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# BMJ Open

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

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3 1 **Gestational diabetes mellitus and offspring's carotid intima-media thickness at**  
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5 2 **birth: *MySweetHeart* Cohort Study**  
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12 5 Younes<sup>2</sup>, Arnaud Chiolero<sup>1,4,5¶</sup>, Nicole Sekarski<sup>3¶\*</sup>, on behalf of *MySweetHeart*  
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3 24 **ABSTRACT**

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5 25 **Objective** Hyperglycemia during pregnancy is associated with cardiometabolic risks  
6  
7 26 for the mother and the offspring. Mothers with gestational diabetes mellitus (GDM)  
8  
9 27 have signs of subclinical atherosclerosis, including increased carotid intima-media  
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11 28 thickness (CIMT). We assessed whether GDM is associated with increased CIMT in  
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14 29 the offspring at birth.  
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19 31 **Design and setting** *MySweetHeart* Cohort is a prospective cohort study conducted in  
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21 32 Switzerland.  
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26 34 **Participants, exposure and outcome measures** This work included pregnant  
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28 35 women with and without GDM at 24 to 32 weeks of gestation and their singleton live-  
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30 36 born offspring with data on the primary outcome of CIMT. GDM was diagnosed based  
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32 37 on the criteria of the International Association of Diabetes and Pregnancy Study  
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34 38 Groups. Offspring's CIMT was measured by ultrasonography after birth (range: 1 to 19  
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36 39 days).  
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42 41 **Results** Data on CIMT were available for 99 offspring of women without GDM and 101  
43  
44 42 offspring of women with GDM. Maternal age ranged from 18 to 47 years. Some 16%  
45  
46 43 of women with GDM and 6% of women without GDM were obese. Smoking during  
47  
48 44 pregnancy was more frequent among women with GDM (18%) than among those  
49  
50 45 without GDM (4%). Neonatal characteristics were comparable between the 2 groups.  
51  
52 46 The difference in CIMT between offspring of women with and without GDM was of 0.00  
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54 47 mm (95% CI: -0.01 to 0.01; p=0.96) and remained similar upon adjustment for potential  
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56 48 confounding factors, such as maternal pre-pregnancy BMI, maternal education,  
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3 49 smoking during pregnancy, family history of diabetes, as well as offspring's sex, age,  
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5 50 and body surface area (0.00 mm (95% CI: -0.02 to 0.01; p=0.45)).  
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10 52 **Conclusions** We found no evidence of increased CIMT in neonates exposed to GDM.  
11  
12 53 A longer-term follow-up that includes additional vascular measures, such as  
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14 54 endothelial function or arterial stiffness, may shed further light on the cardiovascular  
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16 55 health trajectories in children born to mothers with GDM.  
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21 57 **Registration** ClinicalTrials.gov (NCT02872974)  
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26 59 **Keywords** gestational diabetes; carotid intima-media thickness; cardiovascular  
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28 60 prevention; child; neonate  
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33 62 **List of abbreviations** BMI, body mass index; CIMT, carotid intima-media thickness;  
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35 63 CVD, cardiovascular disease; CHUV, Lausanne University Hospital; DOHaD,  
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37 64 developmental origins of health and disease; FPG, fasting plasma glucose; GDM,  
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39 65 gestational diabetes mellitus; HbA1c, glycated hemoglobin; IADPSG, International  
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41 66 Association of Diabetes and Pregnancy Study Groups; I, intervention; OGTT, oral  
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44 67 glucose tolerance test.  
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3 68 **Strengths and limitations of this study**  
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- 5 69 • One important strength of this study is represented by its prospective design  
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7  
8 70 and the enrollment of participants at the time of gestational diabetes diagnosis.  
9  
10 71 • Carotid intima-media thickness was measured in non-sedated neonates by  
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12 72 experienced pediatric cardiologists using automated methods with manual  
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14 73 tracing adjustment, in accordance with published guidelines.  
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17 74 • Limitations of this study include the relatively small sample size, the possibility  
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19 75 of residual confounding and the limited generalizability.  
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## 76 INTRODUCTION

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

85  
86 CIMT is a surrogate marker of atherosclerosis, which has been shown to be increased  
87 in children exposed to risk factors in the first 1000 days of life, such as poor fetal  
88 growth,[8] as well as in children with type 1 diabetes.[9] From a developmental origins  
89 of health and disease (DOHaD) perspective,[10] exposure to adverse experiences in  
90 early life may produce lifelong adaptations in the organs' structure and function and  
91 may program the risk for CVD. For instance, a systematic review and meta-analysis  
92 showed that GDM was associated with a higher systolic blood pressure in  
93 childhood.[11] Whether GDM has an impact on children's CIMT is not clearly  
94 established. The evidence is scarce notably in the very young children although CIMT  
95 measurement is feasible from birth and could help discern between changes that occur  
96 before or after birth.[12] To fill this gap, we conducted *MySweetHeart Cohort* study to  
97 assess the early life cardiovascular consequences of GDM.[13] Herein, we evaluated  
98 CIMT at birth in offspring of mothers with and without GDM.

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## 101 **METHODS**

### 102 **Study design and setting**

103 *MySweetHeart Cohort* is a prospective cohort study conducted at the Lausanne  
104 University Hospital (CHUV), Switzerland. The study has been registered with  
105 ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT02872974) and the study protocol  
106 has been published.[13] Ethical approval was granted by the Ethics Committee for  
107 Human Research of the Canton de Vaud (study number 2016-00745).

### 109 **Study population**

110 This cohort included pregnant women between 24 and 32 weeks of gestation, with and  
111 without GDM. Other inclusion criteria were age 18 years or more and understanding  
112 French or English. The exclusion criteria were pre-existing diabetes mellitus, strict bed  
113 rest, or severe mental disorders. To facilitate recruitment and share resources, a  
114 collaboration was established with *MySweetHeart Trial*,[14] a randomized controlled  
115 trial assessing the effect of a lifestyle and psychosocial intervention on cardiometabolic  
116 outcomes of women with GDM and their offspring. As such, women with GDM were  
117 invited to contribute to both studies. Participating women with and without GDM were  
118 included in the current analysis if CIMT data for their live-born singleton neonates were  
119 available. All families gave a signed informed consent for use of their data.

### 121 **Data collection**

#### 122 **GDM screening**

123 Pregnant women screened at the prenatal care clinic of the CHUV had a fasting plasma  
124 glucose (FPG) test between 24 and 28 weeks of gestation and GDM was diagnosed if  
125 the test result was  $\geq 5.1$  mmol/L.[13] If FPG was  $< 5.1$  mmol/L, but  $\geq 4.4$  mmol/L,

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3 126 women had a 2-hour 75 g oral glucose tolerance test (OGTT) and GDM was diagnosed  
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5 127 based on the criteria of the International Association of Diabetes and Pregnancy Study  
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7 128 Groups (IADPSG).[15] Pregnant women screened by external obstetricians in the  
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9 129 Canton of Vaud underwent the same procedure or directly a 2-hour 75 g OGTT.  
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#### 131 Carotid ultrasound and CIMT measurement

132 A carotid ultrasound assessment was performed between 1 and 7 days of life in the  
133 majority of neonates (n=191). A small share (n=9) had the exam between 8 and 19  
134 days of life due to organizational and logistical constraints. Parents were told to feed  
135 and burp their offspring ahead of the carotid ultrasound to make them more relaxed.  
136 Feeding or administration of a 30% glucose solution were used to comfort the neonates  
137 if they became agitated during the exam. The exam took place in a dark and quiet room  
138 and a cloth was placed under the neonates' shoulders to facilitate the extension of the  
139 neck.  
140

141 Ultrasound image acquisition and analysis were performed by 2 experienced pediatric  
142 cardiologists who were blinded to the maternal glycemic status. Images were acquired  
143 in B-mode with no harmonics, sonoCT, dynamic range of 60dB, at a frame rate of 100-  
144 120Hz, with a depth of 1-2 cm. The right and left carotid arteries were scanned using  
145 a Philips EPIC echocardiograph (Philips Medical, Netherlands) with a L 15-7 MHz high-  
146 resolution linear array transducer, according to the American Heart Association's  
147 recommendations for standard assessment of subclinical atherosclerosis in children  
148 and adolescents.[16] Each observer recorded three consecutive 3-second cine loops  
149 from 2 different angles on each side, which were stored as native DICOM for  
150 subsequent offline analyses (QLab, Philips Medical, Netherlands). Whenever image  
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3 151 quality was optimal enough, 6 right and 6 left frames were selected and, for each, the  
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5 152 maximal IMT of the common carotid artery far wall was measured. Measurements were  
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7 153 performed over a 1-cm region of interest proximal to the carotid bulb, on or closest to  
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9 154 the R-wave of the electrocardiogram, using a semi-automated edge detection software  
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11 155 with manual tracing adjustment when needed. The mean of 12 maximal CIMT  
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13 156 measurements was used in the analysis for the majority of neonates (n=170). Two  
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15 157 neonates had only one measurement available, whereas the rest had between 2 and  
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17 158 11 measurements that were averaged. A good interobserver reliability (coefficient of  
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19 159 variation=5.9%) for measurements in non-sedated infants was proven in our laboratory  
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22 160 previously.[12]  
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#### 27 28 162 Other sample characteristics

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30 163 Data on maternal characteristics (age, country of origin, education, smoking during  
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32 164 pregnancy, pre-pregnancy weight and height, or parity) and family history of diabetes  
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34 165 were record-based or self-reported by the mother at a researcher-administered  
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36 166 interview upon inclusion in the study. Smoking during pregnancy was defined as a  
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38 167 mother who was an active tobacco smoker at study baseline, i.e., between 24 and 32  
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40 168 weeks of gestation. A maternal blood sampling was also performed at baseline and  
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42 169 glycated hemoglobin (HbA1c) was measured. Pre-pregnancy body mass index (BMI)  
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44 170 was computed by dividing the pre-pregnancy weight (kg) by the squared height (m<sup>2</sup>).  
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46 171 Delivery data such as newborn sex, anthropometry, gestational age, or mode of  
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48 172 delivery were obtained from the medical records. Neonatal weight, length and blood  
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50 173 pressure were measured by the study team at the time of the carotid ultrasound. Body  
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52 174 surface area (m<sup>2</sup>) was computed using the Mosteller equation.[17] One systolic and  
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54 175 diastolic blood pressure measurement was taken from the right upper arm, in a supine  
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3 176 position, using a clinically validated and regularly calibrated oscillometric  
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5 177 sphygmomanometer (Accutorr Plus; Datascope, Paramus, New Jersey, USA) with  
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8 178 neonate cuffs.  
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## 12 180 **Data analysis**

14 181 Descriptive statistics on study participants are reported as percentages (%) or as  
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16 182 mean, standard deviation, minimum and maximum values. The relationship of GDM  
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18 183 with CIMT was evaluated by a set of linear regression models with and without  
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20 184 adjustment for potential confounders, i.e., baseline covariates associated with  
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22 185 metabolic and cardiovascular risks, offspring's sex, and anthropometry at CIMT  
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24 186 assessment. Potential confounders were maternal pre-pregnancy BMI, maternal  
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26 187 education (university/no university), smoking during pregnancy (yes/no), and family  
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28 188 history of diabetes (yes/no). The variable family history of diabetes summarized  
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30 189 disease occurrence in a 1<sup>st</sup> degree relative of the mother, 1<sup>st</sup> degree relative of the  
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32 190 father or in the father himself and assumed missing data in any of these variables as  
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34 191 no history of diabetes unless values for all 3 variables were missing. To account for  
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36 192 differences in body size,[18,19] we adjusted for body surface area and age at CIMT  
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38 193 assessment. All statistical analyses were performed in Stata 16 (Stata Corporation,  
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40 194 Texas, USA).  
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## 49 196 **RESULTS**

### 51 197 **Characteristics of study participants**

53 198 Data collection started in September 2016 and ended in October 2020. A total of 137  
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55 199 participants without GDM exposure and 212 participants with GDM exposure were  
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57 200 recruited in the study. Some 101 neonates without GDM exposure and 117 neonates  
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3 201 with GDM exposure attended the cardiovascular follow-up visit early after birth. Of  
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5 202 these, 200 singleton neonates born at more than 36 weeks of gestation (non-GDM:  
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7 203 n=99; GDM: n=101) had CIMT measurements and constitute the analytic sample for  
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9 204 the current analysis.  
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12 205

14 206 Family and neonatal characteristics of study participants are presented in Table 1. The  
15  
16 207 maternal characteristics were generally comparable between the non-GDM and GDM  
17  
18 208 groups. The majority of women were non-Swiss and their age ranged from 18 to 47  
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20 209 years. Approximately half of the women in each group had a high level of education  
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22 210 and no previous deliveries. More women with GDM (16%) were obese (pre-pregnancy  
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24 211 BMI  $\geq$  30 kg/m<sup>2</sup>) compared to women without GDM (6%). Smoking during pregnancy  
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26 212 was more frequent among women with GDM (18%) than among those without GDM  
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28 213 (4%). Offspring of women with and without GDM had similar neonatal characteristics,  
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30 214 such as sex, gestational age, birth weight, length, or blood pressure. The majority were  
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32 215 born at term, i.e., between 37 and 41 weeks (GDM: 96%; non-GDM: 98%) and a small  
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34 216 share had macrosomia, i.e., a birth weight higher than 4'000 g (GDM: 6%; non-GDM:  
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36 217 5%). Offspring of women with GDM (46%) had a higher frequency of family history of  
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38 218 diabetes compared to their non-GDM counterparts (24%).  
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219 **Table 1** Characteristics of study participants by GDM exposure.

	Non-GDM <sup>a</sup> (n=99)				GDM <sup>b</sup> (n=101)			
	mean or %	sd	min	max	mean or %	sd	min	max
<b>MATERNAL</b>								
Age (years)	33	5	18	44	33	5	21	47
Swiss origin (%)	24				33			
University education (%)	60				55			
Primiparous (%)	55				48			
Smoking during pregnancy (%)	4				18			
Pre-pregnancy obesity (BMI ≥ 30 kg/m <sup>2</sup> ) (%)	6				16			
HbA1C (%)	4.9	0.3	4.2	5.7	5.3	0.3	4.7	7.2
<b>NEONATAL</b>								
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	442	2'220	4'340
Macrosomia (Birth weight > 4'000 g) (%)	5				6			
Length (cm)	50	2	45	54	50	2	45	56
Body surface area (m <sup>2</sup> )	0.21	0.02	0.16	0.25	0.21	0.02	0.17	0.26
Systolic BP (mmHg)	78	9	60	101	78	10	60	111
Diastolic BP (mmHg)	47	8	30	66	48	10	28	90
Family history of diabetes (%)	24				46			

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.

<sup>a</sup> 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).

<sup>b</sup> GDM: Missing values for age (n=3), swiss origin (n=3), university education (n=18), primiparous (n=3), smoking (n=5), pre-pregnancy 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).

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3 221 **GDM and CIMT at birth**  
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5 222 The distribution of CIMT values is presented in Fig. 1 and Fig. 2. CIMT ranged from  
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7 223 0.21 to 0.42 mm, with a mean CIMT of 0.30 mm (sd 0.04) overall and in each of the  
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9 224 studied groups (Table 2, Table S1 in Supplementary Material).  
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14 226 **Fig. 1** Histograms of CIMT at birth, overall and by GDM exposure.  
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16 227 **Figure legend** This figure shows the distribution of CIMT values in our sample, overall  
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18 228 (n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line  
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20 229 represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media  
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22 230 thickness; GDM, gestational diabetes mellitus.  
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28 232 **Fig. 2** Box plots of CIMT at birth by GDM exposure and assignment to a lifestyle and  
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30 233 psychosocial intervention.  
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32 234 **Figure legend** This figure shows the distribution of CIMT in the offspring of women  
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34 235 without GDM (*Non-GDM*; n=99) and the offspring of women with GDM who were  
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36 236 assigned to no intervention (*GDM, non-I*; n=48) or to a lifestyle and psychosocial  
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38 237 intervention (*GDM, I*; n=53) as part of their participation in the *MySweetHeart* Trial.  
39  
40 238 Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes  
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42 239 mellitus; I, intervention.  
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240 **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	p	Difference (95% CI), mm	p	Difference (95% CI), mm	p
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	0.00 (-0.02 to 0.01)	0.45

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.

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.

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 and 3 (GDM: 0.00 mm (95% CI: -0.02 to 0.01; p=0.54)).



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3 242 The relationship of GDM with offspring's CIMT early after birth is presented in Table 2.  
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5 243 In the unadjusted analysis (Model 1), the difference in CIMT between offspring of  
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7 244 women with and without GDM was 0.00 mm (95% CI -0.01 to 0.01; p=0.96).  
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9 245 Adjustment for offspring sex and potential confounding factors (Model 2), as well as for  
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11 246 offspring's body surface area and age at CIMT assessment (Model 3), resulted in a  
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13 247 difference of 0 mm (95% CI -0.02 to 0.01; p=0.45). When exposure to GDM was  
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15 248 analyzed separately for offspring whose mothers were assigned or not to a lifestyle  
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17 249 and psychosocial intervention as part of their participation in *MySweetHeart* Trial,  
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19 250 results were similar to those presented above (Table S1 in Supplementary Material).  
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## 252 **DISCUSSION**

### 253 **Summary of findings and comparison with other studies**

254 Our goal was to assess the relationship of GDM with neonatal CIMT. We found no  
255 evidence of an increased CIMT in neonates born to women with GDM as compared to  
256 those born to women without GDM. Our findings are in line with other studies that  
257 evaluated CIMT after intrauterine exposure to maternal hyperglycemia. A recent meta-  
258 analysis pooled data from 3 studies and reported no clear evidence of increased CIMT  
259 in children exposed to maternal hyperglycemia compared to those not exposed (pooled  
260 standardized mean difference (SMD): 0.08 (95% CI -0.16 to 0.33)).[8] Two of these  
261 studies included 6-year and 8-year children, respectively, and found no difference in  
262 CIMT after exposure to GDM (SMD 0.00 (95% CI -0.28 to 0.28) at 6 years and 0.00  
263 (95% CI -0.41 to 0.41) at 8 years).[8,20,21] The third study included neonates and  
264 found a slightly higher CIMT among those exposed to diabetes (SMD 0.46 (95% CI -  
265 0.07 to 1.00)),[8,22] but the imprecision around the estimated difference was high, the

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3 266 study had a very small sample size (n=55) and the authors did not specify whether  
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5 267 they included women with pre-gestational or gestational diabetes.[22]  
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### 10 269 **Strengths and limitations**

11  
12 270 A major strength of this study is its prospective design. Enrollment of study participants  
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14 271 and collection of baseline characteristics took place close to the moment of GDM  
15  
16 272 diagnosis and ahead of the CIMT outcome assessment. This implies that the choice of  
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18 273 participation in the study is unlikely to be related to both the exposure and the outcome,  
19  
20 274 which makes selection bias due to enrollment unlikely. Further, GDM was diagnosed  
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22 275 using the new criteria of the IADPG. These criteria were derived based on the risk of  
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24 276 adverse neonatal outcomes, such as birth weight, cord blood C-peptide levels, or  
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26 277 percent infant body fat > 90th percentile.[15] They were endorsed by the World Health  
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28 278 Organization along with several other bodies to achieve a universal consensus for  
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30 279 GDM diagnosis and increase comparability of the evidence.[23,24] Another strength is  
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32 280 the assessment of ultrasound CIMT using automated methods with manual tracing  
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34 281 adjustment, in accordance with the current guidelines in children.[16,25] The semi-  
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36 282 automated methods are associated with a lower interoperator variability and high  
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38 283 reliability,[16,25] including in infants, as it was previously proved in our laboratory.[12]  
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47 285 This study has some limitations. Firstly, our results have limited generalizability, as we  
48  
49 286 used a convenient sample of pregnant women recruited from health care facilities in  
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51 287 Switzerland. Secondly, the GDM glucose screening test (FPG or 75-g OGTT) varied  
52  
53 288 between participants. This is because our hospital used a 2-step targeted approach for  
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55 289 identifying women with GDM. While the 2-step approach is practical and more  
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57 290 acceptable to patients,[26] it may be related to a lower likelihood of diagnosing GDM  
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3 291 compared to a one-step universal screening based on a 75-g OGTT.[27] On the other  
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5 292 hand, the IADGSP criteria, which have a lower threshold for a positive FPG test ( $\geq 5.1$   
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7 293 mmol/L) compared to other guidelines,[23] may identify as having GDM women who  
8  
9 294 are at low absolute risk for fetal and pregnancy complications and, thus, overdiagnose  
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11 295 GDM in some populations.[28,29] Therefore, misclassification of the exposure cannot  
12  
13 296 be excluded and our estimates of association might be biased, maybe underestimated.  
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15 297 Additionally, women with GDM participated in *MySweetHeart* Trial and approximately  
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17 298 half of them were assigned to a lifestyle and psychosocial intervention with the aim of  
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19 299 improving their cardiometabolic outcomes. Although this intervention could have also  
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21 300 modified the association of GDM with CIMT, this seems not likely, as mean CIMT  
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23 301 values were very similar in offspring of women with GDM who participated in the  
24  
25 302 intervention and the control arms of the trial. Thirdly, CIMT was assessed using  
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27 303 conventional high-resolution ultrasound frequencies ( $< 15$  MHz), which tend to  
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29 304 overestimate the arterial thickness in the young children when compared to very high-  
30  
31 305 resolution ultrasound systems (25 to 55 MHz).[30,31] Measurement error in CIMT  
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33 306 cannot be excluded, but systematic differences between the two groups are unlikely  
34  
35 307 because the outcome assessors were blinded to the glycemic status of the mothers.  
36  
37 308 Fourthly, while we adjusted for key confounders at the analysis stage, there is a  
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39 309 possibility of residual confounding due to the relatively small sample size and some  
40  
41 310 imprecision in the measurement of confounder variables, especially in those self-  
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43 311 reported. Lastly, our study was limited to CIMT, which is a measure of arterial structure.  
44  
45 312 In fact, changes in the vessel function might occur earlier than changes in the vessel  
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47 313 structure, therefore, a combination of vascular measures would be needed for a clearer  
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49 314 view on the cardiovascular status of children exposed to adverse experiences in early  
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51 315 life. However, certain techniques to assess arterial function and stiffness, such as flow-  
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3 316 mediated dilation and pulse-wave velocity, are not currently feasible in the very young  
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5 317 due to limited compliance and technical inconveniences.[18]  
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### 10 319 **Implications and future research**

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12 320 Our results suggest that intrauterine exposure to GDM does not induce changes in the  
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14 321 carotid artery structure that are detectable with conventional ultrasound techniques at  
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16 322 birth and may not be linked to early vascular aging at this arterial site in the short term.  
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18 323 Measurements at other arterial sites, such as the aorta,[32] may be more useful to  
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20 324 investigate early or subtle abnormalities related to accelerated vascular aging or  
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22 325 subclinical atherosclerosis. A long-term follow-up that includes complementary  
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24 326 vascular measures, for instance, endothelium-dependent and endothelium-  
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26 327 independent vasodilation or large-artery stiffness,[20] may shed further light on the  
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28 328 cardiovascular health of children born to mothers with GDM.  
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### 33 329 34 35 330 **Patient and public involvement**

36  
37 331 There was no patient or public involvement in the design, conduct, analysis, or  
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39 332 reporting of this study's findings.  
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343

### 344 **Authors' contributions**

345 AC, NS, SDB, and YM designed the study and the data collection procedures with  
346 input from SEY, AME. SEY and AME collected baseline characteristics for participants  
347 without GDM. SDB and NS collected neonatal cardiovascular characteristics for all  
348 participants. SEY performed data management and curation. AME carried out the  
349 statistical analyses with input and supervision from AC. AME wrote the first draft of the  
350 manuscript with input from AC and NS. SDB, SEY, YM made critical revisions to the  
351 manuscript for important intellectual content. All authors read and approved the content  
352 of the manuscript.

353

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6  
7 367 number 32003B\_176119). The funder had no role in the study design, data collection  
8  
9 368 and analysis, or interpretation of results.  
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12 369

### 14 370 **Competing interests**

16 371 None declared.  
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### 21 373 **Consent for publication**

23 374 Not applicable.  
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### 28 376 **Ethics approval**

30 377 Ethical approval was obtained through the Ethics Committee for Human Research of  
31  
32 378 the Canton of Vaud (2016–00745).  
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35 379

### 37 380 **Data availability statement**

39 381 Data could be made available by the principal investigator and corresponding author  
40  
41 382 (Prof Nicole Sekarski: [nicole.sekarski@chuv.ch](mailto:nicole.sekarski@chuv.ch)) on reasonable request.  
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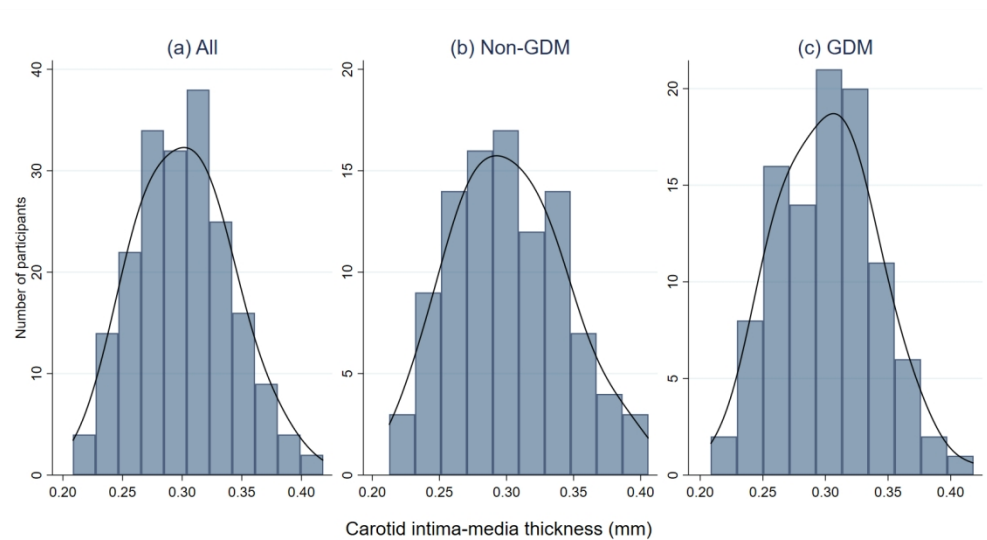
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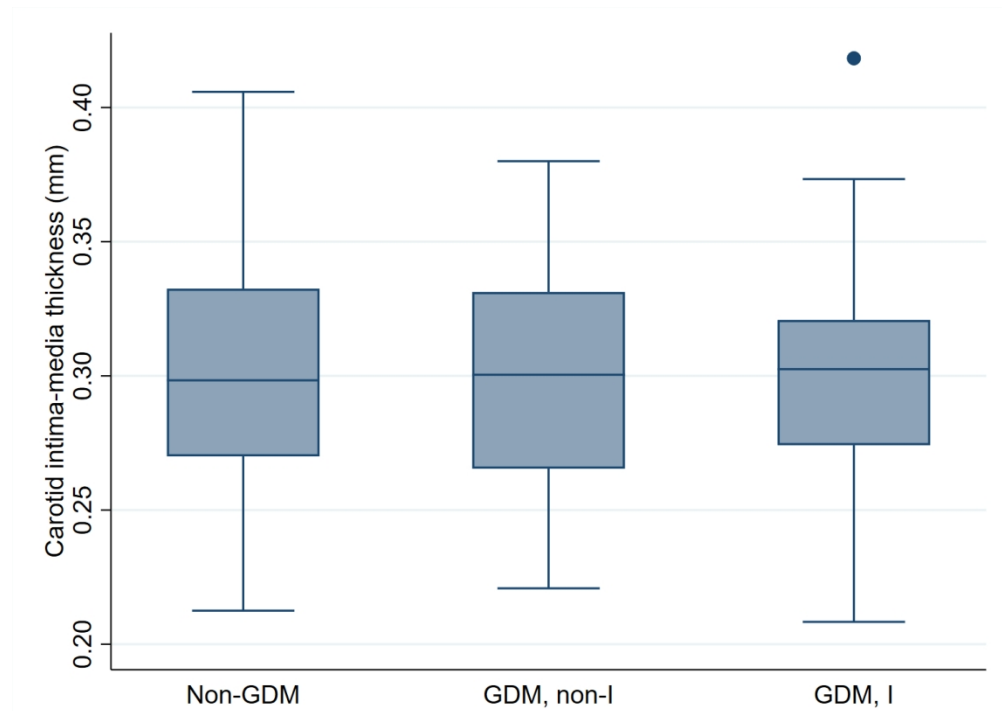
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This figure shows the distribution of CIMT values in our sample, overall (n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus.

599x326mm (72 x 72 DPI)



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.

543x395mm (72 x 72 DPI)

## SUPPLEMENTARY MATERIAL

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

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¶ These authors contributed equally to this work.

**Table S1** Differences in CIMT at birth by GDM exposure and assignment to a lifestyle and psychosocial intervention.

	Mean (sd), mm	<b>Model 1 (n=200)</b>		<b>Model 2 (n=165)</b>		<b>Model 3 (n=165)</b>	
		Difference (95% CI), mm	p	Difference (95% CI), mm	p	Difference (95% CI), mm	p
Non-GDM	0.30 (0.04)	ref	ref	ref	ref	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)	0.91
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 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.

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

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies* [1]**

Section/Topic	Item #	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 [page 1]
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract [page 2-3]
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction (paragraphs 1-2) [page 5]
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction (paragraph 2) [page 5]
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	- Methods (subheadings: Study design and setting; Study population) [page 6] - Published 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] - Published protocol (see reference [2])
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	- Methods (subheadings: Study population) [page 6] - Published protocol (see reference [2])
		(b) For matched studies, give matching criteria and number of exposed and unexposed	- N/A
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]
Bias	9	Describe any efforts to address potential sources of bias	- Methods (subheadings: Data analysis) [page 9] - Discussion (subheadings: Strengths and limitations) [page 15-16]



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	- Methods (subheadings: Data analysis) [page 9]
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	- Methods (subheadings: Study population; Data analysis) [page 6; 9] - Table 1 footnote [page 11]
		(d) If applicable, explain how loss to follow-up was addressed	- Methods (subheadings: Study population) [page 6]
		(e) Describe any sensitivity analyses	- Supplementary material (Table S1)
<b>Results</b>			
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 information on exposures and potential confounders	- Results (subheadings: Characteristics of study participants; Table 1) [page 10-11]
		(b) Indicate number of participants with missing data for each variable of interest	- Results (Table 1) [page 11]
		(c) Summarise follow-up time (eg, average and total amount)	- Methods (subheadings: Study population; Carotid ultrasound 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	(a) 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	- Results (Table 2) [page 13]
		(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	- N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	- Supplementary material (Table S1)

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

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

**Note:** Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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1. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *PLOS Medicine* 2007;4(10):e296. doi: 10.1371/journal.pmed.0040296.
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# BMJ Open

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

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3 1 **Gestational diabetes mellitus and offspring's carotid intima-media thickness at**  
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5 2 **birth: *MySweetHeart* Cohort Study**  
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10 4 Adina Mihaela Epure<sup>1,2</sup>, Stefano Di Bernardo<sup>3</sup>, Yvan Mivelaz<sup>3</sup>, Sandrine Estoppey  
11  
12 5 Younes<sup>2</sup>, Arnaud Chiolero<sup>1,4,5¶</sup>, Nicole Sekarski<sup>3¶\*</sup>, on behalf of *MySweetHeart*  
13  
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3 24 **ABSTRACT**

4  
5 25 **Objective** Hyperglycemia during pregnancy is associated with cardiometabolic risks  
6  
7 26 for the mother and the offspring. Mothers with gestational diabetes mellitus (GDM)  
8  
9 27 have signs of subclinical atherosclerosis, including increased carotid intima-media  
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11 28 thickness (CIMT). We assessed whether GDM is associated with increased CIMT in  
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14 29 the offspring at birth.  
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19 31 **Design and setting** *MySweetHeart* Cohort is a prospective cohort study conducted in  
20  
21 32 Switzerland.  
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26 34 **Participants, exposure and outcome measures** This work included pregnant  
27  
28 35 women with and without GDM at 24 to 32 weeks of gestation and their singleton live-  
29  
30 36 born offspring with data on the primary outcome of CIMT. GDM was diagnosed based  
31  
32 37 on the criteria of the International Association of Diabetes and Pregnancy Study  
33  
34 38 Groups. Offspring's CIMT was measured by ultrasonography after birth (range: 1 to 19  
35  
36 39 days).  
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42 41 **Results** Data on CIMT were available for 99 offspring of women without GDM and 101  
43  
44 42 offspring of women with GDM. Maternal age ranged from 18 to 47 years. Some 16%  
45  
46 43 of women with GDM and 6% of women without GDM were obese. Smoking during  
47  
48 44 pregnancy was more frequent among women with GDM (18%) than among those  
49  
50 45 without GDM (4%). Neonatal characteristics were comparable between the 2 groups.  
51  
52 46 The difference in CIMT between offspring of women with and without GDM was of 0.00  
53  
54 47 mm (95% CI: -0.01 to 0.01; p=0.96) and remained similar upon adjustment for potential  
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56 48 confounding factors, such as maternal pre-pregnancy BMI, maternal education,  
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3 49 smoking during pregnancy, family history of diabetes, as well as offspring's sex, age,  
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5 50 and body surface area (0.00 mm (95% CI: -0.02 to 0.01; p=0.45)).  
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10 52 **Conclusions** We found no evidence of increased CIMT in neonates exposed to GDM.  
11  
12 53 A longer-term follow-up that includes additional vascular measures, such as  
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14 54 endothelial function or arterial stiffness, may shed further light on the cardiovascular  
15  
16 55 health trajectories in children born to mothers with GDM.  
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21 57 **Registration** ClinicalTrials.gov (NCT02872974)  
22  
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24 58

25  
26 59 **Keywords** gestational diabetes; carotid intima-media thickness; cardiovascular  
27  
28 60 prevention; child; neonate  
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31 61

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33 62 **List of abbreviations** BMI, body mass index; CIMT, carotid intima-media thickness;  
34  
35 63 CVD, cardiovascular disease; CHUV, Lausanne University Hospital; DOHaD,  
36  
37 64 developmental origins of health and disease; FPG, fasting plasma glucose; GDM,  
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39 65 gestational diabetes mellitus; HbA1c, glycated hemoglobin; IADPSG, International  
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41 66 Association of Diabetes and Pregnancy Study Groups; I, intervention; OGTT, oral  
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44 67 glucose tolerance test.  
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3 68 **Strengths and limitations of this study**  
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- 5 69 • One important strength of this study is represented by its prospective design  
6  
7 70 and the enrollment of participants at the time of gestational diabetes diagnosis.  
8  
9  
10 71 • Carotid intima-media thickness was measured in non-sedated neonates by  
11  
12 72 experienced pediatric cardiologists using automated methods with manual  
13  
14 73 tracing adjustment, in accordance with published guidelines.  
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17 74 • Limitations of this study include the relatively small sample size, the possibility  
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19 75 of residual confounding and the limited generalizability.  
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## 76 INTRODUCTION

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

85  
86 CIMT is a surrogate marker of atherosclerosis, which has been shown to be increased  
87 in children exposed to risk factors in the first 1000 days of life, such as poor fetal  
88 growth,[8] as well as in children with type 1 diabetes.[9] From a developmental origins  
89 of health and disease (DOHaD) perspective,[10] exposure to adverse experiences in  
90 early life may produce lifelong adaptations in the organs' structure and function and  
91 may program the risk for CVD. For instance, a systematic review and meta-analysis  
92 showed that GDM was associated with a higher systolic blood pressure in  
93 childhood.[11] Whether GDM has an impact on children's CIMT is not clearly  
94 established. The evidence is scarce notably in the very young children although CIMT  
95 measurement is feasible from birth and could help discern between changes that occur  
96 before or after birth.[12] To fill this gap, we conducted *MySweetHeart Cohort* study to  
97 assess the early life cardiovascular consequences of GDM.[13] Herein, we evaluated  
98 CIMT at birth in offspring of mothers with and without GDM.

100

## 101 **METHODS**

### 102 **Study design and setting**

103 *MySweetHeart Cohort* is a prospective cohort study conducted at the Lausanne  
104 University Hospital (CHUV), Switzerland. The study has been registered with  
105 ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT02872974) and the study protocol  
106 has been published.[13] Ethical approval was granted by the Ethics Committee for  
107 Human Research of the Canton de Vaud (study number 2016-00745).

### 109 **Study population**

110 This cohort included pregnant women between 24 and 32 weeks of gestation, with and  
111 without GDM. Other inclusion criteria were age 18 years or more and understanding  
112 French or English. The exclusion criteria were pre-existing diabetes mellitus, strict bed  
113 rest, or severe mental disorders. To facilitate recruitment and share resources, a  
114 collaboration was established with *MySweetHeart Trial*,[14] a randomized controlled  
115 trial assessing the effect of a lifestyle and psychosocial intervention on cardiometabolic  
116 outcomes of women with GDM and their offspring. As such, women with GDM were  
117 invited to contribute to both studies. Participating women with and without GDM were  
118 included in the current analysis if CIMT data for their live-born singleton neonates were  
119 available. All families gave a signed informed consent for use of their data.

### 121 **Data collection**

#### 122 **GDM screening**

123 Pregnant women screened at the prenatal care clinic of the CHUV had a fasting plasma  
124 glucose (FPG) test between 24 and 28 weeks of gestation and GDM was diagnosed if  
125 the test result was  $\geq 5.1$  mmol/L.[13] If FPG was  $< 5.1$  mmol/L, but  $\geq 4.4$  mmol/L,

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3 126 women had a 2-hour 75 g oral glucose tolerance test (OGTT) and GDM was diagnosed  
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5 127 based on the criteria of the International Association of Diabetes and Pregnancy Study  
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7 128 Groups (IADPSG).[15] Pregnant women screened by external obstetricians in the  
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9 129 Canton of Vaud underwent the same procedure or directly a 2-hour 75 g OGTT.  
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### 131 Carotid ultrasound and CIMT measurement

132 A carotid ultrasound assessment was performed between 1 and 7 days of life in the  
133 majority of neonates (n=191). A small share (n=9) had the exam between 8 and 19  
134 days of life due to organizational and logistical constraints. Parents were told to feed  
135 and burp their offspring ahead of the carotid ultrasound to make them more relaxed.  
136 Feeding or administration of a 30% glucose solution were used to comfort the neonates  
137 if they became agitated during the exam. The exam took place in a dark and quiet room  
138 and a cloth was placed under the neonates' shoulders to facilitate the extension of the  
139 neck.  
140

141 Ultrasound image acquisition and analysis were performed by 2 experienced pediatric  
142 cardiologists who were blinded to the maternal glycemic status. Images were acquired  
143 in B-mode with no harmonics, sonoCT, dynamic range of 60dB, at a frame rate of 100-  
144 120Hz, with a depth of 1-2 cm. The right and left carotid arteries were scanned using  
145 a Philips EPIC echocardiograph (Philips Medical, Netherlands) with a L 15-7 MHz high-  
146 resolution linear array transducer, according to the American Heart Association's  
147 recommendations for standard assessment of subclinical atherosclerosis in children  
148 and adolescents.[16] Each observer recorded three consecutive 3-second cine loops  
149 from 2 different angles on each side, which were stored as native DICOM for  
150 subsequent offline analyses (QLab, Philips Medical, Netherlands). Whenever image  
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3 151 quality was optimal enough, 6 right and 6 left frames were selected and, for each, the  
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5 152 maximal IMT of the common carotid artery far wall was measured. Measurements were  
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7 153 performed over a 1-cm region of interest proximal to the carotid bulb, on or closest to  
8  
9 154 the R-wave of the electrocardiogram, using a semi-automated edge detection software  
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11 155 with manual tracing adjustment when needed. The mean of 12 maximal CIMT  
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13 156 measurements was used in the analysis for the majority of neonates (n=170). Two  
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15 157 neonates had only one measurement available, whereas the rest had between 2 and  
16  
17 158 11 measurements that were averaged. A good interobserver reliability (coefficient of  
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19 159 variation=5.9%) for measurements in non-sedated infants was proven in our laboratory  
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22 160 previously.[12]  
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#### 27 28 162 Other sample characteristics

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30 163 Data on maternal characteristics (age, country of origin, education, smoking during  
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32 164 pregnancy, pre-pregnancy weight and height, or parity) and family history of diabetes  
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34 165 were record-based or self-reported by the mother at a researcher-administered  
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36 166 interview upon inclusion in the study. Smoking during pregnancy was defined as a  
37  
38 167 mother who was an active tobacco smoker at study baseline, i.e., between 24 and 32  
39  
40 168 weeks of gestation. A maternal blood sampling was also performed at baseline and  
41  
42 169 glycated hemoglobin (HbA1c) was measured. Pre-pregnancy body mass index (BMI)  
43  
44 170 was computed by dividing the pre-pregnancy weight (kg) by the squared height (m<sup>2</sup>).  
45  
46 171 Delivery data such as newborn sex, anthropometry, gestational age, or mode of  
47  
48 172 delivery were obtained from the medical records. Neonatal weight, length and blood  
49  
50 173 pressure were measured by the study team at the time of the carotid ultrasound. Body  
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52 174 surface area (m<sup>2</sup>) was computed using the Mosteller equation.[17] One systolic and  
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54 175 diastolic blood pressure measurement was taken from the right upper arm, in a supine  
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3 176 position, using a clinically validated and regularly calibrated oscillometric  
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5 177 sphygmomanometer (Accutorr Plus; Datascope, Paramus, New Jersey, USA) with  
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8 178 neonate cuffs.  
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## 12 180 **Data analysis**

14 181 Descriptive statistics on study participants are reported as percentages (%) or as  
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16 182 mean, standard deviation, minimum and maximum values. The relationship of GDM  
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18 183 with CIMT was evaluated by a set of linear regression models with and without  
19  
20 184 adjustment for potential confounders, i.e., baseline covariates associated with  
21  
22 185 metabolic and cardiovascular risks, offspring's sex, and anthropometry at CIMT  
23  
24 186 assessment. Potential confounders were maternal pre-pregnancy BMI, maternal  
25  
26 187 education (university/no university), smoking during pregnancy (yes/no), and family  
27  
28 188 history of diabetes (yes/no). The variable family history of diabetes summarized  
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30 189 disease occurrence in a 1<sup>st</sup> degree relative of the mother, 1<sup>st</sup> degree relative of the  
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32 190 father or in the father himself and assumed missing data in any of these variables as  
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34 191 no history of diabetes unless values for all 3 variables were missing. To account for  
35  
36 192 differences in body size,[18,19] we adjusted for body surface area and age at CIMT  
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38 193 assessment. All statistical analyses were performed in Stata 16 (Stata Corporation,  
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40 194 Texas, USA).  
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## 49 196 **RESULTS**

### 51 197 **Characteristics of study participants**

53 198 Data collection started in September 2016 and ended in October 2020. A total of 137  
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55 199 participants without GDM exposure and 212 participants with GDM exposure were  
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57 200 recruited in the study. Some 101 neonates without GDM exposure and 117 neonates  
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3 201 with GDM exposure attended the cardiovascular follow-up visit early after birth. Of  
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5 202 these, 200 singleton neonates born at more than 36 weeks of gestation (non-GDM:  
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7 203 n=99; GDM: n=101) had CIMT measurements and constitute the analytic sample for  
8  
9 204 the current analysis.  
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12 205

14 206 Family and neonatal characteristics of study participants are presented in Table 1. The  
15  
16 207 maternal characteristics were generally comparable between the non-GDM and GDM  
17  
18 208 groups. The majority of women were non-Swiss and their age ranged from 18 to 47  
19  
20 209 years. Approximately half of the women in each group had a high level of education  
21  
22 210 and no previous deliveries. More women with GDM (16%) were obese (pre-pregnancy  
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24 211 BMI  $\geq$  30 kg/m<sup>2</sup>) compared to women without GDM (6%). Smoking during pregnancy  
25  
26 212 was more frequent among women with GDM (18%) than among those without GDM  
27  
28 213 (4%). Offspring of women with and without GDM had similar neonatal characteristics,  
29  
30 214 such as sex, gestational age, birth weight, length, or blood pressure. The majority were  
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32 215 born at term, i.e., between 37 and 41 weeks (GDM: 96%; non-GDM: 98%) and a small  
33  
34 216 share had macrosomia, i.e., a birth weight higher than 4'000 g (GDM: 6%; non-GDM:  
35  
36 217 5%). Offspring of women with GDM (46%) had a higher frequency of family history of  
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38 218 diabetes compared to their non-GDM counterparts (24%).  
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219 **Table 1** Characteristics of study participants by GDM exposure.

	Non-GDM <sup>a</sup> (n=99)				GDM <sup>b</sup> (n=101)			
	mean or %	sd	min	max	mean or %	sd	min	max
<b>MATERNAL</b>								
Age (years)	33	5	18	44	33	5	21	47
Swiss origin (%)	24				33			
University education (%)	60				55			
Primiparous (%)	55				48			
Smoking during pregnancy (%)	4				18			
Pre-pregnancy obesity (BMI ≥ 30 kg/m <sup>2</sup> ) (%)	6				16			
HbA1C (%)	4.9	0.3	4.2	5.7	5.3	0.3	4.7	7.2
<b>NEONATAL</b>								
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	442	2'220	4'340
Macrosomia (Birth weight > 4'000 g) (%)	5				6			
Length (cm)	50	2	45	54	50	2	45	56
Body surface area (m <sup>2</sup> )	0.21	0.02	0.16	0.25	0.21	0.02	0.17	0.26
Systolic BP (mmHg)	78	9	60	101	78	10	60	111
Diastolic BP (mmHg)	47	8	30	66	48	10	28	90
Family history of diabetes (%)	24				46			

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.

<sup>a</sup> 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).

<sup>b</sup> GDM: Missing values for age (n=3), swiss origin (n=3), university education (n=18), primiparous (n=3), smoking (n=5), pre-pregnancy 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).

### 221 **GDM and CIMT at birth**

222 The distribution of CIMT values is presented in Fig. 1, Fig. 2, and Fig. S2 in  
223 Supplementary Material. CIMT ranged from 0.21 to 0.42 mm, with a mean CIMT of  
224 0.30 mm (sd 0.04) overall and in each of the studied groups (Table 2, Table S1 in  
225 Supplementary Material).

227 **Fig. 1** Histograms of CIMT at birth, overall and by GDM exposure.

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

233 **Fig. 2** Box plots of CIMT at birth by GDM exposure and assignment to a lifestyle and  
234 psychosocial intervention.

235 **Figure legend** This figure shows the distribution of CIMT in the offspring of women  
236 without GDM (*Non-GDM*; n=99) and the offspring of women with GDM who were  
237 assigned to no intervention (*GDM, non-I*; n=48) or to a lifestyle and psychosocial  
238 intervention (*GDM, I*; n=53) as part of their participation in the *MySweetHeart* Trial. The  
239 line inside the box represents the median value of the distribution, while the lower and  
240 upper boundaries of the box represent the first (Q1) and third quartiles (Q3),  
241 respectively. The interquartile range (IQR) corresponds to  $Q3 - Q1$ . The whiskers  
242 extend from either side of the box up to  $1.5 \cdot IQR$  (i.e.,  $Q1 - 1.5 \cdot IQR$  and  $Q3 + 1.5 \cdot IQR$ ).  
243 Outliers are depicted as circles. Abbreviations: CIMT, carotid intima-media thickness;  
244 GDM, gestational diabetes mellitus; I, intervention.



245 **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)	
		Mean difference (95% CI), mm	p	Mean difference (95% CI), mm	p	Mean difference (95% CI), mm	p
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	0.00 (-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 was 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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3 247 The relationship of GDM with offspring's CIMT early after birth is presented in Table 2  
4  
5 248 and Fig. 3. In the unadjusted analysis (Model 1), the difference in CIMT between  
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7 249 offspring of women with and without GDM was 0.00 mm (95% CI -0.01 to 0.01; p=0.96).  
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10 250 Adjustment for offspring sex and potential confounding factors (Model 2), as well as for  
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12 251 offspring's body surface area and age at CIMT assessment (Model 3), resulted in a  
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14 252 difference of 0 mm (95% CI -0.02 to 0.01; p=0.45). When exposure to GDM was  
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17 253 analyzed separately for offspring whose mothers were assigned or not to a lifestyle  
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19 254 and psychosocial intervention as part of their participation in *MySweetHeart* Trial,  
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21 255 results were similar to those presented above (Table S1 and Fig. S1 in Supplementary  
22  
23  
24 256 Material).

257

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

260 **Figure legend** The boxes represent the mean differences in CIMT between offspring  
261 of women with and without GDM (i.e., GDM versus non-GDM). The horizontal lines  
262 represent the 95% CIs. The plot was constructed using regression estimates and  
263 models presented in Table 2. Model specification: Model 1 is unadjusted, while Models  
264 2 and 3 are adjusted for various factors as described in the methods and footnote of  
265 Table 2. Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness;  
266 GDM, gestational diabetes mellitus.

267

## 268 **DISCUSSION**

### 269 **Summary of findings and comparison with other studies**

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

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3 272 those born to women without GDM. Our findings are in line with other studies that  
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5 273 evaluated CIMT after intrauterine exposure to maternal hyperglycemia. A recent meta-  
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7 274 analysis pooled data from 3 studies and reported no clear evidence of increased CIMT  
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10 275 in children exposed to maternal hyperglycemia compared to those not exposed (pooled  
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12 276 standardized mean difference (SMD): 0.08 (95% CI -0.16 to 0.33)).[8] Two of these  
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14 277 studies included 6-year and 8-year children, respectively, and found no difference in  
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16  
17 278 CIMT after exposure to GDM (SMD 0.00 (95% CI -0.28 to 0.28) at 6 years and 0.00  
18  
19 279 (95% CI -0.41 to 0.41) at 8 years).[8,20,21] The third study included neonates and  
20  
21 280 found a slightly higher CIMT among those exposed to diabetes (SMD 0.46 (95% CI -  
22  
23 281 0.07 to 1.00)),[8,22] but the imprecision around the estimated difference was high, the  
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25 282 study had a very small sample size (n=55) and the authors did not specify whether  
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27  
28 283 they included women with pre-gestational or gestational diabetes.[22]  
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31 284

### 32 33 285 **Strengths and limitations**

34  
35 286 A major strength of this study is its prospective design. Enrollment of study participants  
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37 287 and collection of baseline characteristics took place close to the moment of GDM  
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40 288 diagnosis and ahead of the CIMT outcome assessment. This implies that the choice of  
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42 289 participation in the study is unlikely to be related to both the exposure and the outcome,  
43  
44 290 which makes selection bias due to enrollment unlikely. Further, GDM was diagnosed  
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47 291 using the new criteria of the IADPG. These criteria were derived based on the risk of  
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49 292 adverse neonatal outcomes, such as birth weight, cord blood C-peptide levels, or  
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51 293 percent infant body fat > 90th percentile.[15] They were endorsed by the World Health  
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53 294 Organization along with several other bodies to achieve a universal consensus for  
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56 295 GDM diagnosis and increase comparability of the evidence.[23,24] Another strength is  
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58 296 the assessment of ultrasound CIMT using automated methods with manual tracing  
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3 297 adjustment, in accordance with the current guidelines in children.[16,25] The semi-  
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5 298 automated methods are associated with a lower interoperator variability and high  
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7 299 reliability,[16,25] including in infants, as it was previously proved in our laboratory.[12]  
8  
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10 300  
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12 301 This study has some limitations. Firstly, our results have limited generalizability, as we  
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14 302 used a convenient sample of pregnant women recruited from health care facilities in  
15  
16 303 Switzerland. Secondly, the GDM glucose screening test (FPG or 75-g OGTT) varied  
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18 304 between participants. This is because our hospital used a 2-step targeted approach for  
19  
20 305 identifying women with GDM. While the 2-step approach is practical and more  
21  
22 306 acceptable to patients,[26] it may be related to a lower likelihood of diagnosing GDM  
23  
24 307 compared to a one-step universal screening based on a 75-g OGTT.[27] On the other  
25  
26 308 hand, the IADGSP criteria, which have a lower threshold for a positive FPG test ( $\geq 5.1$   
27  
28 309 mmol/L) compared to other guidelines,[23] may identify as having GDM women who  
29  
30 310 are at low absolute risk for fetal and pregnancy complications and, thus, overdiagnose  
31  
32 311 GDM in some populations.[28,29] Therefore, misclassification of the exposure cannot  
33  
34 312 be excluded and our estimates of association might be biased, maybe underestimated.  
35  
36 313 Additionally, women with GDM participated in *MySweetHeart* Trial and approximately  
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38 314 half of them were assigned to a lifestyle and psychosocial intervention with the aim of  
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40 315 improving their cardiometabolic outcomes. Although this intervention could have also  
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42 316 modified the association of GDM with CIMT, this seems not likely, as mean CIMT  
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44 317 values were very similar in offspring of women with GDM who participated in the  
45  
46 318 intervention and the control arms of the trial. Thirdly, CIMT was assessed using  
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48 319 conventional high-resolution ultrasound frequencies ( $< 15$  MHz), which have a lower  
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50 320 spatial resolution and, thus, tend to overestimate the arterial thickness in the young  
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52 321 children when compared to very high-resolution ultrasound systems (25 to 55  
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3 322 MHz).[30,31] Measurement error in CIMT cannot be excluded, but systematic  
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5 323 differences between the two groups are unlikely because the outcome assessors were  
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7 324 blinded to the glycemc status of the mothers. Fourthly, while we adjusted for key  
8  
9 325 confounders at the analysis stage, there is a possibility of bias due to unmeasured  
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11 326 factors, such as family history of premature cardiovascular death, or residual  
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13 327 confounding due to the relatively small sample size and imprecision in the  
14  
15 328 measurement of confounder variables, especially in those self-reported. Lastly, our  
16  
17 329 study was limited to CIMT, which is a measure of arterial structure. In fact, changes in  
18  
19 330 the vessel function might occur earlier than changes in the vessel structure, therefore,  
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21 331 a combination of vascular measures would be needed for a clearer view on the  
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23 332 cardiovascular status of children exposed to adverse experiences in early life.  
24  
25 333 However, certain techniques to assess arterial function and stiffness, such as flow-  
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27 334 mediated dilation and pulse-wave velocity, are not currently feasible in the very young  
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29 335 due to limited compliance and technical inconveniences.[18]  
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### 337 **Implications and future research**

40 338 Our results suggest that intrauterine exposure to GDM does not induce changes in the  
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42 339 carotid artery structure that are detectable with conventional ultrasound techniques at  
43  
44 340 birth and may not be linked to early vascular aging at this arterial site in the short term.  
45  
46 341 Measurements at other arterial sites, such as the aorta,[32] may be more useful to  
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48 342 investigate early or subtle abnormalities related to accelerated vascular aging or  
49  
50 343 subclinical atherosclerosis. A long-term follow-up that includes complementary  
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52 344 vascular measures, for instance, endothelium-dependent and endothelium-  
53  
54 345 independent vasodilation or large-artery stiffness,[20] may shed further light on the  
55  
56 346 cardiovascular health of children born to mothers with GDM.  
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**348 Patient and public involvement**

349 There was no patient or public involvement in the design, conduct, analysis, or  
350 reporting of this study's findings.

351

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361

**362 Authors' contributions**

363 AC, NS, SDB, and YM designed the study and the data collection procedures with  
364 input from SEY, AME. SEY and AME collected baseline characteristics for participants  
365 without GDM. SDB and NS collected neonatal cardiovascular characteristics for all  
366 participants. SEY performed data management and curation. AME carried out the  
367 statistical analyses with input and supervision from AC. AME wrote the first draft of the  
368 manuscript with input from AC and NS. SDB, SEY, YM made critical revisions to the  
369 manuscript for important intellectual content. All authors read and approved the content  
370 of the manuscript.

371

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386 and analysis, or interpretation of results.

## 388 **Competing interests**

389 None declared.

## 391 **Consent for publication**

392 Not applicable.

## 394 **Ethics approval**

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

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6 398 **Data availability statement**  
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8 399 Data could be made available by the principal investigator and corresponding author  
9  
10 400 (Prof Nicole Sekarski: [nicole.sekarski@chuv.ch](mailto:nicole.sekarski@chuv.ch)) on reasonable request.  
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For peer review only



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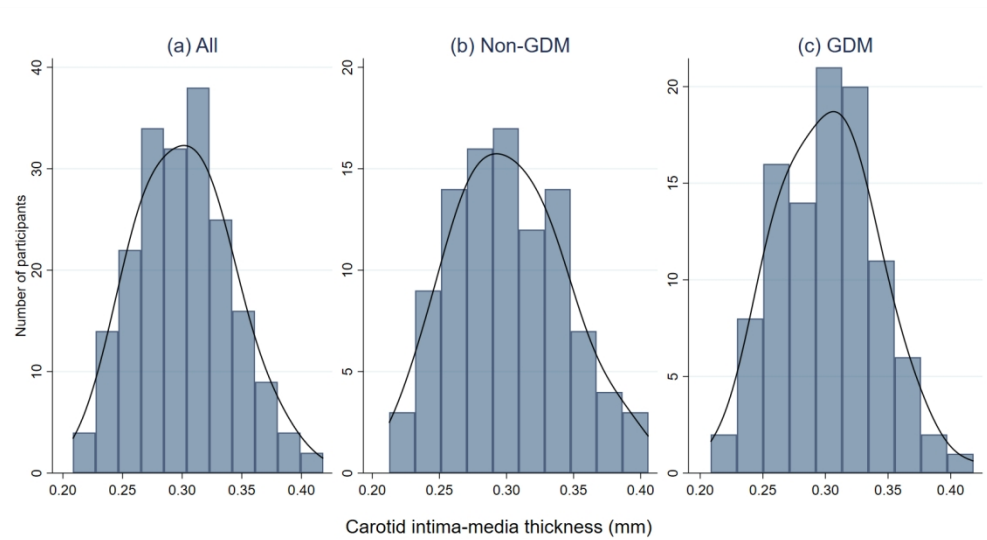
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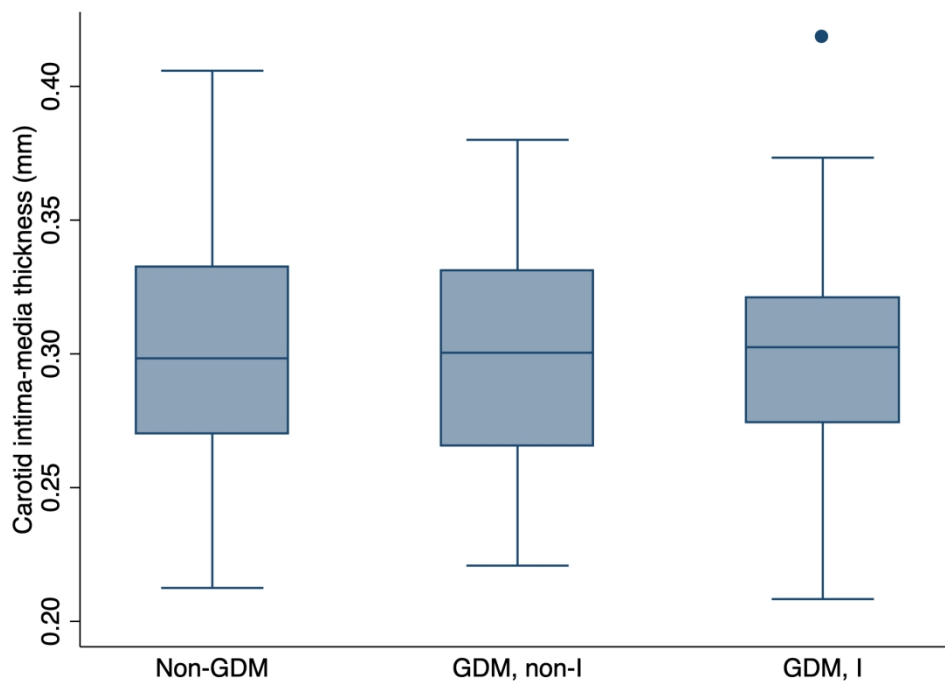
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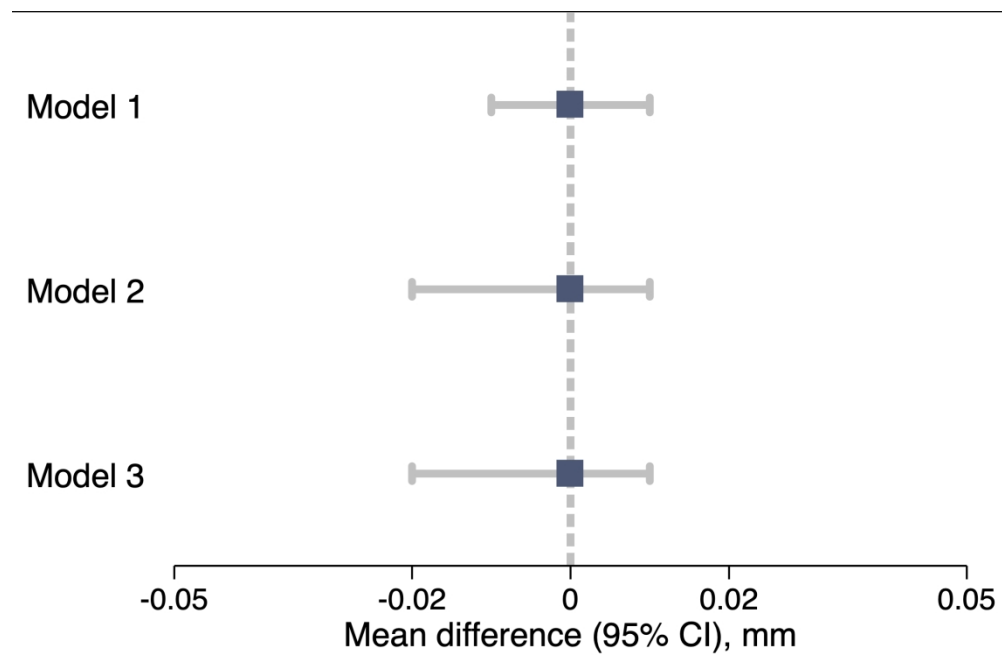
This figure shows the distribution of CIMT values in our sample, overall (n=200) and by GDM exposure (Non-GDM: n=99; GDM: n=101). The black line represents the kernel density estimate. Abbreviations: CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus.

599x326mm (72 x 72 DPI)



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  $1.5 \times \text{IQR}$  (i.e.,  $Q1 - 1.5 \times \text{IQR}$  and  $Q3 + 1.5 \times \text{IQR}$ ).

378x275mm (144 x 144 DPI)



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.

423x275mm (144 x 144 DPI)



## SUPPLEMENTARY MATERIAL

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

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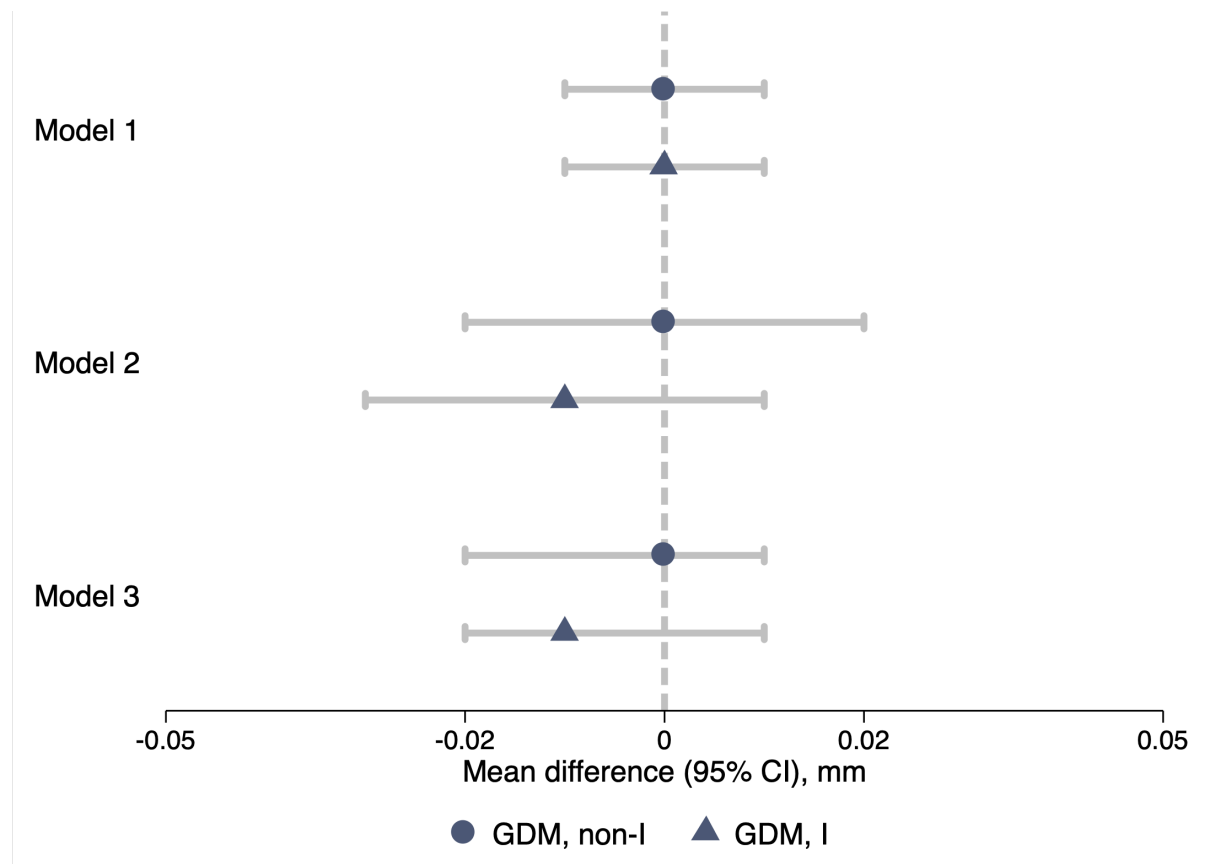
¶ These authors contributed equally to this work.

**Table S1** The relationship of GDM and assignment or not to a lifestyle and psychosocial intervention with offspring’s CIMT at birth.

	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), mm	p
Non-GDM	0.30 (0.04)	ref	ref	ref	ref	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)	0.91
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

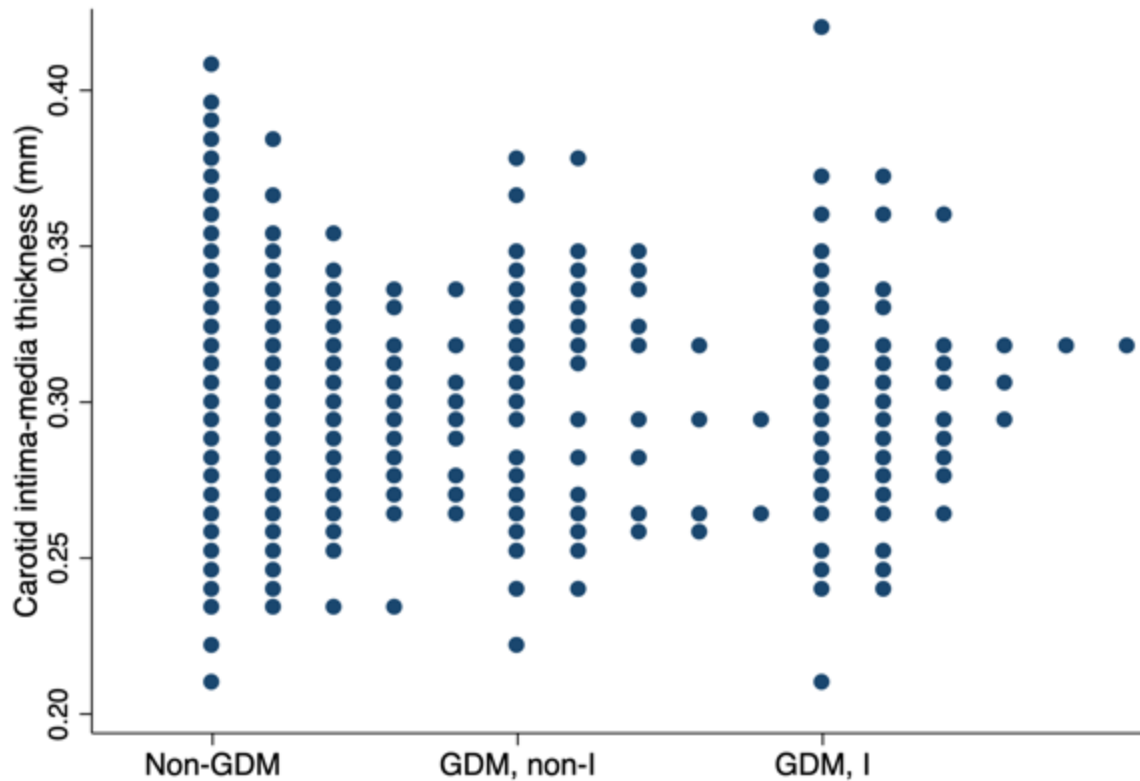
Estimates were obtained from linear regression models with the following specification: Model 1: unadjusted estimates; Model 2: estimates adjusted for maternal pre-pregnancy BMI, education, and tobacco smoking; offspring family history of diabetes and sex; Model 3: estimates adjusted for maternal pre-pregnancy 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 categorical with 3 levels (Non-GDM/ GDM, non-I/ GDM, I; the reference category was 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, 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)). Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; GDM, gestational diabetes mellitus; I, intervention; n, total number of participants; p, p-value; sd, standard deviation; ref, reference group.

**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.