSQs), well-being (WHO-5),[75 76] depression (EPDS),[77 78] perceived stress (PSS),[79 80] loneliness (T-ILS),[81] diabetes-related distress (PAID),[82] fear of hypoglycaemia (HFS-II-w),[83] pregnancy worries (CWS),[84] relationship duration (SSQ), marital satisfaction (SSQ), dyadic coping (DCI),[85] health literacy (HLSAC),[86 87] satisfaction with care (PACIC).[88] Questionnaire at 26–29 weeks of pregnancy: Health status (SF-12, V.2),[68] changes in pregnancy symptoms hampering physical activity (SSQ), physical activity (PPAQ-DK),[69 70] diet (FFQ), changes in diet since pregnancy and changes in supplement use (Danish national birth cohort),[72] changes in binge drinking episodes during pregnancy (Copenhagen Pregnancy Cohort),[73] sleep (PSQI),[74] changes in psychopathology and psychotropic medication use (SSQ), changes in contact with a psychologist/psychiatrist (SSQ), well-being (WHO-5),[75 76] depression (EPDS),[77 78] perceived stress (PSS),[79 80] loneliness (T-ILS),[81] diabetes-related distress (PAID),[82] fear of hypoglycaemia (HFS-II-w),[83] pregnancy worries (CWS),[84] breast feeding intention,[89] prenatal attachment (MAAS),[90 91] satisfaction with care (PACIC).[92]

CWS, Cambridge Worry Scale; DCI, Dyadic Coping Inventory (subscales: Stress communicated by oneself, supportive dyadic coping of the partner, delegated dyadic coping of the partner, negative dyadic coping by partner, common dyadic coping, evaluation of dyadic coping); EPDS, Edinburgh Postnatal Depression Scale; FFQ, Food Frequency Questionnaire; HbA_{1c}, Hemoglobin A1c; HFS-II-w, Hypoglycaemia Fear Survey-II – worry subscale; HLCA, Health Literacy for School-Aged Children; MAAS, Maternal Antenatal Attachment Scale; PACIC, Patients Assessment Chronic Illness Care; PAID, Problem Areas in Diabetes; PAS-2=PPAQ-DK, Pregnancy Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; SF12, 12 Item Short-Form (SF-12); SSQ, Study Specific Question; T-ILS, Three Item Loneliness Scale; TSH, Thyroid-stimulating hormone; WHO-5, WHO - Five Well-Being Index.

Table 2 Measures in the Danish Diabetes Birth Registry-2 for the partners during pregnancy

Timing	Level of participation	
	Basic information	Additional information
During pregnancy		
Partner	Online study-specific questionnaire sent out directly after inclusion: Ethnicity, country of birth, household composition, level of education, employment status, chronic disease/history of disease, height, current weight, alcohol use, smoking status, reading and/or writing problems, family history of diabetes.	Biological samples at 12 weeks: Genetic risk score, epigenetic markers, small RNAs, inflammatory cytokines, metabolic markers, proteomics, serum and plasma for future biobank. Questionnaire around 12 weeks of pregnancy: Health status (SF-12, V.2),[68] physical activity (PAS-2),[93–95] eating habits,[71] diet (FFQ), sleep (PSQI),[74] history of psychopathology and psychotropic medication use (SSQs), history of contact with a psychologist/psychiatrist (SSQs), well-being (WHO-5),[75 76] depression (EPDS),[77 78] perceived stress (PSS),[79 80] loneliness (T-ILS),[81] relationship duration (SSQ), marital satisfaction (SSQ), dyadic coping (DCI),[85] health literacy (HLSAC).[86 87] Questionnaire at 26–29 weeks of pregnancy: Health status (SF-12, V.2),[68] physical activity (PAS-2),[93–95] diet (FFQ), sleep (PSQI),[74] changes in psychopathology and psychotropic medication use (SSQ), changes in contact with a psychologist/psychiatrist (SSQ), well-being (WHO-5),[75 76] depression (EPDS),[77 78] perceived stress (PSS),[79 80] loneliness (T-ILS),[81] prenatal attachment (PAAS).[90 91]

DCI, Dyadic Coping Inventory (subscales: Stress communicated by oneself, supportive dyadic coping of the partner, delegated dyadic coping of the partner, negative dyadic coping by partner, common dyadic coping, evaluation of dyadic coping); EPDS, Edinburgh Postnatal Depression Scale; FFQ, Food Frequency Questionnaire; HLCA, Health Literacy for School-Aged Children; PAAS, Paternal Antenatal Attachment Scale; PAS-2, Physical Activity Scale 2; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; SF12=12, Item Short-Form (SF-12); SSQ, Study Specific Question; T-ILS, Three Item Loneliness Scale; WHO-5, EHO - Five Well-Being Index.

identify a gender-matched and age-matched control group in the registries for both women, partners and children. This allows comparison to pregnancies not affected by diabetes for both short-term and long-term outcomes on morbidity, mortality, socioeconomic status and offspring health.

From the original DDBR study described by Jensen *et al*, we have information on maternal and neonatal complications (eg, pre-eclampsia, preterm birth, stillbirth, children being born LGA and small for gestational age, birth weight) following a pregnancy complicated by maternal diabetes.[12] We will use these data to study how maternal and neonatal complications following pregnancies complicated by pre-existing diabetes have changed over the last 25 years, also after adjusting for confounders (eg, maternal diabetes complications prior to pregnancy, maternal body mass index, ketoacidosis or hypoglycaemia and use of pregestational guidance).

Statistical considerations and methods

As this is an observational study, estimates of the expected precision for primary outcomes of interest are presented. These estimates of precision may serve as indications for the other outcomes, which will also be collected during follow-up. As the study is observational and intends to recruit all eligible women within the study period, a conventional sample size calculation based on power and statistical significance is not relevant.[64]

Using the formulas provided by Rothmann and Greenland and data from prior studies, the expected precision for the main outcomes was calculated.[1 64–67] The expected precision is expressed as the magnitude of the expected SE and the corresponding, expected width of the 95% CI of the relevant parameters.

1. For estimating the mean maternal HbA_{1c} at the end of pregnancy, the expected SE for our study is 0.35% (T1D) and 0.37% (T2D) and thus the expected width of the 95% CIs are 1.35 (T1D) and 1.44 (T2D).[1]
2. For estimating the mean birth weight, the expected SEs are 25.4 g (T1D) and 32.4 g (T2D), with expected widths of 95% CIs of 99.5 g (T1D) and 126.9 g (T2D).[65]
3. For estimating the proportion of children born LGA the associated SEs are 0.016 (T1D) and 0.018 (T2D) with expected widths of 95% CIs of 0.062 (T1D) and 0.070 (T2D).[1]
4. For estimating the risk of LGA in children born to women with T1D using insulin pumps and for those using multiple daily injections (MDI), the expected SEs of the risk are 0.021 (insulin pump) and 0.018

Table 3 Measures in the Danish Diabetes Birth Registry-2 at birth and after birth for women, partners and children

Timing	Level of participation	
	Basic information	Additional information
Birth		
Women	Medical record: Gestational age at birth, date of birth, preterm delivery (<37 weeks), reason for preterm delivery, birth injuries, postpartum bleeding, mortality (cause of death), mode of delivery (indication for caesarean section), induction of delivery (reason to induce the delivery, method), hospitalisation (number of days), use of epidural blockade, fever during delivery.	
Child	Medical record: Demographics (sex, gestational age, birth weight, crown-heel length, head circumference, abdominal circumference, Apgar score). Neonatal outcome (major congenital malformations, birth injury, shoulder dystocia, respiratory distress, transient tachypnoea, neonatal hypoglycaemia, systemic infections, admission to neonatal intensive care unit, number of admission days, hyperbilirubinaemia, cord blood pH), death, reason for death.	Biological samples (cord blood sample or filter paper): Genetic risk score, epigenetic markers, small RNAs, inflammatory cytokines, metabolic markers, proteomics, serum and plasma for future biobank.
1 month after delivery		
Women	Medical record and visit or telephone call: Lactation status, weight, HbA_{1c}, insulin dose, number of mild hypoglycaemia the previous week and severe hypoglycaemia since delivery. CGM uploads.	Questionnaire 3–6 weeks after delivery: Health status (SF-12, version 2),[68] diet (SSQ, FFQ), sleep (PSQI),[74] changes in psychopathology and psychotropic medication use (SSQ), changes in contact with a psychologist/psychiatrist (SSQ) well-being (WHO-5),[75 76] depression (EPDS),[77 78] perceived stress (PSS),[79 80] loneliness (T-ILS),[81] diabetes-related distress (PAID),[79 80] fear of hypoglycaemia (HFS-II-w),[83] breastfeeding practices and experiences,[96–98] satisfaction with care (PACIC).[92]
Child	Medical record and visit or telephone call: Length and weight. If the data are collected by telephone, we will include data on weight and length by using the measurements from the last visit of the routine health nurses (planned visits at 7 days and 1 month after delivery). Presence of congenital malformations. Days with hospitalisation within the first month of life since discharge after delivery.	
Partner		Questionnaire 3–6 weeks after delivery: Health status (SF-12, V.2),[68] physical activity (PAS-2),[93–95] diet (FFQ), sleep (PSQI),[74] changes in psychopathology and psychotropic medication use (SSQ), changes in contact with a psychologist/psychiatrist (SSQ), well-being (WHO-5),[75 76] depression (EPDS),[77 78] perceived stress (PSS),[79 80] loneliness (T-ILS).[81]

CGM, continuous glucose monitoring; EPDS, Edinburgh Postnatal Depression Scale; FFQ, Food Frequency Questionnaire; HbA_{1c}, Hemoglobin A1c; HFS-II-w, Hypoglycaemia Fear Survey-II – worry subscale; PACIC, Patients Assessment Chronic Illness Care; PAID, Problem Areas in Diabetes; PAS-2, Physical Activity Scale 2; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; SF12, 12 Item Short-Form (SF-12); SSQ, Study Specific Question; T-ILS, Three Item Loneliness Scale; WHO-5, WHO - Five Well-Being Index.

Table 4 Biological samples obtained in women, partners and children for planned analysis and biobank for future use

Type	Analysis
Epigenetics	The epigenetic profile of DNA samples extracted from whole blood (10 mL) will be characterised by genome-wide DNA methylation using Infinium HumanMethylation450 BeadChip arrays. Principle component and hierarchical clustering analyses will be used to identify associations between methylation patterns and a range of clinical characteristics and biomarkers in women, offspring and partners.
Genetics	Genomic DNA will be extracted from the buffy coat and will be non-comprehensively genotyped using Illumina Infinium Global Screening Array. After removing individuals with >10% variant missingness, and/or extreme inbreeding coefficient in the quality control procedure, data will be imputed using the most recent updated reference, that is, Haplotype Reference Consortium reference panel build GRCh37. Polygenic risk scores for type 1 diabetes, type 2 diabetes and other cardiometabolic traits (ie, glucose levels, blood pressure, lipid levels, insulin secretion, insulin resistance, BMI, weight, waist corrected for BMI) will be calculated using common SNPs and published weighted scores for phenotypic traits.
Small RNA	The presence of parental small RNAs levels during pregnancy or after delivery will be analysed to identify predictive biomarkers of maternal and offspring health. 500 µL plasma or serum will be used for the measurement of circulating small RNAs by either RT-qPCR or sequencing.
Proteomics	Clinical proteomics will be used to (1) identify/evaluate early biomarkers to predict maternal and neonatal complications as well as metabolic risk profile later in life and (2) investigate if mass spectrometry-based glycated albumin associates with maternal and neonatal outcome.
Inflammatory cytokines	Eg, Tumour necrosis factor alpha, interferon gamma, CD163, various chemokines and interleukins and vascular factors.
Metabolic markers	Eg, C-peptide, fibroblast growth factor 21, leptin, adiponectin, growth/differentiation factor 15, glycated CD-59, adrenomedullin, apolipoproteins, cortisol, corticosteroid binding globulin and prolactin.
Placental markers	Eg, Placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy associated plasma protein A and placental derived exosomes.
Plasma and serum for biobank for future research	

*Obtained from women only.
BMI, body mass index; SNPs, single-nucleotide polymorphisms.

(MDI). Thus, the expected SE of the risk difference is 0.028 and the expected 95% CIs for the risk difference is 0.110.[66]

As an observational study with extensive data collection we plan to report a range of maternal and fetal-neonatal outcomes (see tables 1–3). For these data, we will analyse continuous outcomes with linear regression after the assessment of model assumptions (normally distributed residuals). Binary outcomes will be analysed using risk regression (ie, generalised linear model, family binomial, identity link). Subanalysis for T1D and T2D with and without the use of diabetes technology will be performed separately. To account for dependency among repeat pregnancies of mothers, we will use robust variance estimates.

Patient and public involvement statement

The DDBR2 is directed by a National Research Board representing all departments providing care to women with pre-existing diabetes during pregnancy and patient representatives. The National Research Board's task is to provide input and feedback on both the study set-up and execution throughout the study period and the evaluation process. The National Research Board will, based on protocols, evaluate incoming suggestions for future studies using DDBR2 data.

Ethics and dissemination

The DDBR2 study will be carried out in accordance with the Declaration of Helsinki. Ethical approval for the study has been provided by the Ethical Committee in the Southern Denmark Region (S-20220039). In accordance with Danish legislation, mothers and partners need to provide consent for their own participation and both parents need to provide informed consent for their child(ren) to participate. Anonymity and confidentiality of participants will be ensured by assigning a study ID number to all participants (both the women, their partners and offspring).

Data will be entered and stored in the Research Electronic Data Capture system, REDCap. Data extracted from medical records will be entered in REDCap by study personnel. The questionnaire concerning partner socio-demographic and clinical data and the additional questionnaires will be filled out electronically and thereby entered directly into REDCap. The study adheres to all General Data Protection Regulations and the Danish Act on supplementary provision to the regulation on the protection of persons about the processing of personal data and on free movement of these. Findings will be shared among the participating hospitals, policymakers and academic

Standard visits										
			8 Weeks	12 Weeks	20 Weeks	28 Weeks	32 Weeks	36 Weeks	Delivery	1 month after birth
Women		Consultations	X	X	X	X	X	X	X	
Fetus		Consultations								
		Ultrasound		X	X	X	X	X		
The Danish Diabetes Birth Registry 2 (DDBR2)										
			8 Weeks	12 Weeks	20 Weeks	28 Weeks	32 Weeks	36 Weeks	Delivery	1 month after birth
Women	Basic	Interview/ phone call	X							X
		Medical record review	X	X	X	X	X	X	X	X
	Additional	Interview/ phone call	X							X
		Medical record review	X	X	X	X	X	X	X	X
		Blood samples		X		X				
		Questionnaires		X[1]		X[2]				X[3]
Partner	Basic	Background information questionnaire	X[4]							
	Additional	Blood samples		X						
		Questionnaires		X[1]		X[2]				X[3]
Child	Basic	Medical record review							X	X
	Additional	Medical record review							X	X
		Blood samples							X	

Figure 1 The figure is divided in two, displaying the organisation of standard visits for a pregnant woman with pre-existing diabetes in Denmark at the top and below, the additional visits and data collection included in the Danish Diabetes Birth Registry 2. [1]Early pregnancy questionnaire (sent out directly after the first study visit). [2]Late pregnancy questionnaire (sent out at 26 weeks—based on expected due date inclusion). [3]After birth questionnaire (sent out 3 weeks after birth) [4]Background questionnaire (sent out directly after inclusion).

community (ie, submitted to national and international scientific journals and meetings), to promote quality monitoring and disseminate research results both nationally and internationally. After the project end date, the registry data will be transferred to a future research database under the Danish Steno Diabetes Centers and the biobank samples will be transferred to a biobank for future research. After the project end date, the external researcher can be granted access to data and/or biobank samples by the National Research Board, if presenting a protocol and holding the relevant legal permits.

Author affiliations
[1]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[3]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark
[4]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[5]Department of Clinical Biochemistry, Odense University Hospital, Odense, Syddanmark, Denmark
[6]Center for Pregnant Women with Diabetes, Department of Endocrinology and Metabolism, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[7]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[8]Center for Pregnant Women with Diabetes, Department of Obstetrics, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[9]Steno Diabetes Center Copenhagen, Herlev Hospital, Herlev, Denmark
[10]Department of Obstetrics and Gynecology, Odense University Hospital, Odense, Denmark
[11]Steno Diabetes Center Sjælland, Nykøbing Falster Sygehus, Nykobing, Denmark
[12]Department of Obstetrics and Gynecology, Copenhagen University Hospital Herlev, Herlev, Denmark
[13]Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus N, Denmark
[14]Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark
[15]Department of Obstetrics and Gynecology, Aalborg University Hospital, Aalborg, Denmark
[16]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Contributors The study concept and design were conducted by SK, JA, DMJ and PD. SK, JA, HS, LR and DMJ drafted the manuscript. A statistical analysis plan was drafted by HS. SK, JA, MO, HS, ERM, PD, TDC, UB-C, LLTA, CV, AK-E, JL, UK, JF, PGO, TTC, AS, LR and DMJ all contributed substantially to the study design, creation of the DDBR2 registry and biobank and all authors critically revised and accepted the manuscript before submission.

Funding This work was supported by the Novo Nordic Foundation grant NNF21OC0069751.

Competing interests SK: None. JA: None. MO: MO holds stocks in Novo Nordisk. HS: None. ERM: ERM has participated in clinical studies on the use of insulin in pregnant women with pre-existing diabetes in collaboration with Novo Nordisk. Papers from these studies are still being produced. No personal honorarium was involved. LR: LR has received a grant from Novo Nordisk A/S for an investigator-sponsored study. Grant number: U1111-1209-6358. LR participated in the European Association for the Study of Diabetes annual meeting 2023 as an invite by Novo Nordisk. PD: PD has participated in clinical studies on the use of insulin in pregnant women with pre-existing diabetes in collaboration with Novo Nordisk. Papers from these studies are still being produced. No personal honorarium was involved. TDC: TDC has participated in clinical studies on the use of insulin in pregnant women with pre-existing diabetes in collaboration with Novo Nordisk. Papers from these studies are still being produced. No personal honorarium was involved. UB-C: None. AK-E: None. JL: None. LLTA: None. CV: None. UK: None. JF:

JF holds stocks in Novo Nordisk. PGO: None. TTC: TTC participated in the European Association for the Study of Diabetes annual meeting 2023 as an invite by Novo Nordisk. AS: None. DMJ: None.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Sine Knorr http://orcid.org/0000-0001-6552-5340

REFERENCES

1 Murphy HR, Howgate C, O'Keefe J, *et al*. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. *The Lancet Diabetes & Endocrinology* 2021;9:153–64.
2 Macintosh MCM, Fleming KM, Bailey JA, *et al*. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and northern Ireland: population based study. *BMJ* 2006;333:177.
3 Penney GC, Mair G, Pearson DWM, *et al*. Outcomes of pregnancies in women with type 1 diabetes in Scotland: A national population-based study. *BJOG* 2003;110:315–8.
4 Yang J, Cummings EA, O'Connell C, *et al*. Fetal and neonatal outcomes of diabetic pregnancies. *Obstetrics & Gynecology* 2006;108:644–50.
5 Verheijen ECJ, Critchley JA, Whitelaw DC, *et al*. Outcomes of pregnancies in women with pre-existing type 1 or type 2 diabetes, in an ethnically mixed population. *BJOG* 2005;112:1500–3.
6 Colstrup M, Mathiesen ER, Damm P, *et al*. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent declaration been met concerning foetal and neonatal complications *The Journal of Maternal-Fetal & Neonatal Medicine* 2013;26:1682–6.
7 Tennant PWG, Glinianaia SV, Bilous RW, *et al*. Pre-existing diabetes, maternal Glycated Haemoglobin, and the risks of fetal and infant death: A population-based study. *Diabetologia* 2014;57:285–94.
8 Dunne FP, Chowdhury TA, Hartland A, *et al*. Pregnancy outcome in women with insulin-dependent diabetes mellitus complicated by nephropathy. *QJM* 1999;92:451–4.
9 Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies. *Diabetes Care* 2009;32:2005–9.
10 Eidem I, Vangen S, Hanssen KF, *et al*. Perinatal and infant mortality in term and Preterm births among women with type 1 diabetes. *Diabetologia* 2011;54:2771–8.
11 Vääräsmäki M, Gissler M, Ritvanen A, *et al*. Congenital anomalies and first life year surveillance in type 1 diabetic births. *Diabet Med* 2002;19:589–93.
12 Jensen DM, Damm P, Moelsted-Pedersen L, *et al*. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care* 2004;27:2819–23.
13 Clausen TD, Mathiesen E, Ekbom P, *et al*. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care* 2005;28:323–8.
14 Ludvigsson JF, Neovius M, Söderling J, *et al*. Periconception Glycemic control in women with type 1 diabetes and risk of major birth defects: population-based cohort study in Sweden. *BMJ* 2018;362.
15 Casson IF, Clarke CA, Howard CV, *et al*. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ* 1997;315:275–8.
16 Diabetes PGF. French Multicentric survey of outcome of pregnancy in women with Pregestational diabetes. *Diabetes Care* 2003;26:2990–3.
17 Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004;328:915.
18 Platt MJ, Stanisstreet M, Casson IF, *et al*. St Vincent ' s declaration 10 years on: outcomes Ofdiabetic pregnancies. *Diabet Med* 2002;19:216–20.
19 Child H, Confidential Enquiry into M. Pregnancy in women with type 1 and type 2 diabetes in 2002-3, England. Wales and Northern Ireland; 2007.
20 Vlachová Z, Bytoft B, Knorr S, *et al*. Increased metabolic risk in adolescent offspring of mothers with type 1 diabetes: the EPICOM study. *Diabetologia* 2015;58:1454–63.
21 Clausen TD, Mathiesen ER, Hansen T, *et al*. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes. *Diabetes Care* 2008;31:340–6.
22 Clausen TD, Mathiesen ER, Hansen T, *et al*. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. *J Clin Endocrinol Metab* 2009;94:2464–70.
23 Ringholm L, Damm P, Mathiesen ER. Improving pregnancy outcomes in women with diabetes mellitus: modern management. *Nat Rev Endocrinol* 2019;15:406–16.
24 Nørgaard SK, Vestgaard MJ, Jørgensen IL, *et al*. Diastolic blood pressure is a potentially Modifiable risk factor for Preeclampsia in women with pre-existing diabetes. *Diabetes Res Clin Pract* 2018;138:229–37.
25 Damm JA, Asbjörnsdóttir B, Callesen NF, *et al*. Diabetic nephropathy and Microalbuminuria in pregnant women with type 1 and type 2 diabetes: prevalence, antihypertensive strategy, and pregnancy outcome. *Diabetes Care* 2013;36:3489–94.
26 Billionnet C, Mitanchez D, Weill A, *et al*. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia* 2017;60:636–44.
27 Menichini D, Petrella E, Dipace V, *et al*. n.d. The impact of an early lifestyle intervention on pregnancy outcomes in a cohort of insulin-resistant overweight and obese women. *Nutrients*12:1496.
28 Desoye G-O, Ringholm L-O, Damm P-O, *et al*. Secular trend for increasing birthweight in offspring of pregnant women with type 1 diabetes. n.d.
29 Takagi K, Iwama N, Metoki H, *et al*. Paternal height has an impact on birth weight of their offspring in a Japanese population: the Japan environment and children's study. *J Dev Orig Health Dis* 2019;10:542–54.
30 Meng Y, Groth SW. Fathers count: the impact of paternal risk factors on birth outcomes. *Matern Child Health J* 2018;22:401–8.
31 Gaillard R, Wright J, Jaddoe VWV. Lifestyle intervention strategies in early life to improve pregnancy outcomes and long-term health of offspring: a narrative review. *J Dev Orig Health Dis* 2019;10:314–21.
32 Blackmore ER, Gustafsson H, Gilchrist M, *et al*. Pregnancy-related anxiety: evidence of distinct clinical significance from a prospective longitudinal study. *Journal of Affective Disorders* 2016;197:251–8.
33 ElSayed Na Fau - Aleppo G, *et al*. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes-2023,
34 Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. *Lancet Diabetes Endocrinol* 2015;3:450–60.
35 Callesen NF, Secher AL, Cramon P, *et al*. Mental health in early pregnancy is associated with pregnancy outcome in women with Pregestational diabetes. *Diabet Med* 2015;32:1484–91.
36 Hall M, Oakey H, Penno MAS, *et al*. Mental health during late pregnancy and postpartum in mothers with and without type 1 diabetes: the ENDIA study. *Diabetes Care* 2022.
37 Egan AM, Dunne FP, Lydon K, *et al*. Diabetes in pregnancy: worse medical outcomes in type 1 diabetes but worse psychological outcomes in gestational diabetes. *QJM* 2017;110:721–7.
38 Bahrami J, Tomlinson G, Murphy HR, *et al*. Impaired awareness of Hypoglycaemia in women with type 1 diabetes in pregnancy: Hypoglycaemia fear, Glycaemic and pregnancy outcomes. *Diabet Med* 2022;39:e14789.
39 Timar B, Timar R, Albai A, *et al*. Predictors for pregnancy outcomes in Romanian women with type 1 diabetes mellitus: a prospective study. *Diabetol Metab Syndr* 2014;6:125.
40 Ásbjörnsdóttir B-O, Vestgaard M-O, Do N-O, *et al*. Prevalence of anxiety and depression symptoms in pregnant women with type 2 diabetes and the impact on Glycaemic control. (1464-5491 (electronic)). n.d.
41 Do N-O, Secher AL, Cramon P-O, *et al*. Quality of life, anxiety and depression symptoms in early and late pregnancy in women with Pregestational diabetes. (1600-0412 (electronic)). n.d.
42 Feig DS, Donovan LE, Corcoy R, *et al*. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a Multicentre International randomised controlled trial. *Lancet* 2017;390:2347–59.
43 Rytter K, Schmidt S, Rasmussen LN, *et al*. Education programmes for persons with type 1 diabetes using an insulin pump: a systematic review. *Diabetes Metab Res Rev* 2021;37:e3412.

44 Gehr B, Holder M, Kulzer B, *et al*. SPECTRUM: A training and treatment program for continuous glucose monitoring for all age groups. *J Diabetes Sci Technol* 2017;11:284–9.
45 Ásbjörnsdóttir B, Akueson CE, Ronneby H, *et al*. The influence of carbohydrate consumption on Glycemic control in pregnant women with type 1 diabetes. *Diabetes Res Clin Pract* 2017;127:97–104.
46 Ásbjörnsdóttir B, Ronneby H, Vestgaard M, *et al*. Lower daily carbohydrate consumption than recommended by the Institute of medicine is common among women with type 2 diabetes in early pregnancy in Denmark. *Diabetes Research and Clinical Practice* 2019;152:88–95.
47 Evans M, Ceriello A, Danne T, *et al*. Use of fast-acting insulin Aspart in insulin pump therapy in clinical practice. *Diabetes Obes Metab* 2019;21:2039–47.
48 Lee T-O, Collett C, Bergford S, *et al*. Automated insulin delivery in women with pregnancy complicated by type 1 diabetes. LID. n.d.
49 Harjutsalo V, Reunanen A, Tuomilehto J. Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. *Diabetes* 2006;55:1517–24.
50 Dabelea D, Mayer-Davis EJ, Saydah S, *et al*. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014;311:1778–86.
51 Pociot F, Lorenzen T. [Markers for risk of IDDM in children of Danish patients with IDDM. A population-based, historical prospective study]. (0041-5782 (print)). n.d.
52 Törn C, Liu X, Hagopian W, *et al*. Complement gene variants in relation to Autoantibodies to beta cell specific antigens and type 1 diabetes in the TEDDY study. *Sci Rep* 2016;6:27887.
53 Langenberg C, Lotta LA. Genomic insights into the causes of type 2 diabetes. *Lancet* 2018;391:2463–74.
54 Lyssenko V, Groop L, Prasad RB. Genetics of type 2 diabetes: it matters from which parent we inherit the risk. *Rev Diabet Stud* 2015;12:233–42.
55 Knorr S, Stochholm K, Vlachová Z, *et al*. Multisystem morbidity and mortality in offspring of women with type 1 diabetes (the EPICOM study): A register-based prospective cohort study. *Diabetes Care* 2015;38:821–6.
56 Hjort L, Martino D, Grunnet LG, *et al*. Gestational diabetes and maternal obesity are associated with Epigenome-wide methylation changes in children. *JCI Insight* 2018;3:e122572.
57 Hjort L, Novakovic B, Grunnet LG, *et al*. Diabetes in pregnancy and epigenetic mechanisms—how the first 9 months from conception might affect the child's Epigenome and later risk of disease. *Lancet Diabetes Endocrinol* 2019;7:796–806.
58 Boisen AB, Knorr S, Hansen TK, *et al*. Signs of low-grade inflammation in female offspring of women with type 1 diabetes: the EPICOM study. *Diabetes Metab* 2016;42:462–5.
59 Overgaard M, Ravnsborg T, Lohse Z, *et al*. Apolipoprotein D and Transthyretin are reduced in female adolescent offspring of women with type 1 diabetes: the EPICOM study. *Diabet Med* 2022;39:e14776.
60 Bacon S, Burger D, Tailor M, *et al*. Can Placental growth factors explain birthweight variation in offspring of women with type 1 diabetes. *Diabetologia* 2021;64:1527–37.
61 Salomon C, Rice GE. *Role of Exosomes in Placental Homeostasis and Pregnancy Disorders*. 1st edn. Elsevier Inc, 2017:163–79.
62 Statistics Denmark,
63 Børnedatabasen [Internet]. 2023. Available: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/graviditet-foedsler-og-boern/boernedatabasen
64 Rothman KJ, Greenland S. Planning study size based on precision rather than power. *Epidemiology* 2018;29:599–603.
65 Mackin ST, Nelson SM, Kerssens JJ, *et al*. Diabetes and pregnancy: national trends over a 15 year period. *Diabetologia* 2018;61:1081–8.
66 Neff KJ, Forde R, Gavin C, *et al*. Pre-pregnancy care and pregnancy outcomes in type 1 diabetes mellitus: a comparison of continuous subcutaneous insulin infusion and multiple daily injection therapy. *Ir J Med Sci* 2014;183:397–403.
67 Bland JM. The tyranny of power: is there a better way to calculate sample size. *BMJ* 2009;339:bmj.b3985.
68 Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of Reliability and validity. *Med Care* 1996;34:220–33.
69 Krøner FH, Knudsen S de P, Roland CB, *et al*. Validity and reliability of the Danish version of the pregnancy physical activity questionnaire to assess levels of physical activity during pregnancy. *J Matern Fetal Neonatal Med* 2022;35:4566–72.
70 Chasan-Taber L, Schmidt MD, Roberts DE, *et al*. Development and validation of a pregnancy physical activity questionnaire. *Med Sci Sports Exerc* 2004;36:1750–60.
71 Maindal HT. Development and Evaluation of the" the Ready to Act" Education Intervention Focusing on Action Competence in A Screen-Detected Population with Dysglycaemia: A Randomised Controlled Trial in Primary. Care: Aarhus University, 2009.
72 Olsen J, Melbye M, Olsen SF, *et al*. The Danish national birth cohort - its background, structure and aim. *Scand J Public Health* 2001;29:300–7.
73 Iversen ML, Sørensen NO, Broberg L, *et al*. Alcohol consumption and binge drinking in early pregnancy. A cross-sectional study with data from the Copenhagen pregnancy cohort. *BMC Pregnancy Childbirth* 2015;15:327.
74 Buysse DJ, Reynolds CF 3rd, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
75 World health organisation. Wellbeing measures in primary health care/the Depcare project: report on a WHO meeting: Stockholm, Sweden, 12–13 February 1998. Regional Office for Europe; 1998.
76 Topp CW, Østergaard SD, Søndergaard S, *et al*. The WHO-5 well-being index: a systematic review of the literature. *Psychother Psychosom* 2015;84:167–76.
77 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry* 1987;150:782–6.
78 Smith-Nielsen J, Matthey S, Lange T, *et al*. Validation of the Edinburgh postnatal depression scale against both DSM-5 and ICD-10 diagnostic criteria for depression. *BMC Psychiatry* 2018;18.
79 Eskildsen A, Dalgaard VL, Nielsen KJ, *et al*. Cross-cultural adaptation and validation of the Danish consensus version of the 10-item perceived stress scale. *Scand J Work Environ Health* 2015;41:486–90.
80 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
81 Hughes ME, Waite LJ, Hawkley LC, *et al*. A short scale for measuring loneliness in large surveys: results from two population-based studies. *Res Aging* 2004;26:655–72.
82 Polonsky WH, Anderson BJ, Lohrer PA, *et al*. Assessment of diabetes-related distress. *Diabetes Care* 1995;18:754–60.
83 Gonder-Frederick LA, Schmidt KM, Vajda KA, *et al*. Psychometric properties of the Hypoglycemia fear survey-II for adults with type 1 diabetes. *Diabetes Care* 2011;34:801–6.
84 Green JM, Kafetsios K, Statham HE, *et al*. Factor structure, validity and reliability of the Cambridge worry scale in a pregnant population. *J Health Psychol* 2003;8:753–64.
85 Bodenmann G. Dyadisches coping Inventar (DCI). 2008.
86 Bonde AH, Stjernqvist NW, Klinker CD, *et al*. Translation and validation of a brief health literacy instrument for school-age children in a Danish context. *Health Lit Res Pract* 2022;6:e26–9.
87 Paakkari O, Torppa M, Kannas L, *et al*. Subjective health literacy: development of a brief instrument for school-aged children. *Scand J Public Health* 2016;44:751–7.
88 Maindal HT. Adaptation, data quality and Confirmatory factor analysis of the Danish version of the PACIC questionnaire. n.d.
89 Wen LM, Baur LA, Rissel C, *et al*. Intention to Breastfeed and awareness of health recommendations: findings from first-time mothers in Southwest Sydney, Australia. *Int Breastfeed J* 2009;4:9.
90 Condon JT. The assessment of Antenatal emotional attachment: development of a questionnaire instrument. *British Journal of Medical Psychology* 1993;66:167–83.
91 Condon JT, Corkindale C. The correlates of Antenatal attachment in pregnant women. *Br J Med Psychol* 1997;70 (Pt 4):359–72.
92 Glasgow RE, Wagner EH, Schaefer J, *et al*. Development and validation of the patient assessment of chronic illness care (PACIC). *Med Care* 2005;43:436–44.
93 Andersen LG, Groenvold M, Jørgensen T, *et al*. Construct validity of a revised physical activity scale and testing by cognitive interviewing. *Scand J Public Health* 2010;38:707–14.
94 Aadahl M, Jørgensen T. Validation of a new self-report instrument for measuring physical activity. *Med Sci Sports Exerc* 2003;35:1196–202.
95 Pedersen ESL, Mortensen LH, Brage S, *et al*. Criterion validity of the physical activity scale (Pas2) in Danish adults. *Scand J Public Health* 2018;46:726–34.
96 Nilsson IMS, Kronborg H, Knight CH, *et al*. Early discharge following birth - what Characterises mothers and newborns. *Sex Reprod Healthc* 2017;11:60–8.
97 Nielsen KK, Dahl-Petersen IK, Jensen DM, *et al*. Protocol for a randomised controlled trial of a Co-produced, complex, health promotion intervention for women with prior gestational diabetes and their families: the face-it study. *Trials* 2020;21.
98 Fein SB, Labiner-Wolfe J, Shealy KR, *et al*. Infant feeding practices study II: study methods. *Pediatrics* 2008;122 Suppl 2:S28–35.