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Original Research

Adolescent body mass index and changes in pre-pregnancy body mass index in relation to risk of gestational diabetes

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A R T I C L E I N F O

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A B S T R A C T

Background: Pregestational excessive body mass index (BMI) is linked to an increased risk for gestational diabetes mellitus (GDM), but less is known on the effect of adolescent BMI on GDM occurrence. The study aimed to investigate possible associations of adolescent BMI and changes in BMI experienced before first pregnancy, with gestational diabetes risk.

Methods: This retrospective study was based on linkage of a military screening database of adolescent health status (Israel Defence Forces) including measured height and weight, with medical records (Maccabi Healthcare Services, MHS) of a state-mandated health provider. The latter covers about 25% of the Israeli population; about 90% of pregnant women undergo screening by the two-step Carpenter-Coustan method. Adolescent BMI was categorized according to Center of Disease Control and Prevention percentiles. Only first documented pregnanies were analyzed and GDM was the outcome.

Findings: Of 190,905 nulliparous women, 10,265 (5.4%) developed GDM. Incidence proportions of GDM were 5.1%, 6.1%, 7.3%, and 8.9% among women with adolescent normal BMI, underweight, overweight, and obesity ($p<0.001$), respectively. In models that accounted for age at pregnancy, birth year, and sociodemographic variables, the adjusted odd ratios (aORs) for developing GDM were: 1.2 (95%CI, 1.1-1.3), 1.5 (1.4-1.6), and 1.9 (1.7-2.1) for adolescent underweight, overweight, and obesity (reference group, normal BMI). Adolescent BMI tracked with BMI notes in the pre-pregnancy period (r=63%). Resuming normal pre-pregnancy BMI from overweight or obesity in adolescence diminished GDM risk, but this diminished risk was not observed among those who returned to a normal per-pre-pregnancy BMI from being underweight in adolescence. Sustained overweight or obesity conferred an aOR for developing GDM of 2.5 (2.2-2.7); weight gain from adolescent underweight and normal BMI to pre-pregnancy excessive BMI conferred aORs of 3.1 (1.6-6.2) and 2.6 (2.2-2.7), respectively.

Interpretation: Change in BMI status from adolescence to pre-pregnancy may contribute to GDM risk. Identifying at-risk populations is important for early preventive interventions.

Funding: None.

Abbreviations: BMI, body mass index; CI, confidence intervals; GAM, generalized additive model; GCT, glucose challenge test; GDM, gestational diabetes mellitus; MHS, Maccabi Healthcare Services; OR, odds ratio; SD, standard deviation; SES, socioeconomic status

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Research in Context

Evidence before this study

Pregestational excessive body mass index (BMI) is linked to an increased risk for gestational diabetes mellitus (GDM), but it is unclear if adolescent BMI or different trajectories from adolescence to pregnancy affect GDM risk.

Added value of this study

In a large nationally representative cohort of approximately 190 thousand women who were measured for BMI as part of a systematic health examination at age 17 years and screened for GDM later in life, BMI measurements below or above the normal range in adolescence were associated with an increased GDM risk. Also, the trajectory of BMI from adolescence to pregnancy was predictive for GDM risk.

Implications of all available evidence

Change in BMI status from adolescence to pre-pregnancy might contributes to GDM risk and could help define at-risk populations for early preventive interventions.

1. Introduction

Gestational diabetes mellitus (GDM) is considered the most common medical complication of pregnancy, and a growing health concern globally [1]. Regional prevalences range from 6% in Europe to over 15% in the Middle East, North Africa, and South-East Asia [1]. GDM has been linked to poor maternal and neonatal outcomes [2] such as gestational hypertension, excessive fetal growth, and perinatal morbidity [1]. GDM history is associated with increased metabolic impairment (e.g. type 2 diabetes mellitus) in mothers, over their life courses [3–5]. Additionally, GDM has been associated with the development of adult-onset obesity, type 2 diabetes mellitus, and cardiovascular disease in the offspring [1,6].

Definitions of GDM and screening approaches have changed over the years [7]. In addition, the key drivers of the increase in GDM occurrence include the obesity epidemic, physical inactivity, and rising maternal age [1]. Associations have been reported of pre-pregnancy and early-pregnancy body mass index (BMI), with GDM [8]. However, those studies were mostly based on self-reported BMI or recall of GDM, and were characterized by high heterogeneity [8]. Moreover, longitudinal studies that additionally account for BMI early in life and the long-term risk of GDM are limited [9]. Establishing such association is important given that adolescent obesity may be a modifiable risk factor, and its early recognition could provide an opportunity to engage preventive strategies at earlier stages to mitigate GDM burden. Here we analyzed associations between adolescent BMI, pre-pregnancy BMI, and GDM risk in a population-based cohort study of 190 thousand nulliparous women.

2. Methods

2.1. Study population

This was a retrospective cohort study. Included were all Israeli female members of Maccabi Healthcare Services (MHS), who as adolescents (aged 16-19 years) underwent medical evaluations by the Israel Defence Forces one year prior to their mandatory military service. Examinations were performed between the years 1976 and 2016. Baseline characteristics were generally similar between women insured by MHS and women insured by other Israeli state-mandated health providers (Supplementary Table S1). Data were accessed from MHS records of women's first glucose challenge test (GCT) in their first documented pregnancy after military discharge. Study exclusion criteria were: a diagnosis of diabetes according to the military authority database at baseline (n= 61) or a subsequent diagnosis of any type of diabetes before the first GCT, as indicated by the Diabetes Registry of MHS [10] (n=95); missing adolescent BMI data (n=1,844); and a GCT that was not completed due to technical reasons (n=24). The final study sample included 190,905 women (Figure 1). Ethics approval of the study protocol was granted by the Israel Defense Forces Medical Corps (2018-1860) and MHS Institutional Review Board (0122-19-MHS). The review boards waived the need for informed consent.

2.2. Data from Maccabi Healthcare Service (MHS)

The primary outcome of the study was documented GDM using the computerized datasets of MHS. According to the Israeli National Health Insurance Act, health insurance is mandatory and each resident is free to join any one of four healthcare providers; the second largest of them is MHS. In 2020, MHS covered 26.5% of the 1.78 million Israeli women aged 15–45 years countrywide. The annual number of births in MHS (n = 42,645) comprised 23.5% of all births in Israel [11]. From 2001, MHS has maintained a central digital registry of data of the 50 gr-GCT and of the 100 gr-oral glucose tolerance test (OGTT), which is conducted following an abnormal GCT (≥140 mg/dl). These tests are components of routine medical screening for GDM follow-up during pregnancy, and are provided as a free service, with an overall compliance of 89% [12].

For the purpose of this study, we defined GDM according to the National Diabetes Data Group criteria conversion method [13], based on the presence of two or more of the following values in the 100 g OGTT: fasting serum glucose concentration exceeding 5.3 mmol / l (95 mg / dl); 1 h serum glucose concentration 10.0 mmol / l (180 mg / dl) or above; 2 h serum glucose concentration exceeding 8.6 mmol/l (155 mg / dl); and 3 h serum glucose concentration exceeding 7.8 mmol / l(140 mg / dl). Women with GCT greater or equal to 200 mg/dl were classified as having GDM. Women who did not meet these criteria in the first pregnancy (earliest documented GCT test in the electronic medical records) were defined as non-GDM. OGTT data were missing for 1,543 (of 30,927; 5.0%) women with abnormal GCT (≥140 mg/dl≤GCT<200 mg/dl); these were classified as non-GDM. Pre-pregnancy BMI data were based on weight and height measurements that were recorded during routine visits to the clinic up to three years prior pregnancy.

2.3. Data collection at adolescence and study variables

As part of medical screening for military service, height and weight were measured (wearing light clothing) by trained medics, using a beam balance and stadiometer to the nearest centimeter and 0.1 kg, respectively [14,15]. BMI was calculated (weight [in kilograms] divided by squared height [in meters]). Military physicians reviewed the examinees' medical records, performed medical examinations, and provided diagnostic codes as appropriate. Blood pressure was measured at rest as previously described [16]. During the study period, data regarding education, residential area socioeconomic status (SES), assessment of cognitive performance, and country of birth were routinely received from governmental agencies. Age at examination and year of birth were treated as continuous variables. Education was stratified by ≤11 or 12 years of formal schooling. SES was based on place of residence at the time of examination. This parameter was coded on a 1-10 scale developed by the Israeli Central Bureau of Statistics and grouped to low (SES=1-4), medium (SES=5-7), and high (SES=8-10) categories [17].

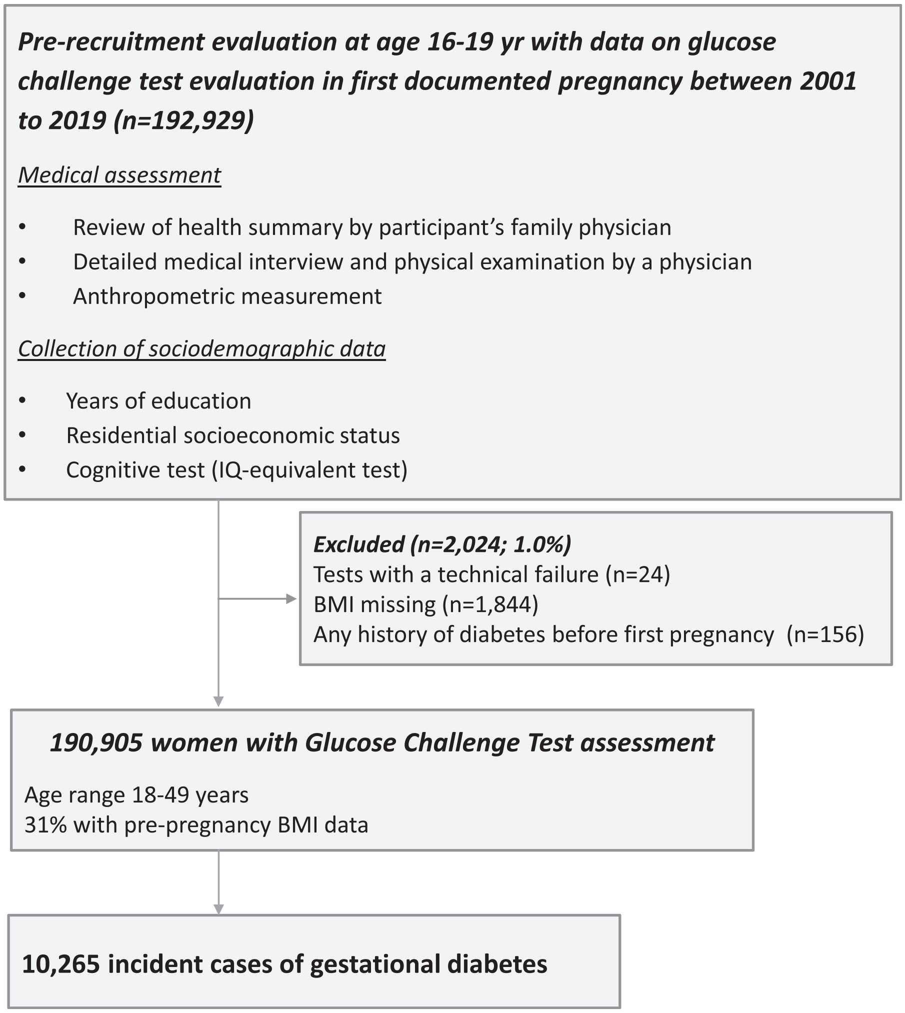

Figure 1. Schematic description of the cohort buildup. The 489,125 women who were born between 1960 and 2000 and were members in Maccabi Health Services after their discharge from mandatory army service were the source of the cohort. Their characteristics are compared in Table S1 to those of women insured by other state-mandated health provider.

Cognitive performance, which was found to be a strong risk marker for dysglycemia [18], type 2 diabetes [19], and diabetes-related mortality [20] in this cohort, was assessed at study entry as part of the pre-recruitment routine by a general and intelligence score [19]. Cognitive assessment was conducted as part of the pre-military assessment and was administered by trained personnel. As described previously [21], the cognitive assessment included four subdomains: Raven's Progressive Matrices-R, which measures non-verbal abstract reasoning and visual-spatial problem-solving abilities; Similarities-R, which assesses verbal abstraction and categorization; Otis-R, verbal comprehension, which assess the ability to understand and carry out verbal instructions; and Arithmetic-R, which assesses mathematical reasoning, concept manipulation and concentration [13]. The sum of the scores of all four tests constitutes a validated global score of overall intelligence [14]. Scored on a 90-point scale, this overall score has demonstrated high correlation ($r>0.8$) with the Wechsler Adult Intelligence Scale (WAIS) total intelligence quotient (IQ) [13,14].

Categories included: low (less than -1 standard deviation[SD]), medium (between -1 and +1 SD), and high (equal or higher than +1 SD), as reported previously [18]. Adolescent BMI was classified according to percentiles established by the US Center of Disease Control and Prevention. These were validated for Israeli adolescents [22], for age (by month) and sex, for the following subgroups: BMI$<5^{th}$ (underweight), $5^{th}\leq$BMI$<85^{th}$ (normal BMI), $85^{th}\leq$BMI$<95^{th}$ (overweight), and obese ($\geq 95^{th}$ percentile). Pre-pregnancy BMI categories included underweight (<18.5 kg/m^2), normal BMI (18.5 to <25 kg/m^2), and overweight/obese (≥ 25 kg/m^2).

2.4. Statistical analysis

Differences in participant characteristics between study groups were assessed using chi-square tests for categorical variables and analysis of variance (ANOVA) with F-tests for continuous variables. The incidence proportion of GDM was calculated for each BMI group. Logistic regression models were applied to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for incident GDM using the normal BMI as the reference. Covariates to the model were pre-specified and included birth year, age at first pregnancy, and sociodemographic variables assessed at baseline: education, residential SES, and cognitive performance. Due to the strong effect of age on both GDM risk and BMI [9,23], the analysis was also stratified by the age of the first pregnancy (18-24, 25-29, 30-34, 35-39, and 40 years or older). We also tested for a multiplicative interaction term between the latter and adolescent BMI, both in unadjusted and multivariable adjusted models.

Several sub-analyses were conducted. We restricted the analysis to women with unimpaired health status at study entry (i.e. the absence of any chronic comorbidity that requires medical therapy, or any history of cancer or major operation). This was aimed to minimize residual confounding by co-existing morbidities, as done previously [15]. In an additional sub-analysis, we included only women with continuous insurance in MHS after army discharge (n=131,255; 69%). This aimed to mitigate misclassification of first pregnancies that could result from transitions between healthcare providers.

For women with pre-pregnancy BMI data, we assessed the baseline characteristics and the strength of the association between adolescent BMI and incident GDM, to assure consistency with the rest of the study population. To make our study comparable with existing literature, we analyzed the association between pre-pregnancy BMI and GDM. We also analyzed ORs for incident GDM, in an adjusted model that accounted for both adolescent and pre-pregnancy BMI. This model included nine categories that were based on stratifications of adolescent and pre-pregnancy BMI to three adolescent BMI groups (underweight, normal BMI, and the combined group of overweight/obese) by three pre-pregnancy BMI categories; the reference group was normal BMI at adolescence and at pre-pregnancy. We limited the study population for the latter analysis to those born from 1980 onwards since during this period we obtained pre-pregnancy data for the majority of the cohort. Persons with missing covariate data (2,322; 1.2% of the cohort) were excluded from the multivariable analysis. Analyses were performed using IBM-SPSS (version 25.0) and R (Language and Environment for Statistical Computing) using the package ggplot2 with GAM method for smoothing graphs.

3. Role of the funding source

There was no funding source for this study. GT and ED had full access to the dataset of the study. All the authors accept responsibility for the decision to submit for publication.

4. Results

4.1. Baseline Characteristics

For the 190,905 women comprising the study population, weight distribution in adolescence was: underweight (n=8941; mean BMI ±SD, 16.6 ±0.6 kg/m^2), normal BMI (n=161,826; 20.9 ±2.0 kg/m^2), overweight (n=15,898, 27.0 ±1.2 kg/m^2), and obesity (n=4240; 32.7 ±2.8 kg/m^2) (Table 1). The demographic characteristics of the study groups are summarized in Table 1. Significantly ($p<0.001$) greater proportions of adolescents with overweight and obesity than with normal BMI had less than 12 years of education and low cognitive performance. Among adolescents with overweight and obesity, elevated blood pressure and coexisting chronic illnesses were more frequent.

4.2. Adolescent BMI and GDM risk

The mean age at the first pregnancy was 31±4.7 years (Table 1). Mean GCT levels by age and adolescent BMI group are shown in Figure 2. Among young adults aged 17-24 years, mean GCT levels were significantly higher among those with adolescent obesity than with normal BMI (mean [SE]=116 [1.47] mg/dl vs. 107 [0.35] mg/dl; $p<0.0001$). Similar differences were recorded for older age groups until 35-39 years, but not for the two oldest groups.

Incidences of GDM were 5.1% (n=8,187), 6.1% (n=546), 7.3% (n=1,154), and 8.9% (n=378) for women with normal BMI, underweight, overweight, and obesity, respectively (Table 2). Logistic regression models adjusted for age at delivery and year of birth showed significant ORs for the development of GDM, among adolescents with underweight, 1.23 (1.12-1.34); overweight, 1.48 (1.39-

Table 1
Baseline characteristics of the study population according to adolescent body mass index (BMI) categories

	Underweightn (%)	Normal BMIn (%)	Overweightn (%)	Obesen (%)	Totaln (%)
Number of women	8,941	161,826	15,898	4,240	190,905
Age, year (M±SD)	17.4 ± 0.4	17.3 ± 0.4	17.3 ± 0.4	17.3 ± 0.4	17.3 ± 0.4
BMI (M±SD)	16.6 ± 0.6	20.9 ± 2	27 ± 1.2	32.7 ± 2.8	21.4 ± 3.2
BMI (min – max)	12.2 – 17.8	17.1 – 26.4	25 – 31.3	29.4 – 47.6	12.2 – 47.6
Height in cm (M±SD)	164 ± 6.4	162.5 ± 6	162 ± 6.2	162.2 ± 6.5	162.6 ± 6.1
Systolic BP mmHg(M±SD)	109.1 ± 11.9	111.7 ± 11.6	116.1 ± 11.7	119.8 ±11.9	112.1 ± 11.8
Diastolic BP mmHg(M±SD)	69.3 ± 8.0	70.4 ± 8.0	72.6 ± 8.0	74.9 ±8.2	70.7 ± 8.1
Unimpaired health	5,677 (63.5)	120,655 (74.6)	11,630 (73.2)	2,854 (67.3)	140,814 (73.8)
Israeli born	7240 (81)	133,898 (82.8)	13,081 (82.3)	3,398 (80.2)	157,617 (82.6)
Years of education					
<12	265 (3)	3,621 (2.2)	489 (3.1)	176 (4.2)	4,551 (2.4)
≥12	8,655 (97)	157,732 (97.8)	15,366 (96.9)	4,053 (95.8)	185,806 (97.6)
Cognitive performance					
Low	1,146 (12.9)	15,992 (9.9)	2,147 (13.6)	777 (18.5)	20,062 (10.6)
Medium	6,732 (75.8)	123,063 (76.5)	11,961 (75.8)	3,076 (73.2)	144,832 (76.4)
High	1,000 (11.3)	21,738 (13.5)	1,679 (10.6)	352 (8.4)	24,769 (13.1)
Socioeconomic status					
Low	1,365 (15.4)	25,255 (15.7)	2,655 (16.8)	777 (18.5)	30,052 (15.9)
Medium	4,768 (53.7)	86,200 (53.7)	8,926 (56.6)	2,424 (57.6)	102,318 (54)
High	2,746 (30.9)	49,037 (30.6)	4,197 (26.6)	1,007 (23.9)	56,987 (30.1)
Age at first pregnancy					
Mean age, year (M±SD)	31 ± 4.7	31 ± 4.7	30.7 ± 4.9	30.3 ±4.9	31 ±4.7
Age, year (median (IQR))	30.4 (27.8 – 33.8)	30.5 (27.8 – 33.9)	30.2 (27.4 - 33.8)	29.9 (26.9 - 33.3)	30.4 (27.8 – 33.9)
18 – 24	710 (7.9)	12,801 (7.9)	1,643 (10.3)	537 (12.7)	15,691 (8.2)
25 – 29	3,422 (38.3)	60,844 (37.6)	6,061 (38.1)	1,630 (38.4)	71,957 (37.7)
30 – 34	3,137 (35.1)	56,694 (35)	5,131 (32.3)	1,352 (31.9)	66,314 (34.7)
35 – 39	1,295 (14.5)	24,557 (15.2)	2,380 (15)	563 (13.3)	28,795 (15.1)
40 – 49	377 (4.2)	6,930 (4.3)	683 (4.3)	158 (3.7)	8,148 (4.3)
Year of birth					
1960-69	1,107 (12.4)	21,362 (13.2)	1,669 (10.5)	269 (6.3)	24,407 (12.8)
1970-79	3,899 (43.6)	72,140 (44.6)	6,825 (42.9)	1,651 (38.9)	84,515 (44.3)
1980-89	3,259 (36.5)	56,038 (34.6)	5,781 (36.4)	1,725 (40.7)	66,803 (35)
1990-2000	676 (7.6)	12,286 (7.6)	1,623 (10.2)	595 (14)	15,180 (8)

M±SD, mean±standard deviation; GDM, gestational diabetes mellitus, BMI, body mass index; BP, blood pressure; IQR, interquartile range; BMI categories, underweight (<18.5 kg/m^2), normal BMI (18.5- <25 kg/m^2) and overweight/obese (≥25 kg/m^2).

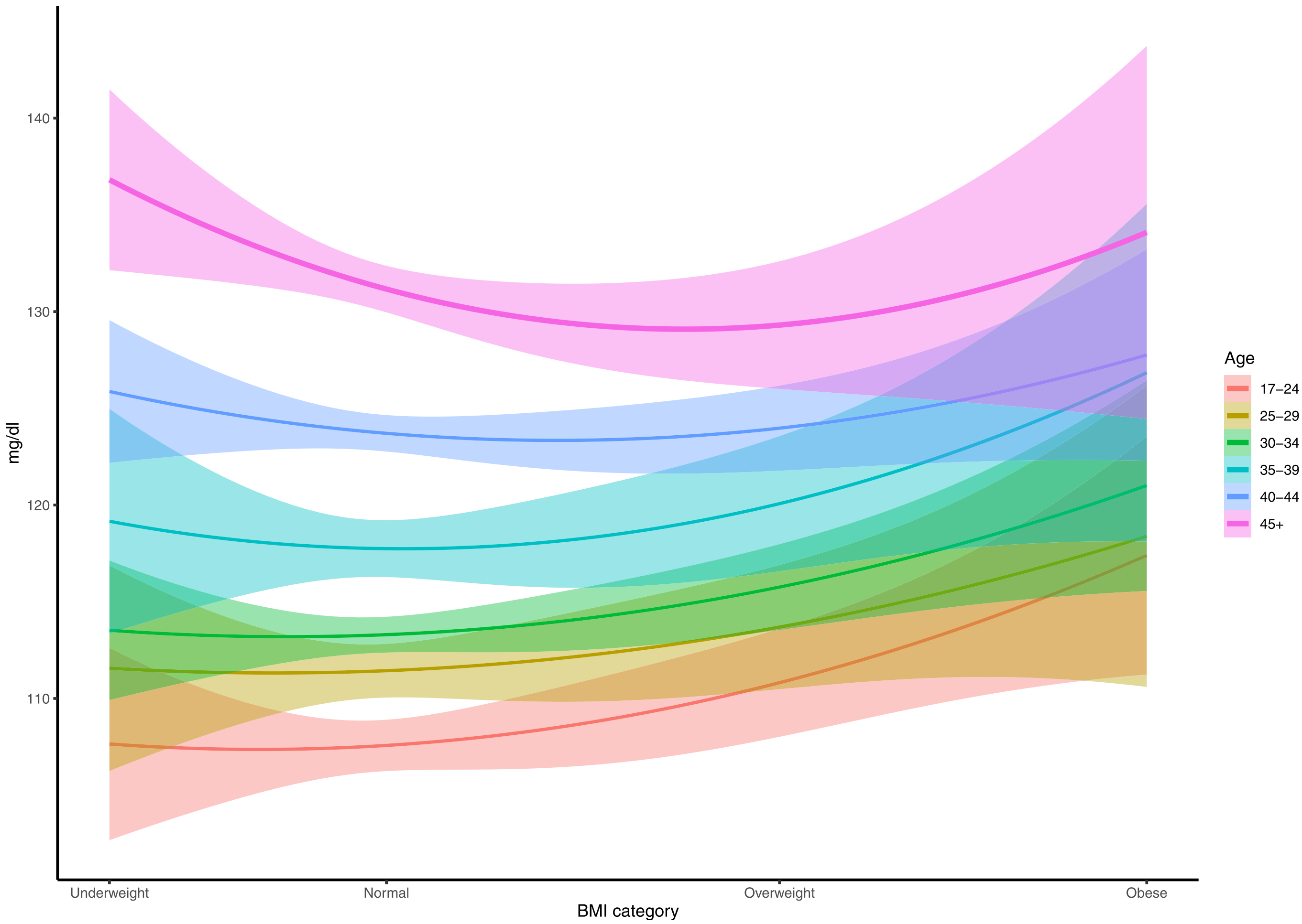

Figure 2. One-hour results of the 50-gram glucose challenge test, by adolescent body mass index (BMI) categories, for various pre-pregnancy age-groups

Gray circles represent mean glucose challenge test values for the four adolescent BMI categories, and pre-pregnancy age ranges. Adolescent BMI categories are plotted by their mean value. Dashed lines represent a second-order (quadratic) polynomial regression, with 95% confidence intervals of the expected mean. Line colours represent age-specific GCT means and shaded ribbons show 95% confidence intervals.

1.58); and obesity, 1.90 (1.70-2.12), compared to normal BMI. These point estimates were materially unaffected by additional adjustments to years of education, residential SES, and cognitive performance (Table 2; supplementary Table S2). In analyses stratified by the age at the first pregnancy, the point estimates were evident from age 18 until 40 years, with the exception of women with underweight who became pregnant before age 25 years ($p_{interaction}$=0.14). For the latter, the odds were comparable to those with normal BMI (Table 2). The strongest associations between adolescent obesity and GDM were observed for ages 18-24 and 30-34 years, and ablated for women who became pregnant after age 40 years. These results persisted when the study sample was limited to women with unimpaired health at baseline (supplementary Table S3), or to those who were permanent members in MHS throughout the follow-up period (supplementary Table S3).

4.3. Pre-pregnancy BMI and GDM

Pre-pregnancy weight was available for 58,727 of the study population (31%); their characteristics are shown in supplementary Table S4. These women were predominantly of later birth decades of the study (1980s or later). Accordingly, their mean BMI and fraction of obesity at study entry were higher than for those without pre-pregnancy weight data (21.7 vs. 21.3 kg/m^2, p<0.0001; 3.2% vs. 1.8%, p<0.0001). Mean pre-pregnancy BMI values were moderately correlated with adolescent BMI, with a correlation of r=0.63 (p<0.001). For this sub-population, the adjusted ORs for GDM across BMI groups at adolescence were consistent with the main analysis (supplementary Table S5A). Pre-pregnancy overweight and obesity were associated with adjusted ORs of 2.10 (1.94-2.30) and 3.35 (3.04-3.70), respectively, compared to normal pre-pregnancy BMI (supplementary Table S5B). ORs for incident GDM according to the change in BMI from adolescence to pre-pregnancy are shown in Figure 3. Compared to women who remained with normal BMI (1,421 of 35,172 women), an increase from normal adolescent BMI to overweight/obesity in pre-pregnancy was associated with an OR of 2.61 (2.39-2.84). Elevated ORs were also observed for 9,808 women (1,036 incidences) with adolescent underweight who had normal pre-pregnancy BMI (1.93, 95%CI 1.58-2.35) and 1,505 women (118 incidences) who had overweight/obesity before pregnancy (3.14, 95%CI 1.60-6.20). BMI reduction from overweight/obesity in adolescence to normal pre-pregnancy BMI (46 of 1,797 women), and from normal adolescent BMI to underweight in pre-pregnancy (96 of 3,350 women), were associated with significant decrements in GDM risk. Detailed numbers of the matrix shown in Figure 3 appear in supplementary Table S6A. We limited the analysis described in Figure 3 to those born from 1980 onwards, a period for which pre-pregnancy BMI data were available for 51% of the study population, with observed similar point estimates (supplementary Table S6B).

Table 2
The association between adolescent body mass index (BMI) and incident gestational diabetes mellitus (GDM).

	Underweight	Normal BMI	Overweight	Obese
Entire population - 10,136 (5.4%) incidences of 188,583 women**				
GDM incidences (%)	541 (6.1)	8,079 (5.1)	1,141 (7.3)	375 (8.9)
OR	1.23	1	1.48	1.90
95% CI	1.12 – 1.34		1.39 – 1.58	1.70 – 2.12
P	<0.001		<0.001	<0.001
Age at first pregnancy 18–24 years - 438 (2.8%) incidences of 15,406 women				
GDM incidences (%)	18 (2.6)	332 (2.6)	57 (3.5)	31 (5.9)
OR	0.98	1	1.34	2.26
95% CI	0.60 – 1.58		1 – 1.78	1.54 – 3.31
P	0.935		0.046	<0.001
Age at first pregnancy 25–29 years 3,054 (4.3%) incidences of 71,252 women				
GDM incidences (%)	168 (5.0)	2399 (4.0)	368 (6.1)	119 (7.4)
OR	1.25	1	1.55	1.84
95% CI	1.06 – 1.46		1.38 – 1.73	1.52 – 2.22
P	0.007		<0.001	<0.001
Age at first pregnancy 30–34 years - 3,494 (5.3%) incidences of 65,593 women				
GDM incidences (%)	180 (5.8)	2805 (5.0)	372 (7.3)	137 (10.3)
OR	1.17	1	1.49	2.12
95% CI	0.99 – 1.36		1.33 – 1.66	1.77 – 2.54
P	0.05		<0.001	<0.001
Age at first pregnancy 35–39 years - 2,199 (7.8%) incidences of 28,345 women				
GDM incidences (%)	123 (9.7)	1752 (7.2)	258 (11.0)	66 (11.9)
OR	1.36	1	1.59	1.73
95% CI	1.12 – 1.65		1.38 – 1.82	1.33 – 2.26
P	0.002		<0.001	<0.001
Age at first pregnancy 40–49 years - 951 (11.9%) incidences of 7,987 women				
GDM incidences (%)	52 (14.1)	791 (11.7)	86 (12.8)	22 (14.0)
OR	1.25	1	1.14	1.33
95% CI	0.92 – 1.69		0.89 – 1.44	0.84 – 2.11
P	0.15		0.28	0.23

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for GDM by BMI at study entry are shown with strata of age at the first pregnancy. The GDM incidences and numbers of women relate to a model adjusted for age at delivery, year of birth, education, residential socioeconomic status, and cognitive score. No interaction was found between age at pregnancy and adolescent BMI, either in an unadjusted ($p_{interaction}$=0.14) or multivariable adjusted models ($p_{interaction}$=0.13). BMI categories, underweight (<18.5 kg/m^2), normal BMI (18.5- <25 kg/m^2) and overweight/obese (≥25 kg/m^2).
** A total of 2322 women with 129 incidences of GDM were excluded from the analysis due to missing data on one or more of the independent variables examined.

5. Discussion

In this population-based cohort study, BMI measurements below and above the normal range at age 17 years were positively associated with a greater risk for GDM; the risk was nearly 2-fold among those with adolescent obesity. This association was broadly consistent for any first pregnancy that occurred before age 40 years and persisted following adjustment for adolescent sociodemographic factors, and following restriction of the study sample to those with unimpaired health. In line with a previous cohort study [9], a significant increase in the risk of GDM was also observed among underweight compared to normal weight adolescents. Interestingly, in a sub-sample of the study population, women who were underweight at adolescence but with normal BMI before pregnancy had higher risk for GDM than did those who sustained normal BMI throughout this period. Furthermore, our study corroborates two meta-analyses [24,25] that demonstrated a lower risk of GDM conferred by pre-pregnancy underweight than normal pre-pregnancy weight.

Our findings are in line with the results of a few smaller studies that examined associations of BMI status at childhood or adolescence with GDM, including the prospective Bogalusa Heart Study [26] in the US and the Copenhagen School Health Records Register [9] study. The latter showed an association of overweight at age 13 years with an adjusted RR of 3.09 (2.15–4.42) for GDM. In addition, the ORs for GDM reported here, of 2.1 and 3.35 among women with pre-pregnancy overweight and obesity, respectively, concur with a recent meta-analysis [24]. There, the pooled ORs for developing GDM in women with pre-pregnancy overweight and obesity were 2.01 and 3.98, respectively. Notable heterogeneity was observed between the included studies (i^2>87%), possibly due to differences in definitions that were used for self-reported BMI or GDM. In line with a recent study [27], we found that the excess risk of GDM at first pregnancy, in women with obesity vs. normal BMI, peaks at age 30-34 years, and declines in older ages. One explanation is that women after age 35 years at first birth may have a healthier lifestyle and be more prudent to health behaviors that mitigate the effect of obesity on GDM [27]. Alternatively, older age at first pregnancy may be a marker of underlying fertility problems, which are associated with a higher frequency of metabolic syndrome, independent of excess body weight [28]. Thus, a higher prevalence of metabolic syndrome among older women with normal weight may have attenuated the association between obesity and GDM.

Several mechanisms may explain associations of adolescent overweight and obesity with GDM. As indicated in this work and elsewhere [29,30], BMI in adolescence is highly correlated with excessive weight during pregnancy [31,32]. Overweight and obesity during pregnancy may add to the physiologic stress on pancreatic β-cells [23] that results from metabolic changes occurring during pregnancy, and particularly from the decrease in insulin sensitivity during late pregnancy. This stress may increase the risk of GDM. Alternatively, it has been suggested that hypersecretion of insulin normally occurs early in pregnancy, regardless of the presence of insulin resistance [33]. This raises the possibility that failure to increase secretion during pregnancy may lead to GDM. In agreement, about 40% of GDM incidence among women with underweight may be explained by impaired β-cell secretory capacity [34]. Such a pathway may explain the different and possibly independent pathophysiological mechanisms of GDM at the two ends of the BMI range.

Previous studies suggested a possible causal relation between the degree of weight gain in pregnancy and the risk of GDM [35]. However, data on the effect of long-term changes in BMI before pregnancy are sparse [36]. Our results underscore the relation between weight gain during adulthood and GDM, which was particularly substantial among women with adolescent underweight. GDM risk was comparable between those who remained underweight and those with sustained normal BMI. In contrast, the risk was increased by over 2-fold for women who were underweight in adolescence and gained weight, particularly those with overweight or obesity before pregnancy. Conversely, reduction in BMI category (from normal BMI to underweight, or from overweight/obesity to normal weight) was associated with a lower OR for GDM, compared to persistent normal BMI. This is supported by studies from Australia [37]and the US[38], in which weight loss was associated with a diminished risk of GDM. Our results underscore the clinical significance of the BMI trend from adolescence to the pre-pregnancy period, in reducing GDM risk.

This study has limitations. We lacked data on family history of diabetes, lifestyle, and physical activity; and on other measures of adiposity, such as waist circumference. The latter might be more sensitive than BMI in the context of this study, and better define the population at long-term risk [39]. However, this difference was found to be less meaningful in women [40]. Second, we examined the risk of GDM at first documented pregnancy only, and therefore were unable to detect GDM in later pregnancies. Third, pre-pregnancy BMI data were available for only 31% of our study population. Nevertheless, the association between adolescent BMI and GDM persisted in this sub-cohort, and the strength of the association of pre-pregnancy overweight or obesity, with GDM, was similar to that previously reported in the literature [9,26]. Also, the results persisted when the

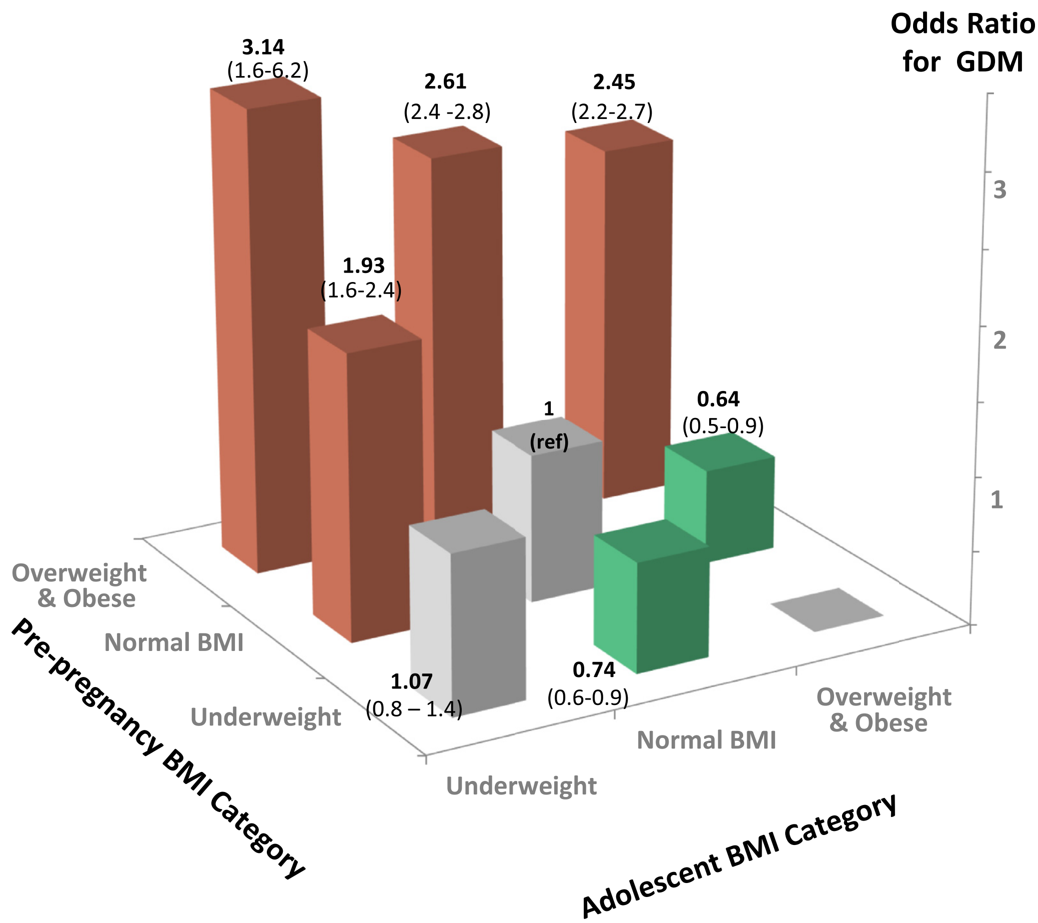

Figure 3. The association between change in body mass index (BMI) from adolescence to pre-pregnancy (n=58,727), and incident gestational diabetes mellitus (GDM) (n=3310). The adjusted odds ratios (ORs) and 95% confidence intervals (with rounded one-digit precision) for GDM relate to a model adjusted for age at delivery, year of birth, education, residential socioeconomic status, and cognitive score (reference group, women with sustained normal BMI). Numbers of case incidence, the population at risk, and statistical significance are detailed in Supplementary Table S6. Red bars denote significantly higher odds ratios, green bars denote significantly lower odds ratios, and gray bars denote comparable odds ratios to the reference group.

analysis was limited to the period during which pre-pregnancy BMI data were available for 51% of the population. Fourth, the two-step Carpenter-Coustan screening may not detect women at a lower risk of GDM complications. This was recently shown in a large pragmatic, randomized clinical trial [41] and a systematic review [42], though, nonetheless, this screening approach was highly representative of clinically-relevant GDM. Further, the greater specificity of this screening compared to the one-step 75 gr OGTT affords the possibility of attenuating misclassification of GDM. Notably, the prevalence of GDM in our cohort (5.4%) was similar to the 6.1% median prevalence calculated for European countries [23]. Limiting the analysis to first documented pregnancies reduced variability by the number of pregnancies, which may also contribute to lower GDM prevalence [43]. Given the retrospective study design, we were limited to utilizing data that were routinely collected as part of clinical care and therefore lacked information of body composition, physical activity, and nutrition. In addition, we were limited to pregnancies that were documented in the electronic medical records since 2000. Finally, this cohort does not represent Arab and orthodox Jewish women, who are not obligated to serve in the army [44]. This may limit the generalizability of our findings to these ethnic groups.

Study strengths include a longitudinal design with a large, population-based sample of nulliparous women in a setup with small selection bias. Further, weight and height were measured at age 17 years along a strict control of adolescent health status; sociodemographic data were systematically collected; and the high case density enabled examining the stability of the association in rigorous sensitivity analyses. The state-mandated coverage by healthcare providers such as MHS ensures free and unselected access to medical care. These represent approximately 90% of pregnancies in MHS, and about one-quarter of the pregnancies in Israel [12].

In conclusion, this study demonstrated that BMI and BMI trends during adolescence and young adulthood are important predictors of GDM risk. This indicates the importance of gathering long-term weight history in assessing GDM risk among pregnant women. The possibility that weight reduction and physical activity pre-pregnancy may reduce GDM risk [45] emphasizes the importance of weight loss to mitigate the risk of GDM. Further, we found indications that women whose BMI normalized from age 17 years to pre-pregnancy had a similar or even lower risk of GDM as those with normal-weight at both points of time. Hence, our findings emphasize the significance of normalizing BMI in mitigating GDM risk. This of increasing relevance given the global prevalence of adolescent obesity and morbid obesity.

6. Author contributions

G.C. and G.T. designed and supervised the study, performed the statistical analyses, interpreted the data, and drafted and revised the manuscript. M.O.G. and G.P. conducted the literature search, interpreted the data, contributed to the discussion, and critically revised the manuscript. E.D acquired data, performed the statistical analysis, interpreted the data, and critically revised the manuscript. D.T. acquired and interpreted the data. R.R. interpreted the data. T.C.Y, O.

P.H., A.S., I.Z., A.T., A.A, and V.S. contributed to the discussion and critically revised the manuscript. G.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Data sharing statement

The data are not publicly available due to privacy and ethical restrictions. Interested parties can contact the corresponding authors.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101211.

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