#### **Cohort profile**

# **BMJ Open** Cohort profile update: the Norwegian STORK Groruddalen (STORK G) pregnancy and birth cohort – the role of ethnicity and causal pathways for obesity, type 2 diabetes, cardiovascular disease and other health issues

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#### ABSTRACT

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Dr Christin W Waage; christin.waage@medisin.uio.no **Purpose** The STORK Groruddalen cohort was set up in 2008 to explore ethnic differences in: (1) *maternal health*, primarily gestational diabetes (GDM) and related health issues during pregnancy and post partum, and effects of exposures on risk for type 2 diabetes, cardiovascular disease and other health issues, and (2) *offspring's growth and body composition*, overweight/obesity and effects of early life exposures.

**Participants** 823 women (74% of invited) were followed from gestational week (GW) 15. Data were collected from 618 fathers. In total, 59% of women and 53% of fathers had origin from non-Western countries. Maternal mean age was 29.9 years (SD 4.9), and body mass index (BMI) 25.3 kg/m<sup>2</sup> (4.9). Data were obtained from 772 women (94%) at GW 28, and 662 women (80%) 14 weeks post partum. Eleven years post partum, 385 women (53% of eligible/47% of original cohort) attended, age was 42.0 years (4.8) and BMI 27.1 kg/m<sup>2</sup> (5.1). We have data for 783 children at birth, and for 586 at last time point, mean age 8.6 (0.5) years, weight 30.7 (6.8) kg and length 133.9 (6.3) cm.

**Findings to date** We collected questionnaire data from parents, clinical measurements and blood samples from mothers, and data on children's growth (mid-pregnancy to 8 years). Our biobank includes maternal blood and urine samples, biopsy material from placentas and umbilical venous cord blood. We found several clinically important differences in *maternal health*, with higher risk in ethnic minority groups for GDM, insulin resistance, vitamin D and iron deficiency, depressive symptoms and physical inactivity. Contrasting patterns of fetal growth and risk of overweight/thinness at preschool age were observed across ethnic groups. Maternal GDM, obesity and high gestational weight gain were associated with children's BMI trajectories.

**Future plans** We will examine the impact of maternal and fetal health and development during pregnancy on long-term outcomes for mothers and offspring.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Population-based multiethnic cohort with baseline data from 823 mothers (59% ethnic minorities), 618 fathers (self-reported data only), data on offspring growth from mid pregnancy to 8 years of age, and a large biobank.
- ⇒ Study methods were adapted to maximise inclusion of ethnic minority women, study material was translated to eight languages (Arabic, English, Sorani, Somali, Tamile, Turkish, Urdu and Vietnamese) and women were interviewed by trained study staff at antenatal primary care facilities.
- ⇒ Women were first followed from early pregnancy to 14 weeks post partum, were offered universal oral glucose tolerance testing in gestational week 28, providing a unique and broad set of high-quality data from questionnaires, clinical measurements, objectively measured physical activity and blood samples.
- ⇒ Eleven years after the index pregnancy, a followup with a similar data collection was performed in 385 women, representing a participation rate of 53% of eligible women/47% of original cohort, despite the ongoing COVID-19 pandemic.
- ⇒ Small numbers in some ethnic groups may limit the power of some analyses.

**Trial registration number** Project title STORK G-2: Women and Risk of Type 2 Diabetes NCT03870724 ( ClinicalTrials.gov).

### INTRODUCTION

Although most multifactorial chronic diseases involve gene–environment interactions, research into the Developmental Origins of Health and Disease has highlighted that early life exposures may have a large impact on

BMJ

later risk of non-communicable diseases.<sup>1 2</sup> The preconceptional and the intrauterine environment, mediated through lifestyle factors and the metabolic and endocrine status of the mother and by the placenta,<sup>3</sup> may induce long-term effects on phenotypic characteristics of the offspring by epigenetic regulation,<sup>4</sup> involving a life history of gene–environment interactions, exacerbated by unfavourable diets and low physical activity during childhood and adolescence.

Along with the worldwide increase in obesity and type 2 diabetes (T2D) in women in reproductive age, an increase in gestational diabetes mellitus (GDM) is observed.<sup>5</sup> Pregnancy itself can be considered a natural stress test for the mother.<sup>6</sup> Complications like GDM and preeclampsia seem to be early markers of disturbances in glucose metabolism, endothelial dysfunction and hypertension<sup>7</sup> that predict future risk of T2D and cardiovascular disease (CVD) in the mother.<sup>6</sup> Further, maternal T2D, GDM, obesity, high gestational weight gain and physical inactivity are associated with neonatal adiposity.<sup>8</sup> Childhood obesity is emerging and may lead to a future epidemic of T2D and CVD in early adulthood.<sup>9</sup> Fetal and child growth and development result from a complex interplay between genetic and environmental factors, and effects may depend on timing and vary across generations.<sup>4</sup> The continuous relationship between maternal weight, glucose levels and risk of complications in mothers and children may have large effects in societies where the whole population is drifting in the direction of overweight and glucose intolerance. In parallel, low birth weight and low adult body height may still serve as markers of adverse environmental influences hampering growth and increasing the risk of later T2D and CVD.<sup>4</sup>

In high-income countries, women with low socioeconomic status or ethnic origin from low-income countries are at particularly high risk for GDM, and are diagnosed with  $T2D^{10}$  and  $CVD^{11}$  at an earlier age. Migration may lead to a rapid 'Westernisation' of dietary habits, typically an increased intake of energy, fat and refined carbohydrates.<sup>12 13</sup> Some studies indicate that socioeconomic deprivation to a large extent explains the ethnic variations in CVD risk,<sup>14–16</sup> but to a lesser extent the higher risk of T2D.<sup>17</sup> We found an alarmingly high prevalence of diabetes in women of South Asian origin compared with Norwegian middle-aged women in Oslo in 2000,<sup>18</sup> and researchers from our centre recently confirmed this finding in a cohort of women examined shortly after a GDM pregnancy.<sup>19</sup> The susceptibility for GDM and T2D in South Asians may track from fetal life, with low birth weight, low lean mass, abdominal adiposity and relative preservation of subcutaneous fat.<sup>20</sup>

Emerging evidence provides a strong rationale to invest in a good start to life to improve public health, pointing to the importance of pregnancy and early childhood as underused windows of opportunity to improve the health of women and children.<sup>4</sup> As more detailed knowledge about causal pathways is necessary to inform public health strategies for pregnant women and children, the ultimate goal for the STORK Groruddalen (STORK G) cohort was to provide new knowledge about socioeconomic and ethnic disparities in pregnancy complications and longterm health risks for women and their offspring.<sup>21</sup> This population-based multiethnic cohort, regarded unique because of its combination of detailed maternal data from early pregnancy to post partum, paternal data, fetal and child growth data and a valuable biobank, has the potential to reduce this knowledge gap. The purpose of this paper is to provide an updated overview of available data from this cohort, emphasising the long-term follow-up data of mothers and children from this multiethnic urban population, with some representing groups often excluded from participation in research.

#### **Overview of research questions**

We wanted to explore *when* and *how* ethnic differences in health emerge, that is, *causal pathways for non-communicable diseases*, applying life-course and transgenerational perspectives. More specifically, the STORK G was set up to address research questions related to the overall magnitude of ethnic differences in:

- maternal health, primarily GDM and related health issues during pregnancy and post partum, but the latest follow-up data will enable studies of effects of a range of exposures during the women's life course (early life, prepregnancy, the index pregnancy and post partum) on later risk for T2D, CVD and other health issues that are socially patterned.
- childrens growth and body composition from mid pregnancy to prepubertal age, the prevalence of overweight/obesity, if effects of intrauterine exposures on children's preschool BMI trajectories persist, diminish or progress, and if other factors emerge that influence the risk of overweight/obesity in school age.

#### **COHORT DESCRIPTION**

#### The original maternal and paternal STORK G data (STORK G-1)

STORK G-1 was set up in 2008 at three Child Health Clinics (CHCs), one in each of three administrative city districts in Oslo: Stovner, Grorud and Bjerke in Groruddalen. These districts covered at that time a population of 82500 where the proportion of adults with non-Western origin was 40.9%, 37.8% and 33.1%, respectively, and corresponding proportions for newborns were 75%, 61% and 38%.<sup>21</sup> During the previous decades, immigration to Norway from non-Western countries had increased, and many had settled in this part of Oslo. Our main focus was on groups with origin in Asia and Africa where most migrants at that time came from, but also on those from Eastern Europe (later referred to as (non-Western), ethnic minority women), all posing new challenges for most health personnel. To facilitate inclusion of ethnic minority women often excluded from research, information material and questionnaires were translated to eight languages: Arabic, English, Sorani, Somali, Tamile, Turkish, Urdu and Vietnamese, covering the largest ethnic minority groups of interest. The translations



Figure 1 Flow chart.

were quality checked by bilingual health professionals. Healthy pregnant women in Norway are offered at least eight controls in primary healthcare free of charge, including one ultrasound scanning. Women can choose if they want follow-ups by a midwife at the CHCs, by their regular general pratitioner or a combination of the two. General practitioners working in the area were asked to refer pregnant women to the CHCs early in pregnancy. Healthy pregnant women attending antenatal care were informed about the study and invited to participate if they (1) were living in one of the districts, (2) planned to give birth at the two nearby study hospitals (Akershus University Hospital and Oslo University Hospital, Ullevål), (3) were in gestational week (GW)<20, (4) were not suffering from diseases necessitating intensive hospital follow-up during pregnancy, (5) were not already included with a pregnancy lasting>22 weeks, (6) could communicate in Norwegian or any of the other eight languages, and (7)were able to give informed consent.

From May 2008 to May 2010, 823 healthy pregnant women were included, and high-quality data from GW 15 (visit 1), GW 28 (visit 2) and about 14 weeks post partum (visit 3) (figure 1 flow chart) were collected by trained study personnel according to protocol.<sup>21</sup> Translators were offered if needed and were used in 22% of interviews of women with origin from outside Europe. The data collection ended in February 2011.

Questionnaire data were collected via interviews, covering demographics, socioeconomic factors, medical history and lifestyle (table 1). Ethnicity may be defined as the social group a person belongs to, or are perceived to belong to, as a result of a mix of shared cultural and other factors such as language, diet, religion, geographical and ancestral origins, as well as physical features traditionally associated with race.<sup>22</sup> Information not only about own and parents' country of birth and other aspects related to ethnicity was therefore collected to be able to explore

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such issues as well (table 1). These included different measures of social integration, religion and social class. Clinical measurements were performed (anthropometrics, blood pressure and objectively recorded data on physical activity) (table 2). Fasting blood and urine samples were collected at all visits and analysed consecutively at Akershus University Hospital and the Hormon Laboratory, Oslo University Hospital (table 2 and online supplemental table 1), biobanked and stored at -80°C. In GW 28, all women were offered a standard oral glucose tolerance test on site. We have genome-wide data on all women participating in STORK G at this time point with available DNA. In the Epigenetics in Pregnancy (EPIPREG) sample, we have quantified epigenome-wide DNA methylation in women of European (n=312) and South Asian (n=168) ancestry with a valid fasting plasma glucose and available DNA (87.2 and 87.5%, respectively, of those who met in GW 28).<sup>23</sup> Maternal data from hospital records around delivery were also collected. Women were asked to invite the fathers to fill out a self-administered questionnaire survey with information about demographics, anthropometrics, family history of T2D and CVD (table 1).

#### Patient and public involvement

We have had close collaboration with users, both representatives for the participating women, local health professionals and user organisations (the Diabetes Association and The Norwegian Women's Public Health Association) regarding the plans for STORK G-2. We did not involve user groups directly in the design of the STORK G study, in the development of research questions and outcome measures, nor in the reporting in this paper. We were, however, informed by priorities, experiences and preferences from user representatives through regular meetings during the planning phase and during data collection. Study participants have been informed about the results by individual letters and through the study webpage.

#### STORK G-2 follow-up study

When planning the STORK G-2 follow-up study in 2017, we first conducted interviews in focus groups with STORK G-1 women, exploring how to reduce barriers for participation in a follow-up study. Next, we conducted a pilot study to test recruitment strategies and study logistics, see online supplemental material for more details. Women still living in Norway, and not excluded for reasons given in flow chart (figure 1) were eligible, contacted by telephone and invited to STORK G-2 (visit 4). Women living in Oslo or the nearby county Akershus were invited to the full data collection, that is, an interviewer-administered digital questionnaire and a physical examination at the same three CHCs as used in STORK G-1 (tables 1 and 2). This took place mostly during afternoons/evenings after opening hours of the CHCs and working hours for most women. Methods were kept as close to those in STORK G-1 as possible, but some new questions (Sense of Coherence,<sup>24</sup> Adverse childhood events Questionnaire,<sup>25</sup> The Table 1

Main variables collected from questionnaires by study visits\*

#### Mother Father Visit Visit 4 Visit (n=385) Reference **Demographic factors** Date of birth V1-V4 385 V2 Childhood socioeconomic position V1 **ISCO 88** Social class (type of work) parents V1 Material standards of household/place of residence MCCS† Adult socioeconomic position V1-V4 381 Marital status MCCS† Number of children (<18 years) living in the same household V1, V4 381 Adults (>18 years) living in the same household V1, V4 381 Education V1, V4 381 V2 MCCS<sup>†</sup> V2 **ISCO 88** Social class (type of work) and work participation V1, V4 381 Material standards of household/place of residence V1 MCCS† Ethnic origin and related variables V1 V2 ‡ Country of birth (own and parents), nationality Religion V1 V2 ‡ V1 Mother tongue ± V1 V2 OIHS\* Length of stay in Norway (if not born in Norway) V1 V2 Reason for immigration (if not born in Norway) OIHS\* Acculturation/experience of discrimination (if not born in V1 OIHS\* Norway) Norwegian language skills V1. V4 381 Reading Norwegian newspapers/watching Norwegian TV V1, V4 381 Use of translater when visiting general practitioner (GP) V1, V4 381 Medical history Family history V2 V2, V4 381 **RIMS\*** CVD/diabetes mother/father/other first-degree relatives Consanguinity, hereditary diseases V1 MCCS† New chronic diseases V1-V4 381 Childhood exposures V1 V2 Own birth weight/born prematurely ‡ V1 ‡ Mother's age at birth of study participant V1 MCCS† Exposed to smoking during fetal life Breastfed in infancy V1 ‡ Obstetric history Parity, year of birth, delivery method, offspring sex, birth weight V1, V3, V4 381 MCCS<sup>†</sup><sup>‡</sup> Weight gain during earlier pregnancies V1 MCCS† 381 MCCS†± Gestational diabetes and other adverse outcomes V1, V4 Actual pregnancy and follow-up V1-V4 Self-rated health 381 OIHS† Body weight (age 18, 25, and prepregnancy) V1 OIHS† V2 Actual body height/weight MCCS<sup>†</sup> CVD/diabetes V1-V3 V2 MCCS<sup>+</sup> Other diseases/pregnancy complications V1-V4 381 MCCS<sup>†</sup><sup>‡</sup>

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Table 1 Continued

	Mother		Father		
	Visit	Visit 4	Visit		
	(n=385)			Reference	
Pregnancy-related pelvic joint pain	V2-V3			PRPJP	
Binge-eating disorders	V2-V3			MCCS†‡	
Depression	V2-V4	379		EPDS	
Negative life events last 6 months	V1–V3			OIHS†	
Adverse life events and stress (ACE), in childhood and as an adult	V4	381		OIHS†	
Subjective health complaints	V4	379		SCH	
Sense of coherence (SOC)	V4	324		SOC-13	
Urinary incontinence	V2-V3			ICIQ	
Medication	V1–V4	381		MCCS†‡	
Duration of lactation	V3–V4	380		SPEDKOST	
Lifestyle behaviours					
Smoking	V1–V4	381	V2	MCCS†‡	
Snuff tobacco	V4	381			
Alcohol	V1–V3			MCCS†‡	
Menstruation	V4	379			
Use of general practitioner	V4	378			
Physical activity and related psychosocial variables	V1–V4	379		See Methods	
Food frequency questionnaire	V2-V3			See Methods‡	
Dietary supplements	V1–V3			MCCS†	
Child born during the Stork Groruddalen study					
Diseases that may have impacted the child's growth	V4	323			
Medication (last 3 months)	V4	323			
Mothers thoughts about the child's current height/weight	V4	323			

\*Visit 1; gestational week 15, visit 2; gestational week 28, visit 3; 14 weeks post partum, visit 4; 11 years after the index pregnancy. †The Norwegian Institute of Public Health: www.fhi.no.

Developed or modified for the Stork Groruddalen study.

§Pregnancy-Related Pelvic Joint Pain.

EPDS, Edinburgh Postnatal Depression Scale; ICIQ, International Consultation of Incontinence; ISCO 88, International Standard Classification of Occupations (www.ssb.no); MCCS, Mother & Child Cohort Study; OIHS, Oslo Immigrant Health Study; PRPJP, Pregnancy-Related Pelvic Joint Pain.; RIMS, Romsås in Motion Study; SCH, The Subjective Health Complaint Inventory; SOC, Sence of coherence, version 13.

Subjective Health Complaints inventory<sup>26</sup>) and about experiences with primary care and examinations (handgrip dynamometer test,<sup>27</sup> hip and waist circumference, buccal swabs) were added. As the motion sensor SWA3device used in STORK G-1 was no longer in production, ActiGraph GT3X-BT (ActiGraphTM, Pensacola, Florida, USA) was used to record sedentary time, energy expenditure, steps per day and PA intensity.<sup>28</sup> Participants wore the ActiGraph at the right hip attached with an elastic belt, preferably for 7 days, were encouraged to perform their daily activities as usual and only remove it for water-based activities. Non-fasting capillary dried blood spots were collected at study sites and biobanked for later analyses by the Vitas laboratory. In addition, women were asked to attend the Fürst laboratory, Groruddalen for a fasting blood sample another day. All participants received a gift

card (NOK 200/approximately 20 Euro) and two subway tickets.

Recruitment of study participants was carried out from August 2019 to March 2022, but was stopped during three periods due to the COVID-19 pandemic (March to August 2020, December 2020 to June 2021, and October 2021 to January 2022). Women defined as eligible were contacted by telephone. The full-scale data collection lasted to October 2021. Thereafter, eligible women who had moved outside Oslo and Akershus (n=96, 95 were ethnic Norwegians), were invited to a less extensive data collection based on telephone interviews from January to March 2022. A few sensitive issues were omitted from the questionnaire used in telephone interviews, and these women were not asked to wear the ActiGraph for technical and logistic reasons. They were encouraged to take Physical activity

Physical activity

Hand grip (kg)

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Table 2 Number of women with valid data from physical examination and blood samples by study visits*							
		Visit 1	Visit 2	Visit 3	Visit 4		
Measurements	Monitor device	N	N	N	N		
Height† (cm)	Fixed Stadiometer	823			385		
Sitting height (cm)	Fixed Stadiometer (sitting upright on a chair)				321		
Body weight (kg)	Tanita (BIA) BC-418MA/(V1–V3)/Tanita (BIA) MC-780MA (V4)	822	768	658	326		
Body weight (kg)	Self-reported				57		
BMI‡ (kg/m²)	Tanita (BIA) BC-418MA (V1–V3)/Tanita (BIA) MC-780MA (V4)	822	768	657	383		
Fat mass (kg)	Tanita (BIA) BC-418MA (V1–V3)/Tanita (BIA) MC-780MA (V4)	822	768	657	325		
Waist circumference (cm)	Seca measuring tape				326		
Hip circumference (cm)	Seca measuring tape				327		
Skinfolds (cm)	Holtain T/W Skinfold Calliper						
Triceps		759	721	606	327		
Subscapularis		758	720	606	326		
Suprailiaca		756	712	603	323		
Upper arm circumference (cm)	Seca measuring tape	819	756	650	327		
Systolic and diastolic blood pressure (mm Hg)	Omron (HEM-7000-E) (V1–V3)/Omron (HBP-1300) (V4)	819	756	650	327		
Pulse rate	Omron (HEM-7000-E) (V1–V3)/Omron (HBP-1300) (V4)	819	756	650	327		

TSH (mU/L) Capillary dried blood spots

Fasting venous blood samples

HbA1c (mmol/mol)

Cholesterol (mmol/L)

Haemoglobin (g/dL)

Glucose (mmol/l)

HbA1c (mmol/mol) Cholesterol (mmol/L)

\*Visit 1; gestational week 15, visit 2; gestational week 28, visit 3; 14 weeks post partum, visit 4; 11 years after the index pregnancy.

+Height (cm) was calculated by using objectively measured height at visit 4 (n=326) and objectively measured height at visit 1 (n=58).

<sup>+</sup>BMI (kg/m<sup>2</sup>) was calculated by using objectively measured weight (n=325) and self-reported weight (n=60).

Sense Wear armband (SWA)§

JAMAR Hydraulic Hand Dynamometer

ActiGraph GT3y-T¶

§Women were asked to wear the SWA across the right triceps brachii continuously for 4-7 days following each of the three visits, and remove it only for water activities.

¶Women were asked to wear ActiGraph on the right hip attached with an elastic belt on the inside or the outside of their clothing, at daytime for 7 days, and only remove it for water activities.

BIA, Bioelectrical Impedance Analysis; BMI, body mass index.

a dried blood spot themselves, supported by oral and written information, but not asked to visit the laboratory in Oslo for fasting samples due to long travel distances. Lastly, we used data for two women from the pilot study in 2017 who did not attend at the 11 years follow-up.

#### **Offspring data**

678

805

806

818

804

817

674

753

768

763

758

762

490

576

581

584

580

584

294

327

213

202

212

213

213

360 360

During pregnancy, fetal ultrasound examinations were performed at mean GW 24, 32 and 37 (online supplemental table 2).<sup>21</sup> Birth weight and other standard measurements were routinely measured on calibrated

electronic scales immediately after birth.<sup>29</sup> Within 72 hours after birth, study-specific anthropometric measurements were collected unless contraindicated for medical reasons (online supplemental table 2). Umbilical cord venous blood was collected at birth, serum extracted and directly frozen at  $-80^{\circ}$ C. Placentas were stored in a refrigerator immediately after birth.<sup>30</sup> The next working day a placental pathologist performed macroscopic examinations, the placentas were fixated in formalin, and standard sections were sampled and paraffin embedded.<sup>30</sup>

Information about children's postnatal growth (weight, length/height at all time points and head circumference up to 15 months age) was retrospectively collected from electronic health records at children's local CHCs/school health services<sup>31</sup> who are obliged to invite all children for routine check-ups (online supplemental table 2). Almost all children attend these check-ups at age 6 weeks, at 3, 6, 12 and 15 months, and at 2, 4, 6 and 8 years. Children's postnatal growth data were collected in two waves:

- 1. During 2014–2015, we collected data up to 5 years age.<sup>31</sup> We had access to health records with growth data of children still living in Oslo (N=592). To get access to such data on children who had moved out of Oslo, we sent letters to 62 CHCs throughout the country, and received growth data from 50 CHCs.
- 2. During 2021–2022, we collected data from school health check-ups at 6 and 8 years age, first for the 401 children still living in Oslo. Of 75 other Norwegian municipal CHCs approached by e-mail, 72 responded, and local public health nurses delivered growth data by telephone or at meetings with IT.

#### Parental samples and characteristics of participants Mothers and fathers (STORK G-1)

Of the 1114 eligible pregnant women attending the CHCs during the data collection period for STORK G-1, 823 women (74%) were included.<sup>21</sup> Participation rates varied between 64% and 83% across the largest ethnic groups. When defining ethnicity by country of birth, or the county of birth of the participant's mother if the participant's mother was born outside Western Europe or North America, a total of 59% were non-Western ethnic minorities, (origin outside Western Europe and North America), while 56% were immigrants (born outside Norway) (online supplemental table 1). At visit 2, 772 (94% of those included) met and 662 (80%) attended the postpartum visit (visit 3) (figure 1, flow chart).

Mean age of the 823 women at inclusion was 29.9 years (SD 4.9), mean BMI was  $25.3 \text{ kg/m}^2$  (4.9), while mean prepregnancy BMI was  $24.6 \text{ kg/m}^2$  (3.8) (online supplemental table 1). At inclusion, 16% had low education, and 46% were nulliparous.<sup>32</sup> Included women were found representative for the largest ethnic groups at visit 1,<sup>21 32</sup> although a slightly higher proportion of non-western women did not attend visit 3, 14 weeks post partum—some because of visits to countries of origin.<sup>33</sup>

Overall, very few missing values were observed, except for the objectively recorded physical activity data.

Although some fathers lived abroad, we obtained data from 626 (76%) of the fathers (online supplemental table 1). The fathers' mean age was 33.5 years (6.5), mean BMI was  $26.4 \text{ kg/m}^2$  (3.8), while 53% of the fathers had ethnic minority background and the distribution of educational level was similar to that of the women (online supplemental table 1).

#### Mothers-the 11 years follow-up (STORK G-2)

In 2019, 729 of the 823 STORK G-1 women were eligible for STORK G-2 (visit 4), while 94 (11%) had moved outside Norway or were excluded for other reasons (figure 1, flow chart). Of these, 385 women (53%) were included (47% of original cohort), 167 (23%) declined to participate, 133 (18%) were not reached by telephone, 42 (6%) did not attend appointed times and two women withdrew their consent. Three partners refused participation on behalf of their wifes. Only one attending woman needed an interpreter, and was interviewed in her mother tongue (urdu).

At the 11-year follow-up (visit 4), women's mean age was 42.0 years (4.8), and mean BMI was  $27.1 \text{ kg/m}^2$  (5.1). Online supplemental table 1 provides selected sample characteristics for those who met at the 11-year follow-up. At this timepoint, 64% of women participating in STORK G-2 reported to have achieved high education compared with 55% when these women met at visit 1 (online supplemental table 2).

Of the 385 women who met at visit 4, we have complete questionnaire data for all with few exceptions (table 1) and 94% provided dried blood spots. In total, 85% attended the full-scale data collection with clinical measurements such as anthropomethrics, blood pressure and hand grip strength (table 2), 76% provided accelerometer data and 56% fasting blood samples (for overview, see figure 1, text box bottom left). Those who attended visit 4 had slightly higher age and education at visit 1 than non-attenders and fewer were ethnic minorities (47% vs 59% at inclusion) (online supplemental table 3). Online supplemental table 4 shows that those who provided fasting samples were slightly younger and had higher education than those who did not.

HbA1c and cholesterol have been analysed from dried blood spots. For the 213 women with valid data for HbA1c both from dried blood spots and from fasting samples, we found a strong positive correlation (r=0.8652) between results from these samples (online supplemental table 4). The Bland-Altman analysis showed good agreement between these methods, as the difference was close to 0 and we found no signs of a systematic error across the range of measurements (online supplemental figure 1).

#### Offspring sample and characteristics

Of the 823 women included in STORK-G1, 783 live, singleton neonates were born and had a valid birth weight (figure 2 flow chart, online supplemental table



Figure 2 Flow chart. All children with registered birth weight had at least one postnatal measurement.

2). Of these, 761 women (97%) attended at least one of three ultrasound examinations, and 555 (71%) attended all. Placentas were collected from 539 (69%), and umbilical venous cord blood from 511 children (65%). We excluded 49 children from further data collection of routine CHC growth data due to refusal of further participation or no-show at visit 2 nor visit 3, medical conditions likely to substantially affect growth, and children born prematurely and admitted to newborn intensive care unit. Of the remaining 734 children, we have at least one ultrasound measurement and one postnatal measurement from each growth period (6weeks-12 months age, 15 months-4 years and 6-8 years age) from 618 children. Some characteristics of children from birth and about 8 years age are presented in online supplemental table 2), with mean age 8.6 (0.5) years, weight 30.7 (6.8) kg and length 133.9 (6.3) cm at the last measurement. We found no significant differences in maternal and offspring characteristics among those with and without longitudinal growth data (online supplemental table 5).

#### **FINDINGS TO DATE**

More than 65 scientific papers have been published from the population-based STORK G-1. In most papers, we have defined ethnicity by the women's or the participant's mother's country of birth if born outside Western Europe or North America compared with women with Western ethnic background, but in some we have explored other aspects of ethnicity. In short, regarding clinically relevant ethnic differences in *maternal health*, we found higher risk for most of the studied adverse health outcomes in non-Western ethnic minority women with some variation between ethnic minority groups.

This includes GDM,<sup>32</sup> insulin resistance,<sup>34</sup> vitamin D<sup>35</sup> and iron deficiency, anaemia<sup>36</sup> and depressive symptoms during pregnancy<sup>37</sup> and post partum<sup>38</sup> and they were less physically active, particularly in the postpartum period.<sup>39</sup> However, very few ethnic minority women were daily smokers. Some groups (Asians and Eastern Europeans) had lower mean BMI than Western women before pregnancy, while other groups (Middle Easterners and Africans) had higher BMI.<sup>40</sup> More than gestational weight gain per se, accumulation of central fat mass increased the risk of GDM.<sup>41</sup> All ethnic minority groups had larger weight retention post partum than women with Western backgrounders,<sup>33</sup> while more Western women were breast feeding.<sup>42</sup> Ethnic differences were still significant for most outcomes after adjusting for adult socioeconomic status. When studying depressive symptoms, not only ethnic minority background, but also a low level of integration doubled the risk, and lack of social support was independently related to post partum depressive symptoms.<sup>38</sup>

Pregnancy seemed to have had a more adverse effect on blood pressure trajectories from early pregnancy to post partum in ethnic minority women than in women with Western origin,<sup>43</sup> and the metabolic profile early post partum was more adverse among ethnic minorities compared with Western women.<sup>44</sup> This may indicate that pregnancy itself-or risk factor changes during pregnancy-affect ethnic groups differentially. In line with this, when we investigated women's BMI trajectories from 18 years age to post partum, we observed an interaction between ethnicity and parity, with multiparous (but not nulliparous) women of ethnic minority origin substantially more prone to long-term weight gain than multiparous Western women.<sup>45</sup> Our findings of ethnic differences in women's risk factors early post partum seem partly to reflect the large ethnic differences in T2D and CVD found in middle-aged women,<sup>18 46</sup> but complex relations are obviously operating.

We participate in the Genetics of Diabetes in pregnancy consortium with genotype summary data.<sup>47</sup> From the EPIPREG sample, we found that genetic principal components distinctly separated Europeans and South Asian women, which fully corresponded with the selfreported ethnicity based on country of birth.<sup>23</sup> Further, in epigenome-wide studies, we have identified several CpG sites of interest associated with maternal phenotypes such as insulin resistance,<sup>48</sup> BMI<sup>49</sup> and serum folate,<sup>50</sup> which in turn identified related genetic variants. The EPIPREG sample is also used for replication of findings from other cohorts with similar data, such as epigenetic clocks<sup>51</sup> and GDM-related CpG sites.<sup>52</sup> Regarding *childrens growth*, we found ethnic differences in body composition and growth during pregnancy.<sup>29 53</sup> At birth, neonates of women with origin from low-income and middle-income countries were relatively 'thin-fat', as indicated by reduced abdominal circumference while relatively preserved length and skin folds, compared with neonates of Western origin.<sup>29</sup> This phenotype, which may predispose to T2D, was most pronounced in South Asian neonates. We also found that the effect of GDM on fetal growth was most prominent in South Asians.<sup>54</sup> Our results further suggest transgenerational modifying effects of maternal past socioeconomic conditions on offspring size and body composition.<sup>55</sup>

At 4–5 years of age, children of Middle Eastern and North African origin had almost the double risk of overweight, compared with children of Western origin.<sup>31</sup> Intrauterine exposures to GDM, prepregnant obesity, and high gestational weight gain were all independently associated with children's BMI trajectories from birth to preschool age, but the effects differed in relation to their effect size, timing, and direction.<sup>56</sup> Maternal ethnicity, glucose and lipid metabolism were also related to placental leptin methylation,<sup>30</sup> further illustrating the complexity involved in the regulation of fetal growth.

Regarding STORK G-2, reaching a participation rate of 53% of those eligible at the 11 year follow-up with extensive clinical data collected during the COVID-19 pandemic in this population, including groups often excluded in research seems better than most similar studies.<sup>1957</sup> Of the original STORK G-1 sample, many had moved out of Oslo and the nearby county Akershus, some had moved abroad, some were not possible to reach by phone. Recruitment to the follow-up study was facilitated by positive experiences from participating in STORK G-1, input from the women during focus groups and the pilot study prior to STORK G-2, easy access to the study site for those still living in Oslo, and not least the approval by The Regional Committee for Medical and Health Research Ethics to contact women directly by phone instead of the usual approach by letter only.

From STORK G-2, we have questionnaire data on all, and a high proportion provided dried blood spots (94%), clinical data and buccal swabs (85%). Although only those who attended the full-scale data collection were asked to provide accelerometer data and fasting venous samples, such data are available from 76% and 56%, respectively. Using relevant data from STORK G-1, it will be possible to study selection bias in detail, provide weighted estimates for prevalence rates and continuous variables and perform multiple imputations under the missing at random assumption. In sum, we are confident that data from this cohort have the potential to answer the research questions addressed, not least related to development of obesity in women and children, its causes and consequences.

#### **Future plans**

We will use the recently collected follow-up data from STORK G-2 to explore longitudinal ethnic differences in women's health. Novel hypotheses related to subjective health problems and women's coping strategies will be explored, as will the unique data about childrens growth from mid pregnancy to prepuberty age. Several of the authors take part in national and international consortia that benefit from our data, and we welcome inititatives for further collaboration.

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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.

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**Data availability statement** Data are available upon reasonable request. Data can be made available to collaborating researchers upon request and decision in the Steering Commitee, provided approval from a Norwegian Regional Committee for Medical and Health Research Ethics.

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