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Gestational diabetes mellitus and offspring's carotid intimamedia thickness at birth: MySweetHeart Cohort Study

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1	Gestational diabetes mellitus and offspring's carotid intima-media thickness at
2	birth: <i>MySweetHeart</i> Cohort Study
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24 ABSTRACT

Objective Hyperglycemia during pregnancy is associated with cardiometabolic risks for the mother and the offspring. Mothers with gestational diabetes mellitus (GDM) have signs of subclinical atherosclerosis, including increased carotid intima-media thickness (CIMT). We assessed whether GDM is associated with increased CIMT in the offspring at birth.

Design and setting *MySweetHeart* Cohort is a prospective cohort study conducted in
 Switzerland.

Participants, exposure and outcome measures This work included pregnant women with and without GDM at 24 to 32 weeks of gestation and their singleton liveborn offspring with data on the primary outcome of CIMT. GDM was diagnosed based on the criteria of the International Association of Diabetes and Pregnancy Study Groups. Offspring's CIMT was measured by ultrasonography after birth (range: 1 to 19 days).

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Results Data on CIMT were available for 99 offspring of women without GDM and 101 41 offspring of women with GDM. Maternal age ranged from 18 to 47 years. Some 16% 42 of women with GDM and 6% of women without GDM were obese. Smoking during 43 pregnancy was more frequent among women with GDM (18%) than among those 44 without GDM (4%). Neonatal characteristics were comparable between the 2 groups. 45 The difference in CIMT between offspring of women with and without GDM was of 0.00 46 mm (95% CI: -0.01 to 0.01; p=0.96) and remained similar upon adjustment for potential 47 confounding factors, such as maternal pre-pregnancy BMI, maternal education, 48

smoking during pregnancy, family history of diabetes, as well as offspring's sex, age, and body surface area (0.00 mm (95% CI: -0.02 to 0.01; p=0.45)). **Conclusions** We found no evidence of increased CIMT in neonates exposed to GDM. A longer-term follow-up that includes additional vascular measures, such as endothelial function or arterial stiffness, may shed further light on the cardiovascular health trajectories in children born to mothers with GDM. **Registration** ClinicalTrials.gov (NCT02872974) Keywords gestational diabetes; carotid intima-media thickness; cardiovascular prevention; child; neonate List of abbreviations BMI, body mass index; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; CHUV, Lausanne University Hospital; DOHaD, developmental origins of health and disease; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; IADPSG, International Association of Diabetes and Pregnancy Study Groups; I, intervention; OGTT, oral glucose tolerance test.

Strengths and limitations of this study

- One important strength of this study is represented by its prospective design and the enrollment of participants at the time of gestational diabetes diagnosis.
 - Carotid intima-media thickness was measured in non-sedated neonates by • experienced pediatric cardiologists using automated methods with manual tracing adjustment, in accordance with published guidelines.
- da. .g and the limite. Limitations of this study include the relatively small sample size, the possibility • of residual confounding and the limited generalizability.

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76 INTRODUCTION

Gestational diabetes mellitus (GDM) is a state of hyperglycemia with onset or first recognition during pregnancy.[1-3] The prevalence of hyperglycemia during pregnancy has increased in recent decades, being estimated at 16% worldwide in 2019, with 84% of cases due to GDM.[4] GDM is associated with long-term metabolic consequences for both the mother and the offspring, such as type 2 diabetes and obesity.[5] Women with GDM also have subclinical atherosclerosis and an increased risk for cardiovascular disease (CVD) later in life.[6,7] However, little is known about the cardiovascular risk of their offspring.

CIMT is a surrogate marker of atherosclerosis, which has been shown to be increased in children exposed to risk factors in the first 1000 days of life, such as poor fetal growth,[8] as well as in children with type 1 diabetes.[9] From a developmental origins of health and disease (DOHaD) perspective, [10] exposure to adverse experiences in early life may produce lifelong adaptations in the organs' structure and function and may program the risk for CVD. For instance, a systematic review and meta-analysis showed that GDM was associated with a higher systolic blood pressure in childhood.[11] Whether GDM has an impact on children's CIMT is not clearly established. The evidence is scarce notably in the very young children although CIMT measurement is feasible from birth and could help discern between changes that occur before or after birth.[12] To fill this gap, we conducted MySweetHeart Cohort study to assess the early life cardiovascular consequences of GDM.[13] Herein, we evaluated CIMT at birth in offspring of mothers with and without GDM.

1		
2 3 4	101	METHODS
5 6	102	Study design and setting
7 8	103	MySweetHeart Cohort is a prospective cohort study conducted at the Lausanne
9 10 11	104	University Hospital (CHUV), Switzerland. The study has been registered with
12 13	105	ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT02872974) and the study protocol
14 15	106	has been published.[13] Ethical approval was granted by the Ethics Committee for
16 17 18	107	Human Research of the Canton de Vaud (study number 2016-00745).
19 20	108	
21 22	109	Study population
23 24 25	110	This cohort included pregnant women between 24 and 32 weeks of gestation, with and
25 26 27	111	without GDM. Other inclusion criteria were age 18 years or more and understanding
28 29	112	French or English. The exclusion criteria were pre-existing diabetes mellitus, strict bed
30 31	113	rest, or severe mental disorders. To facilitate recruitment and share resources, a
32 33 34	114	collaboration was established with MySweetHeart Trial,[14] a randomized controlled
35 36	115	trial assessing the effect of a lifestyle and psychosocial intervention on cardiometabolic
37 38	116	outcomes of women with GDM and their offspring. As such, women with GDM were
39 40 41	117	invited to contribute to both studies. Participating women with and without GDM were
41 42 43	118	included in the current analysis if CIMT data for their live-born singleton neonates were
44 45	119	available. All families gave a signed informed consent for use of their data.
46 47	120	
48 49 50	121	Data collection
51 52	122	GDM screening
53 54	123	Pregnant women screened at the prenatal care clinic of the CHUV had a fasting plasma
55 56 57	124	glucose (FPG) test between 24 and 28 weeks of gestation and GDM was diagnosed if
58 59 60	125	the test result was \geq 5.1 mmol/L.[13] If FPG was < 5.1 mmol/L, but \geq 4.4 mmol/L,

women had a 2-hour 75 g oral glucose tolerance test (OGTT) and GDM was diagnosed based on the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[15] Pregnant women screened by external obstetricians in the Canton of Vaud underwent the same procedure or directly a 2-hour 75 g OGTT.

Carotid ultrasound and CIMT measurement

A carotid ultrasound assessment was performed between 1 and 7 days of life in the majority of neonates (n=191). A small share (n=9) had the exam between 8 and 19 days of life due to organizational and logistical constraints. Parents were told to feed and burp their offspring ahead of the carotid ultrasound to make them more relaxed. Feeding or administration of a 30% glucose solution were used to comfort the neonates if they became agitated during the exam. The exam took place in a dark and quiet room and a cloth was placed under the neonates' shoulders to facilitate the extension of the neck.

Ultrasound image acquisition and analysis were performed by 2 experienced pediatric cardiologists who were blinded to the maternal glycemic status. Images were acquired in B-mode with no harmonics, sonoCT, dynamic range of 60dB, at a frame rate of 100-120Hz, with a depth of 1-2 cm. The right and left carotid arteries were scanned using a Philips EPIC echocardiograph (Philips Medical, Netherlands) with a L 15-7 MHz high-resolution linear array transducer, according to the American Heart Association's recommendations for standard assessment of subclinical atherosclerosis in children and adolescents.[16] Each observer recorded three consecutive 3-second cine loops from 2 different angles on each side, which were stored as native DICOM for subsequent offline analyses (QLab, Philips Medical, Netherlands). Whenever image

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quality was optimal enough, 6 right and 6 left frames were selected and, for each, the maximal IMT of the common carotid artery far wall was measured. Measurements were performed over a 1-cm region of interest proximal to the carotid bulb, on or closest to the R-wave of the electrocardiogram, using a semi-automated edge detection software with manual tracing adjustment when needed. The mean of 12 maximal CIMT measurements was used in the analysis for the majority of neonates (n=170). Two neonates had only one measurement available, whereas the rest had between 2 and 11 measurements that were averaged. A good interobserver reliability (coefficient of variation=5.9%) for measurements in non-sedated infants was proven in our laboratory previously.[12]

Other sample characteristics

Data on maternal characteristics (age, country of origin, education, smoking during pregnancy, pre-pregnancy weight and height, or parity) and family history of diabetes were record-based or self-reported by the mother at a researcher-administered interview upon inclusion in the study. Smoking during pregnancy was defined as a mother who was an active tobacco smoker at study baseline, i.e., between 24 and 32 weeks of gestation. A maternal blood sampling was also performed at baseline and glycated hemoglobin (HbA1c) was measured. Pre-pregnancy body mass index (BMI) was computed by dividing the pre-pregnancy weight (kg) by the squared height (m²). Delivery data such as newborn sex, anthropometry, gestational age, or mode of delivery were obtained from the medical records. Neonatal weight, length and blood pressure were measured by the study team at the time of the carotid ultrasound. Body surface area (m²) was computed using the Mosteller equation.[17] One systolic and diastolic blood pressure measurement was taken from the right upper arm, in a supine

position, using a clinically validated and regularly calibrated oscillometric
sphygmomanometer (Accutorr Plus; Datascope, Paramus, New Jersey, USA) with
neonate cuffs.

180 Data analysis

Descriptive statistics on study participants are reported as percentages (%) or as mean, standard deviation, minimum and maximum values. The relationship of GDM with CIMT was evaluated by a set of linear regression models with and without adjustment for potential confounders, i.e., baseline covariates associated with metabolic and cardiovascular risks, offspring's sex, and anthropometry at CIMT assessment. Potential confounders were maternal pre-pregnancy BMI, maternal education (university/no university), smoking during pregnancy (yes/no), and family history of diabetes (yes/no). The variable family history of diabetes summarized disease occurrence in a 1st degree relative of the mother, 1st degree relative of the father or in the father himself and assumed missing data in any of these variables as no history of diabetes unless values for all 3 variables were missing. To account for differences in body size, [18,19] we adjusted for body surface area and age at CIMT assessment. All statistical analyses were performed in Stata 16 (Stata Corporation, Texas, USA).

7 195

RESULTS

197 Characteristics of study participants

Data collection started in September 2016 and ended in October 2020. A total of 137 participants without GDM exposure and 212 participants with GDM exposure were recruited in the study. Some 101 neonates without GDM exposure and 117 neonates

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with GDM exposure attended the cardiovascular follow-up visit early after birth. Of
these, 200 singleton neonates born at more than 36 weeks of gestation (non-GDM:
n=99; GDM: n=101) had CIMT measurements and constitute the analytic sample for
the current analysis.

Family and neonatal characteristics of study participants are presented in Table 1. The maternal characteristics were generally comparable between the non-GDM and GDM groups. The majority of women were non-Swiss and their age ranged from 18 to 47 years. Approximately half of the women in each group had a high level of education and no previous deliveries. More women with GDM (16%) were obese (pre-pregnancy BMI \geq 30 kg/m²) compared to women without GDM (6%). Smoking during pregnancy was more frequent among women with GDM (18%) than among those without GDM (4%). Offspring of women with and without GDM had similar neonatal characteristics, such as sex, gestational age, birth weight, length, or blood pressure. The majority were born at term, i.e., between 37 and 41 weeks (GDM: 96%; non-GDM: 98%) and a small share had macrosomia, i.e., a birth weight higher than 4'000 g (GDM: 6%; non-GDM: 5%). Offspring of women with GDM (46%) had a higher frequency of family history of diabetes compared to their non-GDM counterparts (24%).

BMJ Open Table 1 Characteristics of study participants by GDM exposure.								
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Table 1 Characteristics of study partic	ipants by GDM e	xposure						
					++ 0	5		
	Non-GDM ^a (n=	99)			GDM ^b (n=101))))		
	mean or %	sd	min	max	mean or %	sd	min	
MATERNAL					33	2		
Age (years)	33	5	18	44			21	
Swiss origin (%)	24				33 55			
University education (%)	60				55 6	<u>}</u>		
Primiparous (%)	55				48 48			
Smoking during pregnancy (%)	4				18 0			
Pre-pregnancy obesity (BMI ≥ 30 kg/m2) (%)	6				16			
HbA1C (%)	4.9	0.3	4.2	5.7	5.3	0.3	4.7	
NEONATAL		h			18 16 5.3 53 32 96			
Male (%)	52				53			
Cesarean section (%)	22				32			
Term birth (37 to 41 weeks) (%)	98				96			
Birth weight (g)	3'352	425	2'190	4'190	3'357		2'220	
Macrosomia (Birth weight > 4'000 g) (%)	5				6	2		
Length (cm)	50	2	45	54	6 20 50 0.21	2	45	_
Body surface area (m ²)	0.21	0.02	0.16	0.25	0.21	0.02	0.17	
Systolic BP (mmHg)	78	9	60	101			60	
Diastolic BP (mmHg)	47	8	30	66	78 48 +	10	28	
Family history of diabetes (%)	24				46 🥨			

nax, maximum; min, minimum; sd, standard deviation. Prot

a Non-GDM: Missing values for swiss origin (n=1), university education (n=2), pre-pregnancy obesity (n=1), HbA1c (n=13), c assaust (n=4), term birth (n=10), systolic BP (n=1), diastolic BP (n=1); family history of diabetes (n=1).

^b GDM: Missing values for age (n=3), swiss origin (n=3), university education (n=18), primiparous (n=3), smoking (n=5), prepregnancy obesity (n=4), HbA1c (n=5), male (n=16), cesarean section (n=6), term birth (n=16), birth weight (n=16); family history of diabetes (n=4). copyright.

221	GDM and CIMT at birth
222	The distribution of CIMT values is presented in Fig. 1 and Fig. 2. CIMT ranged from
223	0.21 to 0.42 mm, with a mean CIMT of 0.30 mm (sd 0.04) overall and in each of the
224	studied groups (Table 2, Table S1 in Supplementary Material).
225	
226	Fig. 1 Histograms of CIMT at birth, overall and by GDM exposure.
227	Figure legend This figure shows the distribution of CIMT values in our sample, overall
228	(n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line
229	represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media
230	thickness; GDM, gestational diabetes mellitus.
231	
232	Fig. 2 Box plots of CIMT at birth by GDM exposure and assignment to a lifestyle and
233	psychosocial intervention.
234	Figure legend This figure shows the distribution of CIMT in the offspring of women
235	without GDM (Non-GDM; n=99) and the offspring of women with GDM who were
236	assigned to no intervention (GDM, non-I; n=48) or to a lifestyle and psychosocial
237	intervention (GDM, I; n=53) as part of their participation in the MySweetHeart Trial.
238	Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes
239	mellitus; I, intervention.
	22 23 24 25 26 27 28 29 30 31 32 33 31 32 33 34 35 36 37 38

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Table 2 The relationship of GDM with offspring's CIMT at birth.

	Mean (SD), mm	Model 1 (n=200)		Model 2 (n=165)		Model 3 (n=165)	
		Difference (95% CI), mm	р	Difference (95% CI), mm	р	bifference (95% CI), mm ₹	р
Non-GDM	0.30 (0.04)	ref	ref	ref	ref	ref	ref
GDM	0.30 (0.04)	0.00 (-0.01 to 0.01)	0.96	0.00 (-0.02 to 0.01)	0.47	9 .00 (-0.02 to 0.01)	0.45

Model 2: estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family histor gof diabetes and sex.

Model 3: estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family history of diabetes, sex, body surface area

and age at CIMT assessment.

Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus; n, teal number of participants; p, p-value; sd, standard deviation; ref, reference group.

Note: Similar results were obtained when Model 1 was run in the sample (n=165) with data on outcome, exposure, and all covariates included in Models 2 mj.com/ on November 2, 2024 by guest. Protected by copyright and 3 (GDM: 0.00 mm (95% CI: -0.02 to 0.01; p=0.54)).

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The relationship of GDM with offspring's CIMT early after birth is presented in Table 2. In the unadjusted analysis (Model 1), the difference in CIMT between offspring of women with and without GDM was 0.00 mm (95% CI -0.01 to 0.01; p=0.96). Adjustment for offspring sex and potential confounding factors (Model 2), as well as for offspring's body surface area and age at CIMT assessment (Model 3), resulted in a difference of 0 mm (95% CI -0.02 to 0.01; p=0.45). When exposure to GDM was analyzed separately for offspring whose mothers were assigned or not to a lifestyle and psychosocial intervention as part of their participation in MySweetHeart Trial, results were similar to those presented above (Table S1 in Supplementary Material).

- - **DISCUSSION**

253 Summary of findings and comparison with other studies

Our goal was to assess the relationship of GDM with neonatal CIMT. We found no evidence of an increased CIMT in neonates born to women with GDM as compared to those born to women without GDM. Our findings are in line with other studies that evaluated CIMT after intrauterine exposure to maternal hyperglycemia. A recent meta-analysis pooled data from 3 studies and reported no clear evidence of increased CIMT in children exposed to maternal hyperglycemia compared to those not exposed (pooled standardized mean difference (SMD): 0.08 (95% CI -0.16 to 0.33)).[8] Two of these studies included 6-year and 8-year children, respectively, and found no difference in CIMT after exposure to GDM (SMD 0.00 (95% CI -0.28 to 0.28) at 6 years and 0.00 (95% CI -0.41 to 0.41) at 8 years).[8,20,21] The third study included neonates and found a slightly higher CIMT among those exposed to diabetes (SMD 0.46 (95% CI -0.07 to 1.00)),[8,22] but the imprecision around the estimated difference was high, the

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study had a very small sample size (n=55) and the authors did not specify whether
they included women with pre-gestational or gestational diabetes.[22]

269 Strengths and limitations

A major strength of this study is its prospective design. Enrollment of study participants and collection of baseline characteristics took place close to the moment of GDM diagnosis and ahead of the CIMT outcome assessment. This implies that the choice of participation in the study is unlikely to be related to both the exposure and the outcome, which makes selection bias due to enrollment unlikely. Further, GDM was diagnosed using the new criteria of the IADPG. These criteria were derived based on the risk of adverse neonatal outcomes, such as birth weight, cord blood C-peptide levels, or percent infant body fat > 90th percentile.[15] They were endorsed by the World Health Organization along with several other bodies to achieve a universal consensus for GDM diagnosis and increase comparability of the evidence.[23,24] Another strength is the assessment of ultrasound CIMT using automated methods with manual tracing adjustment, in accordance with the current guidelines in children.[16,25] The semi-automated methods are associated with a lower interoperator variability and high reliability, [16,25] including in infants, as it was previously proved in our laboratory. [12]

This study has some limitations. Firstly, our results have limited generalizability, as we used a convenient sample of pregnant women recruited from health care facilities in Switzerland. Secondly, the GDM glucose screening test (FPG or 75-g OGTT) varied between participants. This is because our hospital used a 2-step targeted approach for identifying women with GDM. While the 2-step approach is practical and more acceptable to patients,[26] it may be related to a lower likelihood of diagnosing GDM Page 17 of 31

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compared to a one-step universal screening based on a 75-g OGTT [27] On the other hand, the IADGSP criteria, which have a lower threshold for a positive FPG test (≥5.1 mmol/L) compared to other guidelines, [23] may identify as having GDM women who are at low absolute risk for fetal and pregnancy complications and, thus, overdiagnose GDM in some populations. [28,29] Therefore, misclassification of the exposure cannot be excluded and our estimates of association might be biased, maybe underestimated. Additionally, women with GDM participated in *MySweetHeart* Trial and approximately half of them were assigned to a lifestyle and psychosocial intervention with the aim of improving their cardiometabolic outcomes. Although this intervention could have also modified the association of GDM with CIMT, this seems not likely, as mean CIMT values were very similar in offspring of women with GDM who participated in the intervention and the control arms of the trial. Thirdly, CIMT was assessed using conventional high-resolution ultrasound frequencies (< 15 MHz), which tend to overestimate the arterial thickness in the young children when compared to very high-resolution ultrasound systems (25 to 55 MHz).[30,31] Measurement error in CIMT cannot be excluded, but systematic differences between the two groups are unlikely because the outcome assessors were blinded to the glycemic status of the mothers. Fourthly, while we adjusted for key confounders at the analysis stage, there is a possibility of residual confounding due to the relatively small sample size and some imprecision in the measurement of confounder variables, especially in those self-reported. Lastly, our study was limited to CIMT, which is a measure of arterial structure. In fact, changes in the vessel function might occur earlier than changes in the vessel structure, therefore, a combination of vascular measures would be needed for a clearer view on the cardiovascular status of children exposed to adverse experiences in early life. However, certain techniques to assess arterial function and stiffness, such as flow-

1 2		
3 4	316	mediated dilation and pulse-wave velocity, are not currently feasible in the very young
5 6 7 8 9	317	due to limited compliance and technical inconveniences.[18]
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10 11	319	Implications and future research
12 13	320	Our results suggest that intrauterine exposure to GDM does not induce changes in the
14 15 16 17 18	321	carotid artery structure that are detectable with conventional ultrasound techniques at
	322	birth and may not be linked to early vascular aging at this arterial site in the short term.
19 20	323	Measurements at other arterial sites, such as the aorta,[32] may be more useful to
21 22	324	investigate early or subtle abnormalities related to accelerated vascular aging or
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	325	subclinical atherosclerosis. A long-term follow-up that includes complementary
	326	vascular measures, for instance, endothelium-dependent and endothelium-
	327	independent vasodilation or large-artery stiffness,[20] may shed further light on the
	328	cardiovascular health of children born to mothers with GDM.
	329	
	330	Patient and public involvement
	331	There was no patient or public involvement in the design, conduct, analysis, or
	332	reporting of this study's findings.
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Authors' contributions

AC, NS, SDB, and YM designed the study and the data collection procedures with 45 input from SEY, AME. SEY and AME collected baseline characteristics for participants 46 without GDM. SDB and NS collected neonatal cardiovascular characteristics for all 47 participants. SEY performed data management and curation. AME carried out the 48 statistical analyses with input and supervision from AC. AME wrote the first draft of the 49 manuscript with input from AC and NS. SDB, SEY, YM made critical revisions to the 50 51 manuscript for important intellectual content. All authors read and approved the content of the manuscript. 52

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 Competing interests
 None declared.

373 Consent for publication

374 Not applicable.

³ 376 **Ethics approval**

377 Ethical approval was obtained through the Ethics Committee for Human Research of

378 the Canton of Vaud (2016–00745).

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380 Data availability statement

381 Data could be made available by the principal investigator and corresponding author

382 (Prof Nicole Sekarski: <u>nicole.sekarski@chuv.ch</u>) on reasonable request.

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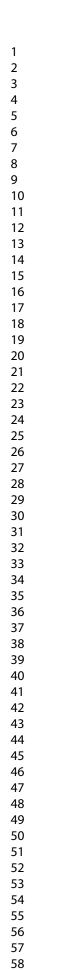
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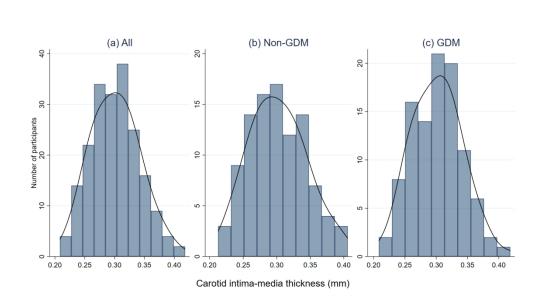
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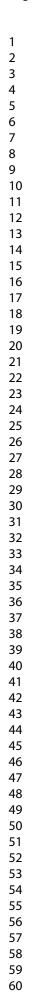
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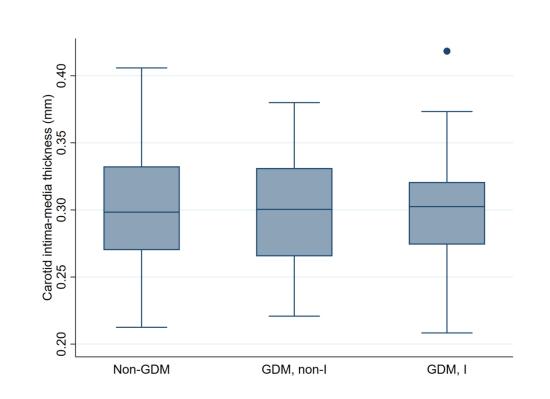
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This figure shows the distribution of CIMT values in our sample, overall (n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus.

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This figure shows the distribution of CIMT in the offspring of women without GDM (Non-GDM; n=99) and the offspring of women with GDM who were assigned to no intervention (GDM, non-I; n=48) or to a lifestyle and psychosocial intervention (GDM, I; n=53) as part of their participation in the MySweetHeart Trial. Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus; I, intervention.

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SUPPLEMENTARY MATERIAL

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Gestational diabetes mellitus and offspring's carotid intima-media thickness at birth: MySweetHeart

Cohort Study

Adina Mihaela Epure^{1,2}, Stefano Di Bernardo³, Yvan Mivelaz³, Sandrine Estoppey Younes², Arnau Chiolero^{1,4,5}, Nicole Sekarski³, on behalf of *MySweetHeart* Research Group

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bmjopen-2022-06 **Table S1** Differences in CIMT at birth by GDM exposure and assignment to a lifestyle and psychos $\hat{\mathbf{g}}$ cial intervention.

	Mean (sd), mm	Model 1 (n=200)		Model 2 (n=165)		Model 3 (n=165)	
		Difference (95% CI), mm	р	Difference (95% CI), mm	р	E EDifference (95% CI), mm	p
Non-GDM	0.30 (0.04)	ref	ref	ref	ref	dref	ref
GDM, non-I	0.30 (0.04)	0.00 (-0.01 to 0.01)	0.94	0.00 (-0.02 to 0.02)	0.93	50.00 (-0.02 to 0.01)	0.91
GDM, I	0.30 (0.04)	0.00 (-0.01 to 0.01)	0.98	-0.01 (-0.03 to 0.01)	0.19	₽ ₽-0.01 (-0.02 to 0.01)	0.25

Model 1: unadjusted estimates.

Model 2: estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family historic diabetes and sex.

Model 3: estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family history of diabetes, sex, body surface area

and age at CIMT assessment.

Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus; I, intervention; n, total number of participants;

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p, p-value; sd, standard deviation; ref, reference group.

and 3 (GDM, non-I: 0.00 mm (95% CI: -0.01 to 0.01; p=0.99); GDM, I: -0.01 mm (95% CI: -0.02 to 0.01; p=0.29)).

		BMJ Open	Page Page P-2022
	ST	FROBE 2007 (v4) Statement—Checklist of items that should be included in reports o	Ņ
Section/Topic	ltem #	Recommendation	Reported in section [page # in Main text]
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title [page 1]
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract [page 2-3]
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Intræduction (paragraphs 1-2) [page 5]
Objectives	3	State specific objectives, including any prespecified hypotheses	Intreduction (paragraph 2) [page 5]
Methods		N o	3
Study design	4	Present key elements of study design early in the paper	- Methods (subheadings: Study design and setting; Study population) [page 6] - Puppished protocol (see reference [2])
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	 Methods (subheadings: Study design and setting; Study population; Data collection) [page 6-9] Results (subheadings: Characteristics of study participants) [page 9] Puglished protocol (see reference [2])
Participants	6	(<i>a</i>) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	- Methods (subheadings: Study population) [page 6] - Pupplished protocol (see reference [2])
		(b) For matched studies, give matching criteria and number of exposed and unexposed 🧹	- N/8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	- Methods (subheadings: Data collection; Data analysis) [page 6-9]
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	- Methods (subheadings: Data collection) [page 6-8] ਸ ਹੁਰੂ
Bias	9	Describe any efforts to address potential sources of bias	- Mathods (subheadings: Data analysis) [page 9] - Discussion (subheadings: Strengths and limitations) [page 15-16]

1		BMJ Open	omjopen-2022	
Study size	10	Explain how the study size was arrived at	- Published protocol[2]	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	- Moonods (subheadings: Data analysis) [page 9] 음	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	- Methods (subheadings: Data analysis) [page 9]	
		(b) Describe any methods used to examine subgroups and interactions		
		(c) Explain how missing data were addressed	- Manods (subheadings: Study population; Data analysis) [page 6; 9]	
		(d) If applicable, explain how loss to follow-up was addressed	- Tal = 1 footnote [page 11]	
			- Methods (subheadings: Study population) [page 6]	
		(e) Describe any sensitivity analyses	់ - Supplementary material (Table S1) ទី	
Results			3	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	- Results (subheadings: Characteristics of study participants) [page 9-10]	
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and	- Results (subheadings: Characteristics of study	
		information on exposures and potential confounders	partgipants; Table 1) [page 10-11]	
		(b) Indicate number of participants with missing data for each variable of interest	- Red Its (Table 1) [page 11]	
		(c) Summarise follow-up time (eg, average and total amount)	- Methods (subheadings: Study population; Carotid	
			ultragound and CIMT measurement) [page 6-7]	
Outcome data	15*	Report numbers of outcome events or summary measures over time	- Results (Table 2) [page 13]	
Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	- Re웣lts (Table 2) [page 13] 오 은	
		(b) Report category boundaries when continuous variables were categorized	- Results (Table 1) [page 11]	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	- Supplementary material (Table S1)	

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18	Summarise key results with reference to study objectives	- Discussion (Summary of findings and comparison
		withother studies) [page 14]
20	Give a cautious overall interpretation of results considering objectives, limitations,	- Discussion (Summary of findings and comparison
	multiplicity of analyses, results from similar studies, and other relevant evidence	with other studies; Strengths and limitations) [page 14
		16] ^N
21	Discuss the generalisability (external validity) of the study results	- Disgussion (Strengths and limitations) [page 15-16]
		load
22	Give the source of funding and the role of the funders for the present study and, if	- Funding statement [page 19]
	applicable, for the original study on which the present article is based	m
	20	20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 21 Discuss the generalisability (external validity) of the study results 22 Give the source of funding and the role of the funders for the present study and, if

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies.

Note: Information on the STROBE Initiative is available at www.strobe-statement.org

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Gestational diabetes mellitus and offspring's carotid intimamedia thickness at birth: MySweetHeart Cohort Study

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23	legends and tables): 2'924

24 ABSTRACT

Objective Hyperglycemia during pregnancy is associated with cardiometabolic risks for the mother and the offspring. Mothers with gestational diabetes mellitus (GDM) have signs of subclinical atherosclerosis, including increased carotid intima-media thickness (CIMT). We assessed whether GDM is associated with increased CIMT in the offspring at birth.

Design and setting *MySweetHeart* Cohort is a prospective cohort study conducted in
 Switzerland.

Participants, exposure and outcome measures This work included pregnant women with and without GDM at 24 to 32 weeks of gestation and their singleton liveborn offspring with data on the primary outcome of CIMT. GDM was diagnosed based on the criteria of the International Association of Diabetes and Pregnancy Study Groups. Offspring's CIMT was measured by ultrasonography after birth (range: 1 to 19 days).

Results Data on CIMT were available for 99 offspring of women without GDM and 101 offspring of women with GDM. Maternal age ranged from 18 to 47 years. Some 16% of women with GDM and 6% of women without GDM were obese. Smoking during pregnancy was more frequent among women with GDM (18%) than among those without GDM (4%). Neonatal characteristics were comparable between the 2 groups. The difference in CIMT between offspring of women with and without GDM was of 0.00 mm (95% CI: -0.01 to 0.01; p=0.96) and remained similar upon adjustment for potential confounding factors, such as maternal pre-pregnancy BMI, maternal education,

smoking during pregnancy, family history of diabetes, as well as offspring's sex, age,
and body surface area (0.00 mm (95% CI: -0.02 to 0.01; p=0.45)).

52 Conclusions We found no evidence of increased CIMT in neonates exposed to GDM.
53 A longer-term follow-up that includes additional vascular measures, such as
54 endothelial function or arterial stiffness, may shed further light on the cardiovascular
55 health trajectories in children born to mothers with GDM.

Registration ClinicalTrials.gov (NCT02872974)

Keywords gestational diabetes; carotid intima-media thickness; cardiovascular 60 prevention; child; neonate

List of abbreviations BMI, body mass index; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; CHUV, Lausanne University Hospital; DOHaD, developmental origins of health and disease; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; IADPSG, International Association of Diabetes and Pregnancy Study Groups; I, intervention; OGTT, oral glucose tolerance test.

Strengths and limitations of this study

- One important strength of this study is represented by its prospective design and the enrollment of participants at the time of gestational diabetes diagnosis.
 - Carotid intima-media thickness was measured in non-sedated neonates by • experienced pediatric cardiologists using automated methods with manual tracing adjustment, in accordance with published guidelines.
- da. .g and the limite. Limitations of this study include the relatively small sample size, the possibility • of residual confounding and the limited generalizability.

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76 INTRODUCTION

Gestational diabetes mellitus (GDM) is a state of hyperglycemia with onset or first recognition during pregnancy.[1-3] The prevalence of hyperglycemia during pregnancy has increased in recent decades, being estimated at 16% worldwide in 2019, with 84% of cases due to GDM.[4] GDM is associated with long-term metabolic consequences for both the mother and the offspring, such as type 2 diabetes and obesity.[5] Women with GDM also have subclinical atherosclerosis and an increased risk for cardiovascular disease (CVD) later in life.[6,7] However, little is known about the cardiovascular risk of their offspring.

CIMT is a surrogate marker of atherosclerosis, which has been shown to be increased in children exposed to risk factors in the first 1000 days of life, such as poor fetal growth, [8] as well as in children with type 1 diabetes. [9] From a developmental origins of health and disease (DOHaD) perspective, [10] exposure to adverse experiences in early life may produce lifelong adaptations in the organs' structure and function and may program the risk for CVD. For instance, a systematic review and meta-analysis showed that GDM was associated with a higher systolic blood pressure in childhood.[11] Whether GDM has an impact on children's CIMT is not clearly established. The evidence is scarce notably in the very young children although CIMT measurement is feasible from birth and could help discern between changes that occur before or after birth.[12] To fill this gap, we conducted MySweetHeart Cohort study to assess the early life cardiovascular consequences of GDM.[13] Herein, we evaluated CIMT at birth in offspring of mothers with and without GDM.

1		
2 3 4	101	METHODS
5 6	102	Study design and setting
7 8	103	MySweetHeart Cohort is a prospective cohort study conducted at the Lausanne
9 10 11	104	University Hospital (CHUV), Switzerland. The study has been registered with
12 13	105	ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT02872974) and the study protocol
14 15	106	has been published.[13] Ethical approval was granted by the Ethics Committee for
16 17 18	107	Human Research of the Canton de Vaud (study number 2016-00745).
19 20	108	
21 22	109	Study population
23 24 25	110	This cohort included pregnant women between 24 and 32 weeks of gestation, with and
25 26 27	111	without GDM. Other inclusion criteria were age 18 years or more and understanding
28 29	112	French or English. The exclusion criteria were pre-existing diabetes mellitus, strict bed
30 31	113	rest, or severe mental disorders. To facilitate recruitment and share resources, a
32 33 34	114	collaboration was established with MySweetHeart Trial,[14] a randomized controlled
35 36	115	trial assessing the effect of a lifestyle and psychosocial intervention on cardiometabolic
37 38	116	outcomes of women with GDM and their offspring. As such, women with GDM were
39 40 41	117	invited to contribute to both studies. Participating women with and without GDM were
41 42 43	118	included in the current analysis if CIMT data for their live-born singleton neonates were
44 45	119	available. All families gave a signed informed consent for use of their data.
46 47	120	
48 49 50	121	Data collection
51 52	122	GDM screening
53 54	123	Pregnant women screened at the prenatal care clinic of the CHUV had a fasting plasma
55 56 57	124	glucose (FPG) test between 24 and 28 weeks of gestation and GDM was diagnosed if
58 59 60	125	the test result was \geq 5.1 mmol/L.[13] If FPG was < 5.1 mmol/L, but \geq 4.4 mmol/L,

women had a 2-hour 75 g oral glucose tolerance test (OGTT) and GDM was diagnosed based on the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[15] Pregnant women screened by external obstetricians in the Canton of Vaud underwent the same procedure or directly a 2-hour 75 g OGTT.

Carotid ultrasound and CIMT measurement

A carotid ultrasound assessment was performed between 1 and 7 days of life in the majority of neonates (n=191). A small share (n=9) had the exam between 8 and 19 days of life due to organizational and logistical constraints. Parents were told to feed and burp their offspring ahead of the carotid ultrasound to make them more relaxed. Feeding or administration of a 30% glucose solution were used to comfort the neonates if they became agitated during the exam. The exam took place in a dark and quiet room and a cloth was placed under the neonates' shoulders to facilitate the extension of the neck.

Ultrasound image acquisition and analysis were performed by 2 experienced pediatric cardiologists who were blinded to the maternal glycemic status. Images were acquired in B-mode with no harmonics, sonoCT, dynamic range of 60dB, at a frame rate of 100-120Hz, with a depth of 1-2 cm. The right and left carotid arteries were scanned using a Philips EPIC echocardiograph (Philips Medical, Netherlands) with a L 15-7 MHz high-resolution linear array transducer, according to the American Heart Association's recommendations for standard assessment of subclinical atherosclerosis in children and adolescents.[16] Each observer recorded three consecutive 3-second cine loops from 2 different angles on each side, which were stored as native DICOM for subsequent offline analyses (QLab, Philips Medical, Netherlands). Whenever image

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quality was optimal enough, 6 right and 6 left frames were selected and, for each, the maximal IMT of the common carotid artery far wall was measured. Measurements were performed over a 1-cm region of interest proximal to the carotid bulb, on or closest to the R-wave of the electrocardiogram, using a semi-automated edge detection software with manual tracing adjustment when needed. The mean of 12 maximal CIMT measurements was used in the analysis for the majority of neonates (n=170). Two neonates had only one measurement available, whereas the rest had between 2 and 11 measurements that were averaged. A good interobserver reliability (coefficient of variation=5.9%) for measurements in non-sedated infants was proven in our laboratory previously.[12]

Other sample characteristics

Data on maternal characteristics (age, country of origin, education, smoking during pregnancy, pre-pregnancy weight and height, or parity) and family history of diabetes were record-based or self-reported by the mother at a researcher-administered interview upon inclusion in the study. Smoking during pregnancy was defined as a mother who was an active tobacco smoker at study baseline, i.e., between 24 and 32 weeks of gestation. A maternal blood sampling was also performed at baseline and glycated hemoglobin (HbA1c) was measured. Pre-pregnancy body mass index (BMI) was computed by dividing the pre-pregnancy weight (kg) by the squared height (m²). Delivery data such as newborn sex, anthropometry, gestational age, or mode of delivery were obtained from the medical records. Neonatal weight, length and blood pressure were measured by the study team at the time of the carotid ultrasound. Body surface area (m²) was computed using the Mosteller equation.[17] One systolic and diastolic blood pressure measurement was taken from the right upper arm, in a supine

position, using a clinically validated and regularly calibrated oscillometric
sphygmomanometer (Accutorr Plus; Datascope, Paramus, New Jersey, USA) with
neonate cuffs.

180 Data analysis

Descriptive statistics on study participants are reported as percentages (%) or as mean, standard deviation, minimum and maximum values. The relationship of GDM with CIMT was evaluated by a set of linear regression models with and without adjustment for potential confounders, i.e., baseline covariates associated with metabolic and cardiovascular risks, offspring's sex, and anthropometry at CIMT assessment. Potential confounders were maternal pre-pregnancy BMI, maternal education (university/no university), smoking during pregnancy (yes/no), and family history of diabetes (yes/no). The variable family history of diabetes summarized disease occurrence in a 1st degree relative of the mother, 1st degree relative of the father or in the father himself and assumed missing data in any of these variables as no history of diabetes unless values for all 3 variables were missing. To account for differences in body size, [18,19] we adjusted for body surface area and age at CIMT assessment. All statistical analyses were performed in Stata 16 (Stata Corporation, Texas, USA).

7 195

RESULTS

197 Characteristics of study participants

Data collection started in September 2016 and ended in October 2020. A total of 137 participants without GDM exposure and 212 participants with GDM exposure were recruited in the study. Some 101 neonates without GDM exposure and 117 neonates

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with GDM exposure attended the cardiovascular follow-up visit early after birth. Of
these, 200 singleton neonates born at more than 36 weeks of gestation (non-GDM:
n=99; GDM: n=101) had CIMT measurements and constitute the analytic sample for
the current analysis.

Family and neonatal characteristics of study participants are presented in Table 1. The maternal characteristics were generally comparable between the non-GDM and GDM groups. The majority of women were non-Swiss and their age ranged from 18 to 47 years. Approximately half of the women in each group had a high level of education and no previous deliveries. More women with GDM (16%) were obese (pre-pregnancy BMI \geq 30 kg/m²) compared to women without GDM (6%). Smoking during pregnancy was more frequent among women with GDM (18%) than among those without GDM (4%). Offspring of women with and without GDM had similar neonatal characteristics, such as sex, gestational age, birth weight, length, or blood pressure. The majority were born at term, i.e., between 37 and 41 weeks (GDM: 96%; non-GDM: 98%) and a small share had macrosomia, i.e., a birth weight higher than 4'000 g (GDM: 6%; non-GDM: 5%). Offspring of women with GDM (46%) had a higher frequency of family history of diabetes compared to their non-GDM counterparts (24%).

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bmjopen-2022-061649 o Table 1 Characteristics of study participants by GDM exposure. 219 GDM[♭] (n=101 Non-GDM^a (n=99) mean or % sd mean or % July min sd min max MATERNAL 2022. 33 5 18 44 33 5 21 Age (years) Down Swiss origin (%) 24 33 University education (%) 60 lloa 55 ĩded Primiparous (%) 55 48 from Smoking during pregnancy (%) 4 18 Pre-pregnancy obesity (BMI ≥ 30 kg/m2) (%) 6 16 http d://br HbA1C (%) 4.9 0.3 4.2 5.7 5.3 0.3 4.7 NEONATAL njoplen.bmj.dom, Male (%) 52 53 Cesarean section (%) 22 32 Term birth (37 to 41 weeks) (%) 98 96 3'352 on Birth weight (g) 425 2'190 4'190 3'357 442 2'220 Nov Macrosomia (Birth weight > 4'000 g) (%) 5 6 ember 2 Length (cm) 50 2 45 54 50 2 45 Body surface area (m²) 0.21 0.02 0.02 0.16 0.25 0.21 0.17 Systolic BP (mmHg) 78 9 60 101 78 2024 10 60 Diastolic BP (mmHg) 47 8 48 10 30 66 28

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44 45 46 Family history of diabetes (%)

Abbreviations: BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin n, total number of participants; max, maximum; min, minimum; sd, standard deviation.

a Non-GDM: Missing values for swiss origin (n=1), university education (n=2), pre-pregnancy obesity (n=1), HbA1c (n=13), cesarean section (n=4), term birth (n=10), systolic BP (n=1), diastolic BP (n=1); family history of diabetes (n=1).

^b GDM: Missing values for age (n=3), swiss origin (n=3), university education (n=18), primiparous (n=3), smoking (n=5), prepregnancy obesity (n=4), HbA1c (n=5), male (n=16), cesarean section (n=6), term birth (n=16), birth weight (n=16); family history of diabetes (n=4). copyright

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1 2		
2 3 4	221	GDM and CIMT at birth
5 6	222	The distribution of CIMT values is presented in Fig. 1, Fig. 2, and Fig. S2 in
7 8	223	Supplementary Material. CIMT ranged from 0.21 to 0.42 mm, with a mean CIMT of
9 10 11	224	0.30 mm (sd 0.04) overall and in each of the studied groups (Table 2, Table S1 in
12 13	225	Supplementary Material).
14 15	226	
16 17 18	227	Fig. 1 Histograms of CIMT at birth, overall and by GDM exposure.
19 20	228	Figure legend This figure shows the distribution of CIMT values in our sample, overall
21 22	229	(n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line
23 24	230	represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media
25 26 27	231	thickness; GDM, gestational diabetes mellitus.
28 29	232	
30 31	233	Fig. 2 Box plots of CIMT at birth by GDM exposure and assignment to a lifestyle and
32 33 34	234	psychosocial intervention.
35 36	235	Figure legend This figure shows the distribution of CIMT in the offspring of women
37 38	236	without GDM (Non-GDM; n=99) and the offspring of women with GDM who were
39 40	237	assigned to no intervention (GDM, non-l; n=48) or to a lifestyle and psychosocial
41 42 43	238	intervention (GDM, I; n=53) as part of their participation in the MySweetHeart Trial. The
44 45	239	line inside the box represents the median value of the distribution, while the lower and
46 47	240	upper boundaries of the box represent the first (Q1) and third quartiles (Q3),
48 49 50	241	respectively. The interquartile range (IQR) corresponds to Q3 – Q1. The whiskers
50 51 52	242	extend from either side of the box up to 1.5*IQR (i.e., Q1-1.5*IQR and Q3+1.5*IQR).
53 54	243	Outliers are depicted as circles. Abbreviations: CIMT, carotid intima-media thickness;
55 56 57 58 59 60	244	GDM, gestational diabetes mellitus; I, intervention.

Table 2 The relationship of GDM with offspring's CIMT at birth.

	Mean (SD), mm	Model 1 (n=200)		Model 2 (n=165)		Nodel 3 (n=165)	
		Mean difference (95% CI), mm	р	Mean difference (95% CI), mm	р	∰rean difference (95% CI), mm	p
Non-GDM	0.30 (0.04)	ref	ref	ref	ref	rèf	ref
GDM	0.30 (0.04)	0.00 (-0.01 to 0.01)	0.96	0.00 (-0.02 to 0.01)	0.47	e 00 (-0.02 to 0.01)	0.45

Estimates were obtained from linear regression models with the following specification: Model 1: unadjusted estimates; Model 2: estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family history of diabetes and sex; Model 3 estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family history of diabetes, sex, body surface area and age at CIMT assessment. The outcome variable (i.e., CIMT) was continuous. The exposure variable was binary (GDM/Non-GDM; the reference category avas Non-GDM). Similar results were obtained when Model 1 was run in the sample (n=165) with data on outcome, exposure, and all covariates included in Models 2 and 3 (GDM: 0.00 mm (95% CI: -0.02 to 0.01; p=0.54)). Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus; n, total number of participants; p, p-value; sd, standard deviation; ref, reference group.

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The relationship of GDM with offspring's CIMT early after birth is presented in Table 2 and Fig. 3. In the unadjusted analysis (Model 1), the difference in CIMT between offspring of women with and without GDM was 0.00 mm (95% CI -0.01 to 0.01; p=0.96). Adjustment for offspring sex and potential confounding factors (Model 2), as well as for offspring's body surface area and age at CIMT assessment (Model 3), resulted in a difference of 0 mm (95% CI -0.02 to 0.01; p=0.45). When exposure to GDM was analyzed separately for offspring whose mothers were assigned or not to a lifestyle and psychosocial intervention as part of their participation in MySweetHeart Trial, results were similar to those presented above (Table S1 and Fig. S1 in Supplementary Material).

Fig 3 Illustration of the relationship of GDM with offspring's CIMT at birth through a forest plot.

Figure legend The boxes represent the mean differences in CIMT between offspring of women with and without GDM (i.e., GDM versus non-GDM). The horizontal lines represent the 95% CIs. The plot was constructed using regression estimates and models presented in Table 2. Model specification: Model 1 is unadjusted, while Models 2 and 3 are adjusted for various factors as described in the methods and footnote of Table 2. Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus.

DISCUSSION

Summary of findings and comparison with other studies

Our goal was to assess the relationship of GDM with neonatal CIMT. We found no evidence of an increased CIMT in neonates born to women with GDM as compared to

those born to women without GDM. Our findings are in line with other studies that evaluated CIMT after intrauterine exposure to maternal hyperglycemia. A recent meta-analysis pooled data from 3 studies and reported no clear evidence of increased CIMT in children exposed to maternal hyperglycemia compared to those not exposed (pooled standardized mean difference (SMD): 0.08 (95% CI -0.16 to 0.33)).[8] Two of these studies included 6-year and 8-year children, respectively, and found no difference in CIMT after exposure to GDM (SMD 0.00 (95% CI -0.28 to 0.28) at 6 years and 0.00 (95% CI -0.41 to 0.41) at 8 years).[8,20,21] The third study included neonates and found a slightly higher CIMT among those exposed to diabetes (SMD 0.46 (95% CI -0.07 to 1.00)),[8,22] but the imprecision around the estimated difference was high, the study had a very small sample size (n=55) and the authors did not specify whether they included women with pre-gestational or gestational diabetes.[22]

Strengths and limitations

A major strength of this study is its prospective design. Enrollment of study participants and collection of baseline characteristics took place close to the moment of GDM diagnosis and ahead of the CIMT outcome assessment. This implies that the choice of participation in the study is unlikely to be related to both the exposure and the outcome, which makes selection bias due to enrollment unlikely. Further, GDM was diagnosed using the new criteria of the IADPG. These criteria were derived based on the risk of adverse neonatal outcomes, such as birth weight, cord blood C-peptide levels, or percent infant body fat > 90th percentile.[15] They were endorsed by the World Health Organization along with several other bodies to achieve a universal consensus for GDM diagnosis and increase comparability of the evidence. [23,24] Another strength is the assessment of ultrasound CIMT using automated methods with manual tracing

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adjustment, in accordance with the current guidelines in children.[16,25] The semi-automated methods are associated with a lower interoperator variability and high reliability, [16,25] including in infants, as it was previously proved in our laboratory. [12]

This study has some limitations. Firstly, our results have limited generalizability, as we used a convenient sample of pregnant women recruited from health care facilities in Switzerland. Secondly, the GDM glucose screening test (FPG or 75-g OGTT) varied between participants. This is because our hospital used a 2-step targeted approach for identifying women with GDM. While the 2-step approach is practical and more acceptable to patients [26] it may be related to a lower likelihood of diagnosing GDM compared to a one-step universal screening based on a 75-g OGTT.[27] On the other hand, the IADGSP criteria, which have a lower threshold for a positive FPG test (≥5.1 mmol/L) compared to other guidelines, [23] may identify as having GDM women who are at low absolute risk for fetal and pregnancy complications and, thus, overdiagnose GDM in some populations. [28,29] Therefore, misclassification of the exposure cannot be excluded and our estimates of association might be biased, maybe underestimated. Additionally, women with GDM participated in *MySweetHeart* Trial and approximately half of them were assigned to a lifestyle and psychosocial intervention with the aim of improving their cardiometabolic outcomes. Although this intervention could have also modified the association of GDM with CIMT, this seems not likely, as mean CIMT values were very similar in offspring of women with GDM who participated in the intervention and the control arms of the trial. Thirdly, CIMT was assessed using conventional high-resolution ultrasound frequencies (< 15 MHz), which have a lower spatial resolution and, thus, tend to overestimate the arterial thickness in the young children when compared to very high-resolution ultrasound systems (25 to 55

MHz).[30,31] Measurement error in CIMT cannot be excluded, but systematic differences between the two groups are unlikely because the outcome assessors were blinded to the glycemic status of the mothers. Fourthly, while we adjusted for key confounders at the analysis stage, there is a possibility of bias due to unmeasured factors, such as family history of premature cardiovascular death, or residual confounding due to the relatively small sample size and imprecision in the measurement of confounder variables, especially in those self-reported. Lastly, our study was limited to CIMT, which is a measure of arterial structure. In fact, changes in the vessel function might occur earlier than changes in the vessel structure, therefore, a combination of vascular measures would be needed for a clearer view on the cardiovascular status of children exposed to adverse experiences in early life. However, certain techniques to assess arterial function and stiffness, such as flow-mediated dilation and pulse-wave velocity, are not currently feasible in the very young due to limited compliance and technical inconveniences.[18]

337 Implications and future research

Our results suggest that intrauterine exposure to GDM does not induce changes in the carotid artery structure that are detectable with conventional ultrasound techniques at birth and may not be linked to early vascular aging at this arterial site in the short term. Measurements at other arterial sites, such as the aorta, [32] may be more useful to investigate early or subtle abnormalities related to accelerated vascular aging or subclinical atherosclerosis. A long-term follow-up that includes complementary vascular measures, for instance, endothelium-dependent and endothelium-independent vasodilation or large-artery stiffness, [20] may shed further light on the cardiovascular health of children born to mothers with GDM.

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2 3 4	347	
5 6	348	Patient and public involvement
7 8	349	There was no patient or public involvement in the design, conduct, analysis, or
9 10 11	350	reporting of this study's findings.
12 13	351	
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16 17 18	353	¹ Population Health Laboratory (#PopHealthLab), University of Fribourg, Fribourg,
19 20	354	Switzerland;
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26 27	357	³ Paediatric Cardiology Unit, Woman-Mother-Child Department, Lausanne University
28 29	358	Hospital (CHUV), Lausanne, Switzerland;
30 31 32	359	⁴ Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland;
33 34	360	⁵ School of Global and Population Health, McGill University, Montréal, Canada
35 36	361	
37 38	362	Authors' contributions
39 40 41	363	AC, NS, SDB, and YM designed the study and the data collection procedures with
42 43	364	input from SEY, AME. SEY and AME collected baseline characteristics for participants
44 45	365	without GDM. SDB and NS collected neonatal cardiovascular characteristics for all
46 47 48	366	participants. SEY performed data management and curation. AME carried out the
49 50	367	statistical analyses with input and supervision from AC. AME wrote the first draft of the
51 52	368	manuscript with input from AC and NS. SDB, SEY, YM made critical revisions to the
53 54 55	369	manuscript for important intellectual content. All authors read and approved the content
56 57	370	of the manuscript.
58 59 60	371	

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8 374 9 375 11 375 12 376 14 377 15 377 16 379 20 379 21 380 22 380 23 381 26 382 29 383 30 384 32 386 37 386 36 386 37 383 36 386 37 383 38 387 39 40 388 41 390 42 389 44 390 45 390 46 391 47 391 48 392 51 393 52 393 54 394 55 395 56 395 58 396	6	373
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59 ³⁹⁶	56	395
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1 2

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Competing interests 388

None declared. 389

Consent for publication 391

Not applicable. 392

Ethics approval 394

Ethical approval was obtained through the Ethics Committee for Human Research of 395 the Canton of Vaud (2016–00745). 396

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5 6	398	Data availability statement
7 8	399	Data could be made available by the principal investigator and corresponding author
9 10 11	400	(Prof Nicole Sekarski: nicole.sekarski@chuv.ch) on reasonable request.
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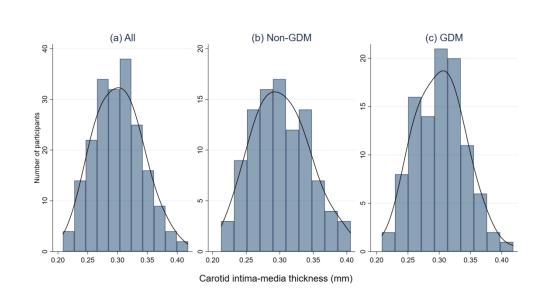
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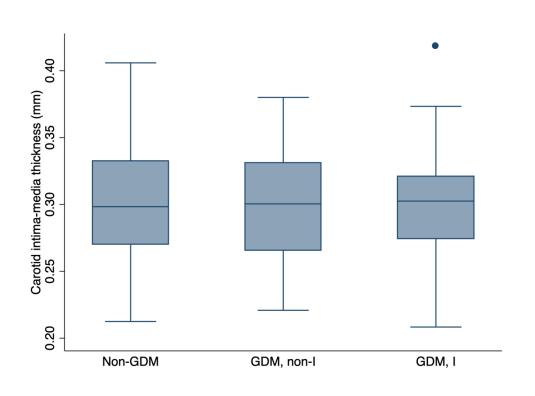
This figure shows the distribution of CIMT values in our sample, overall (n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus.

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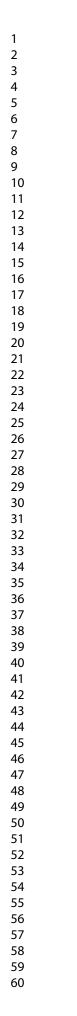
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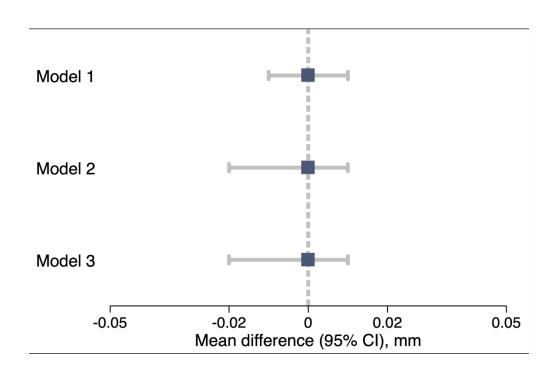


This figure shows the distribution of CIMT in the offspring of women without GDM (Non-GDM; n=99) and the offspring of women with GDM who were assigned to no intervention (GDM, non-I; n=48) or to a lifestyle and psychosocial intervention (GDM, I; n=53) as part of their participation in the MySweetHeart Trial. The line inside the box represents the median value of the distribution, while the lower and upper boundaries of the box represent the first (Q1) and third quartiles (Q3), respectively. The interquartile range (IQR) corresponds to Q3 – Q1. The whiskers extend from either side of the box up to 1.5*IQR (i.e., Q1-1.5*IQR and Q3+1.5*IQR).

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The boxes represent the mean differences in CIMT between offspring of women with and without GDM (i.e., GDM versus non-GDM). The horizontal lines represent the 95% CIs. The plot was constructed using regression estimates and models presented in Table 2. Model specification: Model 1 is unadjusted, while Models 2 and 3 are adjusted for various factors as described in the methods and footnote of Table 2. Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus.

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 SUPPLEMENTARY MATERIAL
 SUPPLEMENTARY MATERIAL

 Gestational diabetes mellitus and offspring's carotid intima-media thickness
 at birth: MySweetHeart

Cohort Study

Adina Mihaela Epure^{1,2}, Stefano Di Bernardo³, Yvan Mivelaz³, Sandrine Estoppey Younes², Arnaud Chiolero^{1,4,5¶}, Nicole Sekarski^{3¶}, on behalf of MySweetHeart Research Group

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	Mean (sd), mm	Model 1 (n=200)		Model 2 (n=165)		Model 3 (n=165)	
		Mean difference (95% CI), mm	p	Mean difference (95% CI), mm	p	Mean difference (95% CI),	р
Non-GDM	0.30 (0.04)	ref	ref	ref	ref	p §ref	ref
GDM, non-I	0.30 (0.04)	0.00 (-0.01 to 0.01)	0.94	0.00 (-0.02 to 0.02)	0.93	0.00 (-0.02 to 0.01)	0.9
GDM, I	0.30 (0.04)	0.00 (-0.01 to 0.01)	0.98	-0.01 (-0.03 to 0.01)	0.19	ਊ-0.01 (-0.02 to 0.01)	0.2
maternal pre- pregnancy BN variable (i.e.,	pregnancy BMI, edu /II, education, and to CIMT) was continuo	ear regression models with the f acation, and tobacco smoking; off obacco smoking; offspring family us. The exposure variable was ca and when Model 1 was run in the s	spring fa history o tegorica	mily history of diabetes and sex f diabetes, sex, body surface ar l with 3 levels (Non-GDM/ GDM,	k; Mode rea and non-l/ (age at CIMT assessment. The of Superior of the reference category w	outc outc
maternal pre- pregnancy BM variable (i.e., GDM). Simila	pregnancy BMI, edu /II, education, and to CIMT) was continuo r results were obtain	ucation, and tobacco smoking; off obacco smoking; offspring family us. The exposure variable was ca	ispring fa history o ategorica sample (amily history of diabetes and sev of diabetes, sex, body surface and I with 3 levels (Non-GDM/ GDM, n=165) with data on outcome, e	k; Mode rea and non-I/ (xposure	age at CIMT assessment. The of GDM, I; the reference category w	rnal outco vas N Mode
maternal pre- pregnancy BM variable (i.e., GDM). Simila and 3 (GDM, CIMT, carotid	pregnancy BMI, edu /II, education, and to CIMT) was continuo r results were obtain non-I: 0.00 mm (95 intima-media thickn	ucation, and tobacco smoking; off obacco smoking; offspring family us. The exposure variable was ca ned when Model 1 was run in the s	ispring fa history o ntegorica sample (M, I: -0.0	amily history of diabetes and sex of diabetes, sex, body surface and I with 3 levels (Non-GDM/ GDM, n=165) with data on outcome, ex 01 mm (95% CI: -0.02 to 0.01;	k; Mode rea and non-l/ (xposure p=0.29)	age at CIMT assessment. The of GDM, I; the reference category w and all covariates included in M bbbreviations: CI, confidence bants; p, p-value; sd, standard d	ernal outco vas N Mode inter
maternal pre- pregnancy BN variable (i.e., GDM). Similar and 3 (GDM,	pregnancy BMI, edu /II, education, and to CIMT) was continuo r results were obtain non-I: 0.00 mm (95 intima-media thickn	ucation, and tobacco smoking; off obacco smoking; offspring family us. The exposure variable was ca led when Model 1 was run in the s % Cl: -0.01 to 0.01; p=0.99); GD	ispring fa history o ntegorica sample (M, I: -0.0	amily history of diabetes and sev of diabetes, sex, body surface and I with 3 levels (Non-GDM/ GDM, n=165) with data on outcome, ea 01 mm (95% CI: -0.02 to 0.01;	k; Mode rea and non-l/ (xposure p=0.29)	age at CIMT assessment. The of GDM, I; the reference category w and all covariates included in M bbbreviations: CI, confidence bants; p, p-value; sd, standard d	ernal outco vas N Mode inter
maternal pre- pregnancy BM variable (i.e., GDM). Simila and 3 (GDM, CIMT, carotid	pregnancy BMI, edu /II, education, and to CIMT) was continuo r results were obtain non-I: 0.00 mm (95 intima-media thickn	ucation, and tobacco smoking; off obacco smoking; offspring family us. The exposure variable was ca led when Model 1 was run in the s % Cl: -0.01 to 0.01; p=0.99); GD	ispring fa history o ntegorica sample (M, I: -0.0	amily history of diabetes and sev of diabetes, sex, body surface and I with 3 levels (Non-GDM/ GDM, n=165) with data on outcome, ea 01 mm (95% CI: -0.02 to 0.01;	k; Mode rea and non-l/ (xposure p=0.29)	age at CIMT assessment. The of GDM, I; the reference category w and all covariates included in M bbbreviations: CI, confidence cafts; p, p-value; sd, standard d	ernal outco vas N Mode inter
maternal pre- pregnancy BM variable (i.e., GDM). Simila and 3 (GDM, CIMT, carotid	pregnancy BMI, edu /II, education, and to CIMT) was continuo r results were obtain non-I: 0.00 mm (95 intima-media thickn	ucation, and tobacco smoking; off obacco smoking; offspring family us. The exposure variable was ca led when Model 1 was run in the s % Cl: -0.01 to 0.01; p=0.99); GD	ispring fa history o ntegorica sample (M, I: -0.0	amily history of diabetes and sev of diabetes, sex, body surface and I with 3 levels (Non-GDM/ GDM, n=165) with data on outcome, ea 01 mm (95% CI: -0.02 to 0.01;	k; Mode rea and non-l/ (xposure p=0.29)	GLAM, I; the reference category w and all covariates included in M bbbreviations: CI, confidence catts; p, p-value; sd, standard d	ernal outco vas N Mode inte

Fig. S1 Illustration of the relationship of GDM and assignment or not to a lifestyle and psychosocial intervention with offspring's CIMT through a forest plot.

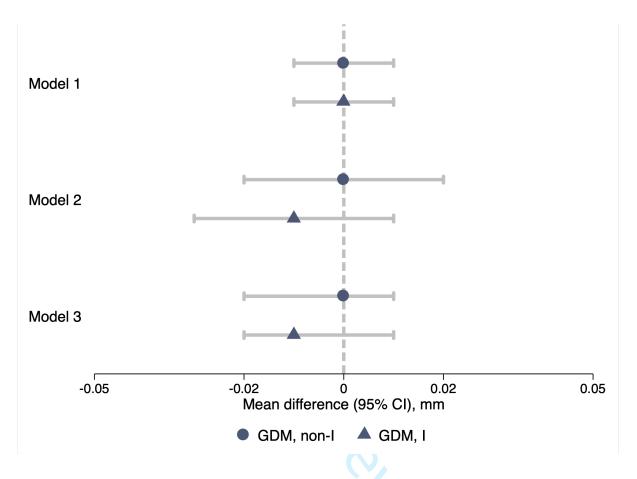


Figure legend The circles represent mean differences in CIMT between offspring of women with GDM assigned to no intervention (*GDM, non-I*) and offspring of women without GDM (*Non-GDM*). The triangles represent mean differences in CIMT between offspring of women with GDM assigned to a lifestyle and psychosocial intervention (*GDM, I*) and offspring of women without GDM (*Non-GDM*). The horizontal lines represent the 95% CIs. The plot was constructed using regression estimates and models presented in Table S1. Model specification: Model 1 is unadjusted, while Models 2 and 3 are adjusted for various factors as described in the methods and footnote of Table S1. Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes; I, intervention.

Fig. S2 Dot plot of CIMT at birth by gestational diabetes mellitus (GDM) and assignment to a lifestyle and psychosocial intervention (I).

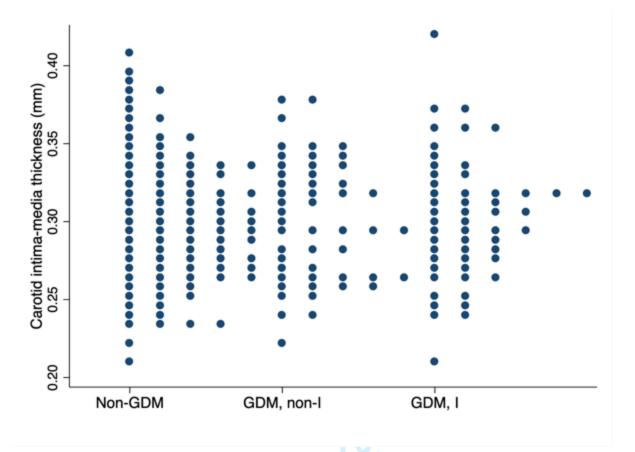


Figure legend This figure shows the distribution of CIMT in the offspring of women without GDM (*Non-GDM*) and the offspring of women with GDM who were assigned to no intervention (*GDM, non-I*) or to a lifestyle and psychosocial intervention (*GDM, I*) as part of their participation in the *MySweetHeart* Trial. Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus; I, intervention.