OBJECTIVE
Type 2 diabetes (T2D) is increasingly diagnosed at younger ages. We investigated the association of adolescent obesity with incident T2D at early adulthood.

RESEARCH DESIGN AND METHODS
A nationwide, population-based study evaluated 1,462,362 adolescents (59% men, mean age 17.4 years) during 1996–2016. Data were linked to the Israeli National Diabetes Registry. Weight and height were measured at study entry. Cox proportional models were applied.

RESULTS
During 15,810,751 person-years, 2,177 people (69% men) developed T2D (mean age at diagnosis 27 years). There was an interaction among BMI, sex, and incident T2D ($P_{interaction} = 0.023$). In a model adjusted for sociodemographic variables, the hazard ratios for diabetes diagnosis were 1.7 (95% CI 1.4–2.0), 2.8 (2.3–3.5), 5.8 (4.9–6.9), 13.4 (11.5–15.7), and 25.8 (21.0–31.6) among men in the 50th–74th percentile, overweight, mild obesity, and severe obesity groups, respectively, and 2.2 (1.6–2.9), 3.4 (2.5–4.6), 10.6 (8.3–13.6), 21.1 (16.0–27.8), and 44.7 (32.4–61.5), respectively, in women. An inverse graded relationship was observed between baseline BMI and mean age of T2D diagnosis: 27.8 and 25.9 years among men and women with severe obesity, respectively, and 29.5 and 28.5 years among low-normal BMI (5th–49th percentile; reference), respectively. The projected fractions of adult-onset T2D that were attributed to high BMI (≥85th percentile) at adolescence were 56.9% (53.8–59.9%) and 61.1% (56.8–65.2%) in men and women, respectively.

CONCLUSIONS
Severe obesity significantly increases the risk for incidence of T2D in early adulthood in both sexes. The rise in adolescent severe obesity is likely to increase diabetes incidence in young adults in coming decades.

Diabetes is a major public health burden associated with high rates of morbidity, hospitalization, health care service utilization, and mortality. Diabetes affects over 400 million people worldwide, and the global prevalence has been growing, with a disproportionate increase at young ages (1). For example, in the U.S., the prevalence of type 2 diabetes (T2D) in people age <45 years doubled during two decades, reaching a prevalence of 4.0% (representing 12 million adults) by 2015 (2,3). Notably, younger age of T2D onset was linked to more severe disease, as recently exemplified by increased risk for cardiovascular mortality (4).

Several epidemiologic studies have reported a strong relationship between obesity in youth and subsequent T2D (5–12). However, these studies generally focused on...
people who developed T2D after age 40 years and used self-recall of body weight during adolescence as a measure of risk factor (6, 9, 10, 12). Moreover, they generally excluded diagnoses of diabetes before the age of 30 years, were limited to men (5, 8), and did not capture the impact on diabetes incidence of the rapid rise in the prevalence of severe obesity in adolescents. Here, we analyzed associations of BMI in adolescent males and females with incident diabetes in a nationwide cohort of 1.46 million adolescents with a follow-up into young adulthood.

RESEARCH DESIGN AND METHODS

Study Population
This study included all Israeli male and female adolescents who underwent a medical evaluation in the year before their mandatory military service. Individuals were between the ages of 16 and 19 years. Males were included if they were evaluated between 1 January 1996 and 31 December 2016 and females if evaluated between 1 January 1997 and 31 December 2016. Individuals were excluded from the analysis if they had diabetes or dysglycemia at the time of their examination (as reported by their primary care physician on the basis of fasting plasma glucose ≥100 mg/dL or glycated hemoglobin ≥5.7%), if they died before the Israel National Diabetes Registry (INDR) was established in 2012 (because diabetes status before their death could not be determined) (Fig. 1), or if BMI data were not available. The final study sample included 1,462,362 examinees for whom we had a continuous follow-up from age 17 years until diabetes onset, death, or 31 December 2016, whichever came first. Of note, some minorities (mostly Arab adolescents of both sexes) and Orthodox and ultra-Orthodox Jewish females are not obligated to serve in the army and are thus underrepresented in this cohort. On the other hand, the sample of Jewish men can be regarded as nationally representative (13). The Israel Defense Forces Medical Corps institutional review board approved this study, waiving the requirement for informed consent.

The INDR and Diagnosis of Diabetes
The primary outcomes of the study were incident T2D that was diagnosed either during military service or later in life as recorded by the INDR. All health medical organizations in Israel have been required by law to annually report prevalent cases of diabetes to the INDR since 2012.

For the purpose of this research, we used data from the INDR to attain the recordings of all diabetes diagnoses that were recorded in Israel between 1 January 2000 and 31 December 2011 and to attain the prospective recording of all new diagnoses from 1 January 2012 onward. In addition, the INDR database includes a set of clinical variables that are updated annually on the basis of measurements obtained during the previous calendar year. Data in the INDR were linked to the Israel Defense Forces database using national identity numbers. This enables linkage of medical data obtained at adolescence, including weight and height measurements, with diabetes incidence recorded later in life. Health medical organizations were required to report diabetes to the INDR when one or more of the following criteria were met in the previous year of the report to the registry: 1) glycated hemoglobin ≥6.5% (47.5 mmol/mol), 2) serum glucose concentrations of ≥200 mg/dL (11.1 mmol/L) in two tests performed at an interval of at least 1 month, and 3) greater than or equal to three purchases of glucose-lowering medications in different months. Individuals who did not meet these criteria were assumed not to have diabetes. The registry captures nearly 100% of all diabetes diagnoses among permanent residents in Israel on the basis of these criteria. The sensitivity of the INDR is 95%, and the specificity is 93%.

While the INDR does not receive data regarding the types of diabetes, it includes data regarding prescribed diabetes medications. Using this information, we excluded from the analysis individuals with a diagnosis of type 1 diabetes according to the application of the following criteria to those who were actively treated with short-acting insulin: 1) the treatment with short-acting insulin was initiated within 1 year of diabetes onset, and 2) insulin treatment, but not oral antidiabetic drugs, was prescribed. If information on antidiabetic medications was missing, the diagnosis was referred to as diabetes of uncertain type. Gestational diabetes is not reported to the INDR and was therefore not included in this study. The INDR also includes weight and height measurements that were obtained during routine clinic visits and were available at the time that an individual with diabetes was recorded in the diabetes registry. Post-baseline BMI levels were not available for people who were not diagnosed with diabetes.

Data Collection and Study Variables
Weight and height were measured (barefoot and in underwear) at baseline by trained medics using a beam balance and stadiometer to the nearest 0.1 kg and centimeter, respectively. BMI was calculated (weight [in kilograms] divided by squared height [in meters]). The health examination was performed by military physicians who reviewed the examinees’ medical records and provided diagnostic codes when applicable. Data regarding education, socioeconomic status (SES), cognitive performance score, and country of origin were recorded as well.

Age at examination and year of birth were treated as continuous variables. Education was divided into three groups: ≤10, 11, or 12 years of formal schooling. SES was based on place of residence at the time of examination and classified into low, medium, and high, as reported previously (14). Cognitive performance was assessed by a general intelligence score, which was shown to correlate with >85% with intelligence quotient (14). Cognitive performance categories were low (<−1 SD), medium (−1 to <1 SD), and high (>1 SD), as reported previously (14). Country of origin (classified by father’s or grandfather’s country of birth if the father was born abroad) and country of birth were grouped as reported previously (13). BMI was classified according to the U.S. Centers for Disease Control and Prevention—established percentiles, which were validated for Israeli adolescents (15), for age (by month) and sex for the following subgroups: BMI <5th (underweight), 5th ≤BMI <50th (low-normal), 50th ≤BMI <75th, 75th ≤BMI <85th, 85th ≤BMI <95th (overweight), mild obesity (also referred to as class I obesity) (≥95th percentile to <120% of the 95th percentile), and severe obesity that grouped both class II obesity (≥120% to <140% of the 95th percentile or BMI ≥35 kg/m², whichever was lower) and class III obesity (≥140% of the 95th percentile or BMI ≥40 kg/m², whichever was lower) (16).

Statistical Analysis
The incidence rate of T2D was calculated per person-years of follow-up. Kaplan-Meier survival curves were computed for
Pre-recruitment evaluation during 1996-2016 (n=1,487,325) 
Adolescents, aged 16-19 years

Medical assessment
- Review of health summary by examinees’ family physician
- Detailed medical interview and physical examination by a physician
- Anthropometric measurement

Collection of sociodemographic data
- Years of education
- Residential socioeconomic status
- Cognitive test (IQ-equivalent test)

Excluded (n=60,963)
Deaths before 2012 (n=2,547)  
History of diabetes or dysglycemia (n=3,289)  
Missing BMI data (n=55,193)

1,426,362 participants
834,050 men  
592,312 women

2,177 incident diagnoses of type 2 diabetes
- 1,490 (0.17%) among men
- 687 (0.18%) among women

405 diagnoses of diabetes of uncertain type
777 diagnoses of incident type 1 diabetes

Figure 1—Study design and cohort buildup. The main analysis comprised 2,177 individuals with incident diagnoses of T2D. Additionally, for 405 diagnosed with diabetes, the type of diagnosis was uncertain; these individuals were analyzed separately. Another 777 individuals were diagnosed with type 1 diabetes during the study period. Data were missing for 406 diagnoses of incident T2D; of these, 267 were analyzed separately on the basis of the first year the individuals appeared in the INDR. IQ, intelligence quotient.

RESULTS

Baseline characteristics of the 834,050 men and 592,312 women included in the study are presented in Table 1. Ages at study entry were similar across all BMI groups. As BMI increased from the low-normal range to severe obesity, proportions increased in both sexes of individuals from lower residential SES, individuals with lower scores on cognitive tests, and Israeli-born individuals.

In total, 2,177 people (1,490 men, 68%) were diagnosed with incident T2D during 15,810,751 person-years. The median follow-up periods were 11.3 years (interquartile range 5.8–16.6) and 10.9 years (5.7–15.9) among men and women, respectively. The mean follow-up length was shorter for individuals with a higher BMI, reflecting the rising obesity prevalence in this cohort in recent years (Supplementary Table 1). The cumulative incidence for T2D was more than twofold higher among those with severe obesity than those with mild obesity (Fig. 2B). Adjustment for age at study entry, birth year, education, and cognitive performance had a minimal effect on the BMI-defined risk. HRs were 1.7 (95% CI 1.4–2.0), 2.8 (2.3–3.5), 5.8 (4.9–6.9), 13.4 (11.5–15.7), and 25.8 (21.0–31.6) among men in the 50th–74th percentile, 75th–84th percentile categories with 95% CIs. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% CIs for incident diabetes using the 5th–49th BMI percentile group as the reference or the entire normal BMI range in specific sensitivity analyses. Covariates were added in a stepwise manner to a model adjusted for age and birth year. Variables that appear in Table 1 and were significant (P < 0.05) in the minimally adjusted model were included in the final multivariable analysis. Analysis was stratified by sex and by the interaction between sex and BMI (treated as a continuous variable). Incident T2D was tested in unadjusted models and multivariable models that were adjusted for age at study entry, birth year, education, and cognitive performance. The assumption of proportionality of the hazards was visually confirmed for all variables. There was no interaction between BMI or any of the study covariates included in the multivariable model with time and incident T2D (P > 0.2 for all tests in both sexes).

Several subanalyses were conducted. First, we restricted the Cox analysis to those with unimpaired health status at study entry (i.e., absence of any chronic comorbidity that requires medical therapy or any history of cancer or major operation) to minimize residual confounding by coexisting morbidities (Supplementary Table 1). Second, the study outcome was T2D onset by age 25 years (Supplementary Table 1). Third, we considered the contribution to the model of diabetes diagnoses that were classified as uncertain type (Supplementary Table 2). Finally, we accounted for cases with missing date of T2D diagnosis (Supplementary Table 3).

The population-attributable risk percent (PAR%) of T2D incidence (and 95% CI) was calculated for overweight and obesity (≥85th BMI percentile) as follows:

\[
P \left( \frac{HR - 1}{Pe(\frac{HR - 1}{Pe + 1})} \times 100 \right)
\]

in which HR is the unadjusted HR for diabetes of the overweight and obesity group, and Pe is its average prevalence. To capture the effect of the secular trend of the increasing prevalence of adolescent obesity (16), we also reestimated PAR% for every 5-year interval. Individuals with missing data (10,401, 0.7% of the cohort) were excluded from multivariable analysis. Analyses were performed using SPSS version 25.0 statistical software.
### Table 1—Characteristics of the study cohort at baseline, according to BMI groups

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>&lt;5th percentile</th>
<th>5th–49th percentile</th>
<th>50th–74th percentile</th>
<th>75th–84th percentile</th>
<th>85th–94th percentile</th>
<th>Mild obesity</th>
<th>Severe obesity</th>
<th>P value for linear trend</th>
</tr>
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<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Examinees, n</td>
<td>834,050</td>
<td>62,569</td>
<td>351,425</td>
<td>190,002</td>
<td>79,194</td>
<td>87,456</td>
<td>49,990</td>
<td>13,414</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>17.3 ± 0.5</td>
<td>17.5 ± 0.6</td>
<td>17.3 ± 0.5</td>
<td>17.3 ± 0.5</td>
<td>17.3 ± 0.5</td>
<td>17.3 ± 0.5</td>
<td>17.3 ± 0.5</td>
<td>17.3 ± 0.5</td>
<td>0.21</td>
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<tr>
<td>Mean BMI ± SD (kg/m²)</td>
<td>22.2 ± 4.0</td>
<td>17.1 ± 0.8</td>
<td>19.8 ± 1.0</td>
<td>22.4 ± 0.7</td>
<td>24.3 ± 0.6</td>
<td>26.5 ± 1.0</td>
<td>30.6 ± 1.6</td>
<td>37.1 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI range (kg/m²)*</td>
<td>12.1–47.1</td>
<td>12.1–17.8</td>
<td>17.9–21.4</td>
<td>21.4–23.6</td>
<td>23.6–25.1</td>
<td>25.1–28.4</td>
<td>28.4–34.1</td>
<td>34.1–47.1</td>
<td></td>
</tr>
<tr>
<td>Mean weight ± SD (kg)</td>
<td>67.5 ± 13.3</td>
<td>51.5 ± 4.8</td>
<td>60.0 ± 5.6</td>
<td>68.0 ± 5.7</td>
<td>73.8 ± 6.0</td>
<td>80.6 ± 7.1</td>
<td>93.3 ± 8.9</td>
<td>113.2 ± 12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean height ± SD (cm)</td>
<td>174.1 ± 6.8</td>
<td>173.7 ± 7.0</td>
<td>174.0 ± 6.8</td>
<td>174.1 ± 6.8</td>
<td>174.2 ± 6.8</td>
<td>174.2 ± 6.9</td>
<td>174.4 ± 6.9</td>
<td>174.5 ± 7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Full education, %†</td>
<td>85</td>
<td>81</td>
<td>84</td>
<td>86</td>
<td>85</td>
<td>83</td>
<td>78</td>
<td>78</td>
<td>0.156</td>
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<td>High SES, %</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>0.033</td>
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<td>High cognitive score, %</td>
<td>14</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>0.012</td>
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<tr>
<td>Israeli born, %</td>
<td>83</td>
<td>80</td>
<td>82</td>
<td>83</td>
<td>84</td>
<td>85</td>
<td>85</td>
<td>86</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| **Women**         |        |                 |                     |                     |                     |                     |               |                |                          |
| Examinees, n      | 592,312| 27,684          | 249,547             | 155,965             | 65,843              | 65,810              | 21,136        | 6,327          |                          |
| Mean age ± SD (years) | 17.2 ± 0.4  | 17.3 ± 0.5      | 17.2 ± 0.4          | 17.2 ± 0.4          | 17.2 ± 0.4          | 17.2 ± 0.4          | 17.2 ± 0.4    | 17.3 ± 0.5    | 0.51                      |
| Mean BMI ± SD (kg/m²) | 22.0 ± 3.8   | 16.5 ± 0.7      | 19.4 ± 1.0          | 22.1 ± 0.7          | 24.3 ± 0.6          | 27.0 ± 1.3          | 31.8 ± 1.5    | 37.9 ± 2.6    | <0.001                    |
| BMI range (kg/m²)* | 12.6–47.7   | 12.6–17.3       | 17.3–21.0           | 21.0–23.5           | 23.5–25.3           | 25.3–29.8           | 29.8–35.0     | 35.0–47.7     |                          |
| Mean weight ± SD (kg) | 57.8 ± 11.0  | 44.0 ± 3.8      | 51.0 ± 4.6          | 57.9 ± 4.8          | 63.6 ± 5.1          | 70.9 ± 6.5          | 83.8 ± 7.7    | 100.1 ± 10.7  | <0.001                    |
| Mean height ± SD (cm) | 162.1 ± 6.3  | 163.1 ± 6.5     | 162.3 ± 6.2         | 161.7 ± 6.2         | 161.8 ± 6.2         | 161.8 ± 6.3         | 162.3 ± 6.4   | 162.4 ± 6.6   | 0.49                      |
| Full education, %† | 90      | 88              | 91                   | 91                  | 90                  | 89                  | 84            | 84             | 0.29                      |
| High SES, %       | 23      | 22              | 24                   | 24                  | 23                  | 20                  | 18            | 17             | 0.025                     |
| High cognitive score, % | 10      | 8               | 11                   | 11                  | 10                  | 8                   | 7             | 5              | 0.063                     |
| Israeli born, %   | 83      | 78              | 82                   | 83                  | 84                  | 85                  | 87            | 88             | <0.001                    |

*The BMI range refers to a mean age of 17.3 years. Note that for each of the 48 months between ages 16.0 and 19.99 years, different sex- and age-specific BMI ranges determine the U.S. Centers for Disease Control and Prevention percentiles. †Full education: either a higher school student at the time of the examination or completed 12 years of formal education.
percentile, overweight, mild obesity, and severe obesity groups, respectively, and 2.2 (1.6–2.9), 3.4 (2.5–4.6), 10.6 (8.3–13.6), 21.1 (16.0–27.8), and 44.7 (32.4–61.5) among women, respectively. These results persisted when the study sample was limited to individuals with unimpaired health at baseline to minimize confounding by pre- or coexisting morbidities (Supplementary Table 1). High HRs for overweight and mild and severe obesity also withstood when diabetes onset before age 25 years served as the outcome: 3.2 (2.1–4.9), 12.1 (8.5–17.5), and 27.0 (17.9–40.7) among men, respectively, and 6.6 (4.4–9.8), 12.8 (8.2–20.0), and 45.3 (28.9–71.0) among women, respectively (Supplementary Table 1). We analyzed separately 405 diagnoses of diabetes of uncertain type and found a consistent increase in point estimates in both sexes across BMI groups; HRs were 6.0 (3.5–10.5) and 9.0 (3.8–21.4) among men and women with severe obesity, respectively (Supplementary Table 1). We analyzed separately 405 diagnoses of diabetes of uncertain type and found a consistent increase in point estimates in both sexes across BMI groups; HRs were 6.0 (3.5–10.5) and 9.0 (3.8–21.4) among men and women with severe obesity, respectively (Supplementary Table 1). We analyzed separately 405 diagnoses of diabetes of uncertain type and found a consistent increase in point estimates in both sexes across BMI groups; HRs were 6.0 (3.5–10.5) and 9.0 (3.8–21.4) among men and women with severe obesity, respectively (Supplementary Table 1). To minimize misclassification of type 1 diabetes as T2D cases, we set as the outcome diabetes cases in which treatment did not include insulin and found similar results to those presented in Table 2 (Supplementary Table 2).

For 406 incident diagnoses of diabetes, the date of diagnosis was missing. Of these, 267 were not reported to the INDR in its first year but during 2013 or later. Therefore, the date of diabetes diagnosis was assumed to be 1 July, 1 year before reporting to the INDR. We found similar point estimates in a subanalysis that included only these diagnoses (Supplementary Table 3).

Age at diagnosis showed an inverse graded relationship. The mean ages of diabetes onset were 27.8 and 25.9 years among men and women with severe obesity, respectively, compared with 30.4 and 29.0 years in the normal BMI reference group. Notably, approximately one-half of those who developed T2D and had a normal BMI at adolescence were overweight or obese at the year of diagnosis (Table 2).

The fractions of incident T2D that were attributed to overweight and obesity were 51.5% (48.3–54.7%) for men and 54.6% (50.2–59.0%) for women on the basis of mean prevalences of 17.9% and 15.6% during the study period, respectively. The PAR% calculated for 5-year intervals has gradually risen in both sexes (Supplementary Fig. 2). The projected PAR% for the 23.0% and 19.8% prevalences of overweight and obesity among men and women, respectively, for the years 2015–2016 were 56.9% (53.8–59.9%) and 60.6% (56.2–65.6%).

Figure 2—The association between adolescent obesity and incident T2D in young adulthood. A: Kaplan-Meier one-minus survival curves are plotted with 95% CIs. The number of individuals at risk is indicated below each panel for the given BMI category. B: The histogram shows the cumulative incidence values (with 95% CIs) at ages 25 and 30 years (corresponding to 7.7 and 12.7 years of follow-up, respectively).
Table 2—Risk estimates of the association between adolescent BMI and incident T2D in young adulthood

<table>
<thead>
<tr>
<th></th>
<th>BMI category at adolescence</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>&lt;5th percentile (underweight)</td>
<td>5th–49th percentile (low normal)</td>
<td>50th–74th percentile</td>
<td>75th–84th percentile</td>
<td>85th–94th percentile (overweight)</td>
<td>Mild obesity</td>
<td>Severe obesity</td>
<td>P value for trend</td>
<td></td>
</tr>
<tr>
<td>Men Incident cases, n</td>
<td>1,490</td>
<td>44</td>
<td>302</td>
<td>217</td>
<td>139</td>
<td>292</td>
<td>353</td>
<td>143</td>
<td></td>
<td></td>
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<tr>
<td>Mean follow-up ± SD (years)</td>
<td>11.7 ± 6.1</td>
<td>12.0 ± 6.1</td>
<td>11.8 ± 6.1</td>
<td>11.2 ± 6.0</td>
<td>10.8 ± 6.0</td>
<td>10.3 ± 5.9</td>
<td>9.8 ± 5.8</td>
<td>8.8 ± 5.5</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Person-years of follow-up</td>
<td>9,412,455</td>
<td>753,711</td>
<td>4,158,394</td>
<td>2,136,497</td>
<td>851,800</td>
<td>902,214</td>
<td>491,455</td>
<td>118,382</td>
<td></td>
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</tr>
<tr>
<td>Incidence* (per 10⁻⁵ person-years)</td>
<td>15.8</td>
<td>5.8</td>
<td>7.3</td>
<td>10.2</td>
<td>16.3</td>
<td>32.3</td>
<td>71.8</td>
<td>120.9</td>
<td>0.008</td>
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</tr>
<tr>
<td>Mean age at end of follow-up ± SD (years)</td>
<td>28.6 ± 6.1</td>
<td>29.5 ± 6.2</td>
<td>29.2 ± 6.1</td>
<td>28.5 ± 6.1</td>
<td>28.0 ± 6.1</td>
<td>27.6 ± 6.0</td>
<td>27.1 ± 5.9</td>
<td>26.1 ± 5.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean age at diagnosis ± SD (years)</td>
<td>30.0 ± 4.3</td>
<td>31.3 ± 4.0</td>
<td>30.4 ± 4.6</td>
<td>30.6 ± 4.1</td>
<td>30.8 ± 4.0</td>
<td>30.4 ± 4.0</td>
<td>29.3 ± 4.1</td>
<td>27.8 ± 4.6</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Mean BMI at year of diagnosis ± SD (kg/m²)</td>
<td>31.1 ± 6.3</td>
<td>23.7 ± 4.7</td>
<td>25.8 ± 4.3</td>
<td>29.7 ± 5.1</td>
<td>30.3 ± 4.6</td>
<td>31.9 ± 5.1</td>
<td>34.4 ± 5.5</td>
<td>37.3 ± 6.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Overweight or obese at year of diagnosis, %</td>
<td>83.8</td>
<td>36.4</td>
<td>52.7</td>
<td>85.7</td>
<td>92.8</td>
<td>93.8</td>
<td>97.5</td>
<td>98.1</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>HR adjusted†</td>
<td>0.61</td>
<td>1</td>
<td>1.66</td>
<td>2.82</td>
<td>5.81</td>
<td>13.42</td>
<td>25.8</td>
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<tr>
<td>95% CI</td>
<td>0.44–0.84</td>
<td>1.39–1.98</td>
<td>2.30–3.47</td>
<td>4.92–6.85</td>
<td>11.47–15.72</td>
<td>21.0–31.61</td>
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<tr>
<td>P value</td>
<td>0.003</td>
<td>7.4 × 10⁻¹⁰</td>
<td>2.5 × 10⁻¹³</td>
<td>9.2 × 10⁻⁹⁷</td>
<td>8.3 × 10⁻²²⁹</td>
<td>3.5 × 10⁻²¹³</td>
<td></td>
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</tr>
<tr>
<td>Women Incident cases, n</td>
<td>687</td>
<td>10</td>
<td>92</td>
<td>115</td>
<td>69</td>
<td>209</td>
<td>123</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean follow-up ± SD (years)</td>
<td>10.8 ± 5.8</td>
<td>11.1 ± 5.7</td>
<td>11.2 ± 5.7</td>
<td>10.8 ± 5.8</td>
<td>10.5 ± 5.8</td>
<td>10.1 ± 5.8</td>
<td>9.6 ± 5.7</td>
<td>8.8 ± 5.4</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Person-year follow-up</td>
<td>6,407,296</td>
<td>308,543</td>
<td>2,797,131</td>
<td>1,686,554</td>
<td>691,622</td>
<td>665,386</td>
<td>202,436</td>
<td>55,624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence* (per 10⁻⁵ person-year)</td>
<td>10.7</td>
<td>3.2</td>
<td>3.3</td>
<td>6.8</td>
<td>10.0</td>
<td>31.4</td>
<td>60.8</td>
<td>124.4</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Age at end of follow-up ± SD (years)</td>
<td>28.0 ± 5.9</td>
<td>28.4 ± 5.8</td>
<td>28.4 ± 5.8</td>
<td>28.0 ± 5.9</td>
<td>27.7 ± 5.9</td>
<td>27.3 ± 5.9</td>
<td>26.7 ± 5.8</td>
<td>26.0 ± 5.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean age at diagnosis ± SD (years)</td>
<td>27.7 ± 5.9</td>
<td>29.0 ± 3.8</td>
<td>29.0 ± 4.7</td>
<td>28.2 ± 4.3</td>
<td>28.0 ± 3.8</td>
<td>28.1 ± 4.0</td>
<td>28.0 ± 4.5</td>
<td>25.9 ± 4.7</td>
<td>0.181</td>
<td></td>
</tr>
<tr>
<td>Mean BMI at year of diagnosis ± SD (kg/m²)</td>
<td>32.1 ± 7.2</td>
<td>23.0 ± 4.7</td>
<td>25.1 ± 5.2</td>
<td>28.5 ± 5.6</td>
<td>30.2 ± 5.0</td>
<td>32.7 ± 5.4</td>
<td>37.7 ± 6.6</td>
<td>39.3 ± 6.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Overweight or obese at year of diagnosis, %</td>
<td>82.3</td>
<td>25</td>
<td>46.4</td>
<td>70.3</td>
<td>86</td>
<td>91.1</td>
<td>98.1</td>
<td>100</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>HR adjusted†</td>
<td>0.90</td>
<td>1</td>
<td>2.17</td>
<td>3.38</td>
<td>10.63</td>
<td>21.08</td>
<td>44.66</td>
<td></td>
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<tr>
<td>95% CI</td>
<td>0.47–1.78</td>
<td>1.64–2.87</td>
<td>2.46–4.63</td>
<td>8.29–13.64</td>
<td>16.00–27.77</td>
<td>32.42–61.52</td>
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</tr>
<tr>
<td>P value</td>
<td>0.76</td>
<td>5.3 × 10⁻¹⁰</td>
<td>3.6 × 10⁻¹⁴</td>
<td>4.4 × 10⁻⁷⁷</td>
<td>3.0 × 10⁻⁵⁰⁴</td>
<td>1.4 × 10⁻¹⁵⁹</td>
<td></td>
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</table>

*Parentheses denote 95% CI. †The model was adjusted for age at study entry, birth year, education, and cognitive performance score.
CONCLUSIONS

This nationwide study showed increased incidence of T2D in early adulthood among individuals with severe obesity in late adolescence. HRs were 26 and 45 among men and women, respectively, compared with their peers with normal BMI at adolescence. The absolute risk for incident T2D was substantially higher in severe versus mild obesity in both sexes. This is evident by the >1.5% incidence rate for diabetes development before the age of 30 years among those with severe obesity compared with less than one-half the fraction among those with mild obesity. The constancy of the risk estimates following adjustment by sociodemographic background, country of origin, and baseline medical status suggests that the results are likely generalizable to populations of other sociodemographic backgrounds.

Previous works that emphasized the importance of adolescent BMI to future cardiometabolic health excluded diagnoses of incident T2D in the first three decades of life (5,8). Other studies that examined the effect of changes in BMI during the life course showed that even modest weight gain might be associated with an increased risk of T2D. However, these studies included diagnoses in the sixth decade of life and later (10,12).

In other studies, relative risks for incident T2D among young adults with obesity were reported to span between 4.2 and 27.8 compared with their counterparts with normal BMI (17,18). Longer duration of follow-up, higher female-to-male ratio, and larger study size were usually associated with higher risk estimates (19). Several studies on the BMI-diabetes association were based on recall weight and height, which might lead to underestimation of the actual HR (20,21). Finally, early versus mid-adulthood age at study entry was associated with higher risk estimates (9). These are likely due to lower prevalences of concomitant diabetes risk factors (22) and lead to a minimal incidence in the reference group. The higher risk estimates among female adolescents with obesity, observed herein, is consistent with a meta-analysis that reported relative risks of 8.4 and 6.5 among women and men with obesity, respectively, compared with their sex-matched counterparts with normal BMI (19). U.S. data also show that girls, but not boys, who became obese before age 16 years had a more than twofold higher risk for diabetes in adulthood than those who became obese at or after the age of 18 years (23,24). In addition, among adolescents who developed T2D at a mean age of 13–14 years, girls are more susceptible than boys, with an overall female-to-male ratio of 1.7:1, regardless of race (25). Early age of onset of puberty among girls with decreased insulin sensitivity during puberty as well as decreased physical activity among girls are possible explanations (26). Another potential explanation is that BMI may better reflect fat mass in female adolescents than in males because of increased muscle mass in the latter, especially among those in the normal BMI range (27). In addition to biological differences, sex differences may be attributed to social and cultural factors. Our findings are important because females with T2D have a higher mortality rate, with BMI being the leading modifiable risk factor (28).

While adolescent BMI is recognized as a strong risk factor for incident T2D (29), relatively few works have examined associations between various degrees of adolescent obesity and incident diabetes at early adulthood (30). Severe obesity became much more prevalent in recent years and has increased disproportionally compared with mild obesity. For example, among both U.S. (31,32) and Israeli (16) adolescents, mild obesity has less than doubled in the past two decades, whereas severe obesity has increased by almost fourfold. In parallel to this increase, a disproportionate rise in incident T2D in early adulthood has been reported in the U.S. for both sexes (33). The reported prevalence is in the range of 2.5–4.4% among adults age <35 years (23,34).

We report a projected PAR% for diabetes related to overweight and obesity in adolescence as 57% and 61% for men and women, respectively, on the basis of the mean prevalence of overweight and obesity between 2015 and 2016. Previous studies reported a wide range of PAR%s for diabetes related to overweight and obesity (3–66%), albeit in middle-aged adults from age 35 to ≥40 years (35,36). These estimates deserve public health attention given the implications of diabetes on disability (37), morbidity (38), and health care expenditures (39), especially when diagnosed among young adults (40).

Our work has limitations. We lacked data on repeated anthropometric measurements to allow assessment of cumulative exposure to high BMI as well as longitudinal data into adulthood for those who remained diabetes free. Nevertheless, the effect of BMI was well evident before age 25 years, during which a meaningful drift in BMI percentiles is less likely to occur (8). We also lacked lifestyle data and other measures of adiposity, such as waist circumference, which might be a more sensitive measure than BMI and better define the population at risk (41), especially among men, as mentioned above. Nevertheless, BMI is considered as the preferable method for screening according to the U.S. Preventive Services Task Force (42). In addition, while individuals with known dysglycemia at baseline were excluded, we did not have data regarding fasting blood glucose at adolescence, and therefore we could not assess the risk associated with increased glucose levels within the normal range and diabetes incident at adulthood (43). We cannot exclude the possibility that individuals with type 1 diabetes, including latent autoimmune diabetes in adults, were included. Yet, such misclassification is likely to result in underestimation of the point estimates in relation to obesity. The definition of type 1 diabetes used in this study, on the basis of the primary use of insulin, likely minimized such misclassification. Our study predominantly represents non-Hispanic whites, and is unrepresentative of other ethnicities, such as Native Americans, Hispanics, African Americans, and East Asians. Glucose-lowering drugs such as metformin might have been prescribed for indications other than diabetes, such as menstrual irregularities. The strengths of this study include the linkage of two detailed national databases with systematic data collection of sociodemographic variables; measured, rather than reported, weight and height values; strict control of coexisting morbidities; and heterogenous genetic ancestry (44).

The transition from adolescence to early adulthood is a sensitive period for the development of diabetes (23,45). Data regarding actual risk for incident diabetes is of clinical value to better define populations at risk, to identify early abnormal weight gain patterns, and to direct health care policy in the evaluation and management of obesity among youth. Among adolescents with obesity, and particularly females with severe obesity, the higher risk for incident T2D is of clinical and public health
importance, especially given the ongoing increasing size of this subpopulation.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. G.T. conceived and designed the study; analyzed and interpreted the data; wrote the first draft of and revised the manuscript, incorporating contributions from co-authors; and decided on submission. I.Z., M.L., T.S., and D.T. conducted database management quality assurance, interpreted the data, contributed to the discussion, and critically revised the manuscript. A.A., T.C.-Y., O.M., O.P.-H., I.R., and H.C.G. interpreted the data, contributed to the discussion, and critically revised the manuscript. C.D.B. and S.T. analyzed the data, contributed to the discussion, and critically revised the manuscript. E.D. conducted the statistical analysis and critically revised the manuscript. A.T. designed the study, analyzed and interpreted the data, wrote the first draft, and decided on submission. 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.

References
35. Magliano DJ, Martin VJ, Owen AJ, Zomer E, Liew D. The productivity burden of diabetes at a
population level. Diabetes Care 2018;41:979–984
45. RISE Consortium. Metabolic contrasts between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: II. Observations using the oral glucose tolerance test. Diabetes Care 2018;41:1707–1716