Adolescent Hypertension and Risk for Early-Onset Type 2 Diabetes: A Nationwide Study of 1.9 Million Israeli Adolescents

Diabetes Care 2021;44:e6–e8 | https://doi.org/10.2337/dc20-1752

Boris Fishman,[1,2,3,4] Ehud Grossman,[3,4] Inbar Zucker,[4,5] Omri Orr,[1,2] Miri Lutski,[4,5] Aya Bardugo,[1,2] Cole D. Bendor,[1,2] Yoav Leiba,[1,2] Tali Cukierman-Yaffe,[4,6] Estela Derazne,[4] Ofri Mosenzon,[7] Dorit Tzur,[1,2] Zivan Beer,[1,2] Orit Pinhas-Hamiel,[4,8] Tamar Fishman,[9] Arnon Afek,[4,10] Amir Tirosh,[4,6] Itamar Raz,[7] Hertzel C. Gerstein,[11] and Gilad Twig[1,2,4,6]

The incidence of adolescent hypertension is growing worldwide, mostly in conjunction with the growing obesity prevalence (1,2). Adolescent hypertension was shown to be a risk factor for cardiovascular and renal outcomes later in life, thus promoting current guidelines to screen all pediatric and adolescent population for hypertension (1,3). Here, we elucidate the association of adolescent hypertension and early-onset type 2 diabetes in a nationwide cohort of adolescents.

In this population-based, retrospective cohort study we linked the Israeli Defense Forces conscription center database with the Israeli National Diabetes Registry (INDR). One year prior to mandatory military service at age 17 years, Israeli adolescents undergo comprehensive medical evaluation based on their medical history, an interview and physical examination that includes measurements of height, weight, and blood pressure. Included were adolescents who were examined between 1 January 1993 and 31 December 2016. Excluded were those with prior diagnosis of dysglycemia and those with missing baseline height or weight data (3.8% in total).

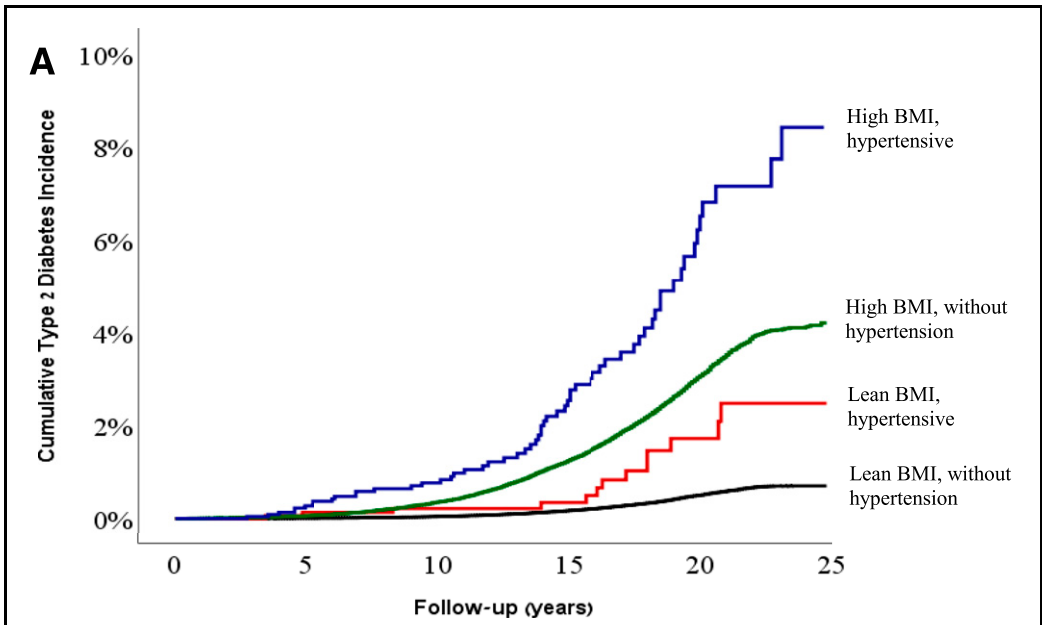
Essential hypertension diagnosis was confirmed by a board-specified nephrologist based on a preexisting diagnosis or screening for hypertension as described previously (1). Briefly, adolescents with blood pressure measurement during the screening assessment of >140/90 mmHg were referred for further investigation. The final diagnosis was made when the average of 10 additional outpatient blood pressure measurements was >140/90 mmHg, when at least 50% of the measurements were above this level, and after exclusion of secondary hypertension. The primary outcome was incident type 2 diabetes as documented by the INDR, which captures all cases of diabetes in Israel with a sensitivity of 95.1% (2).

Cox models were applied. Follow-up started at the day of the first medical examination and ended at the date of diabetes diagnosis, 31 December 2016, or death—whichever came first. Due to the previously described significant interaction among BMI, hypertension, and type 2 diabetes, which was also evident in our cohort ($P_{interaction} < 0.01$ for BMI used as either a categorical or a continuous variable), we analyzed separately adolescents with lean and high BMI by overweight cutoff (85th BMI percentile of the Centers for Disease Control and Prevention, age and sex matched). We prespecified the multivariable model to include the following variables that were assessed or received from other governmental ministries at study entry: birth year, age, sex, BMI (continuous), country of birth, residential socioeconomic status, education level, and cognitive performance, as used previously (2).

[1]Department of Military Medicine, Hebrew University, Jerusalem, Israel
[2]The Israel Defense Forces Medical Corps, Ramat Gan, Israel
[3]Internal Medicine D Department and Hypertension Unit, Sheba Medical Center, Ramat Gan, Israel
[4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[5]Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel
[6]Institute of Endocrinology, Sheba Medical Center, Ramat Gan, Israel
[7]Diabetes Unit, Department of Internal Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel
[8]Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel
[9]Pharmacy Services, Meir Medical Center, Kfar-Saba, Israel
[10]Central Management, Sheba Medical Center, Ramat Gan, Israel
[11]Department of Medicine, McMaster University Hamilton, Ontario, Canada

Corresponding author: Gilad Twig, gilad.twig@gmail.com

Received 13 July 2020 and accepted 2 October 2020



Lean BMI:

Number at risk	1,146,162	877,847	591,088	279,646
Cumulative PY	6,455,899	11,530,134	15,224,596	17,405,349
Cumulative T2D cases	112	462	1,391	2,753

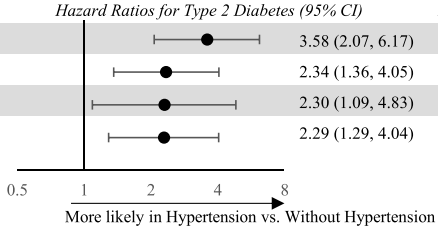
High BMI:

Number at risk	207,463	143,762	88,304	37,466
Cumulative PY	1,234,845	2,108,161	2,687,956	2,997,271
Cumulative T2D cases	152	651	1,693	2,780

B

Lean BMI

	Without Hypertension	Hypertensive	Hazard Ratios for Type 2 Diabetes (95% CI)	P Value
	no. of cases/total no. of participants			
Total population$_{crude}$	3,166/1,384,665	13/1,645	3.58 (2.07, 6.17)	<0.001
Total population$_{adjusted}$^	3,131/1,375,719	13/1,636	2.34 (1.36, 4.05)	0.002
Unimpaired health^§	2,031/953,717	7/793	2.30 (1.09, 4.83)	0.028
Men only^	1,919/779,476	12/1,517	2.29 (1.29, 4.04)	0.004



C

High BMI

	Without Hypertension	Hypertensive	Hazard Ratios for Type 2 Diabetes (95% CI)	P Value
	no. of cases/total no. of participants			
Total population$_{crude}$	3,025/270,389	59/2,498	2.05 (1.69, 2.66)	<0.001
Total population$_{adjusted}$^	2,993/268,679	58/2,493	1.32 (1.02, 1.72)	0.039
Unimpaired health^§	1,853/188,512	28/1,173	1.38 (0.96, 2.00)	0.086
Men only^	1,785/161,777	52/2,278	1.34 (1.02, 1.77)	0.040

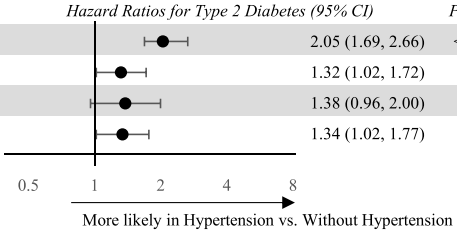


Figure 1—*A*: Cumulative incidence of type 2 diabetes according to BMI group and hypertension status ($N = 1,659,197$). The table presents (for lean- and high-BMI groups separately) the number of persons at risk, cumulative person-years, and cumulative type 2 diabetes cases by the following follow-up time intervals since study entry: 5, 10, 15, and 20 years. PY, person-years; T2D, type 2 diabetes. *B* and *C*: The association of adolescent hypertension and incident type 2 diabetes in young adults according to adolescent BMI. ^Adjustment for age at study entry, sex (except in the analysis limited for men), birth year, country of birth, BMI (continuous), residential socioeconomic status, years of formal education, and cognitive performance. Description of these covariates and their classification was previously published (2). §Unimpaired health was defined as absence of any chronic comorbidities (apart from hypertension) that require medical treatment or follow-up, history of a major surgery, or cancer.

Of 1,659,197 adolescents in total, 4,143 (0.3%) were diagnosed with essential hypertension at study entry. Of the 1,386,310 (83.6%) adolescents in the lean group, 1,645 (0.1%) had hypertension. Of the 272,887 adolescents in the high-BMI group, 2,498 (0.9%) had hypertension. Men comprised 57% of the cohort but >90% of those with hypertension. The mean BMI at study entry was higher among those with than without hypertension, both for the lean-BMI group, 21.6 vs. 20.3 kg/m^2, and for the high-BMI group, 30.9 vs. 28.3 kg/m^2.

During a cumulative follow-up of 21,171,855 person-years (median follow-up 12.8 years [interquartile range 6.7–18.7]), 6,263 persons were diagnosed with type 2 diabetes (3,179 [0.2%] in the lean-BMI group and 3,084 [1.1%] in the high-BMI group). Among those with hypertension at study entry, 13 (0.8%) and 59 (2.3%) developed type 2 diabetes in the lean- and high-BMI groups, respectively. The mean ± SD age of diagnosis of type 2 diabetes was 32.0 ± 4.8 years. Figure 1*A* presents Kaplan-Meier survival curves of cumulative incidence of type 2 diabetes by BMI group and hypertension status. Crude rates of incidence of type 2 diabetes (per 10^5 person-years) were 17.5 for those without hypertension in the lean-BMI group, 59.7 for those with hypertension in the lean-BMI group, 98.9 for those without hypertension in the high-BMI group, and 198.5 for those with hypertension in the high-BMI group.

In unadjusted models, the hazard ratio (HR) for incident type 2 diabetes among adolescents with compared with adolescents without hypertension was 3.6 (95% CI 2.1–6.2) for those who were lean at study entry and 2.1 (1.7–2.7) for those with high BMI (Fig. 1*B* and *C*). The adjusted models yielded HRs of 2.3 (1.4–4.1) in the lean-BMI and 1.3 (1.02–1.7) in the high-BMI groups (Fig. 1*B* and *C*). Results persisted when the study sample was limited to men or to individuals with unimpaired health at study entry (Fig. 1*B* and *C*). Logistic regression models that included an additional 383 persons (6% of the overall incident cases) with missing date of diabetes diagnosis resulted in adjusted odds ratios that were similar to those of the Cox modeling: 2.6 (95% CI 1.6–4.4) in the lean-BMI group and 1.4 (1.04–1.8) in the high-BMI group.

Previous longitudinal studies on associations of hypertension or increased blood pressure with incident type 2 diabetes reported HRs that ranged between 1.4 and 2.4. Most of those studies included middle-aged adults who developed diabetes usually in the 6th decade of life or later. We are unaware of similar longitudinal studies among adolescents or studies that specifically examined the incidence of early-onset type 2 diabetes, which was shown to have even more deleterious effects than older age of diabetes onset (4).

In our study, 60% of those with hypertension had high BMI at study entry. Hypertension among overweight and obese adolescents remained a risk factor for incident type 2 diabetes in both BMI groups. Importantly, the substantial absolute attributable risk of hypertension for incident type 2 diabetes was higher in the high-BMI group. This corroborates the evidence in adults that hypertension significantly augments the obesity-driven risk for type 2 diabetes. Therefore, our study adds that adolescent hypertension, in the presence and even in the absence of high BMI, and without other comorbidities, is a potential risk factor or risk marker for early-onset type 2 diabetes. Several mechanisms may underlie this association such as insulin resistance as a common pathway for both hypertension and type 2 diabetes and vascular damage induced by hypertension leading to endothelial dysfunction (5).

Our study is limited by absence of longitudinal data regarding weight, blood pressure, lifestyle, and pharmacological treatment for hypertension. Also, detailed assessment of body composition, with particular relevance to the high-BMI group, was not available. Finally, our study poorly represents some ethnicities, such as East Asians and sub-Saharan Africans. The strengths of our study include systematic screening of a young population for hypertension, systematic collection of medical and sociodemographic data, and linkage between two national databases that provided sufficient statistical power to detect an association with onset of diabetes that occurred before the age of 40 years.

In conclusion, our results emphasize the association between two growing public health issues among young adults. Adolescent hypertension was associated with future early-onset adulthood type 2 diabetes, both among individuals with lean and high BMI at adolescence. These individuals should be viewed as a population at risk and warrant awareness regarding the need for a tight medical follow-up and preventive and early therapeutic interventions.

Acknowledgments. The authors thank Cindy Cohen for assistance in language editing.

Funding. This study was partially supported by a grant from the Israel Defense Forces Medical Corps (award number 4440917164).

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

Author Contributions. B.F. designed the study, statistically analyzed and interpreted the data, and drafted and revised the manuscript. E.G., O.O., A.B., and C.D.B. interpreted the data, contributed to the discussion, and critically revised the manuscript. I.Z., M.L., and Y.L. acquired the data, contributed to the discussion, and critically revised the manuscript. T.C.-Y., O.M., Z.B., O.P.-H., T.F., A.A., A.T., I.R., and H.C.G. contributed to the discussion and critically revised the manuscript. E.D. and D.T. acquired data and statistically analyzed the data. G.T. designed and supervised the study, statistically analyzed and interpreted the data, and drafted and 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.

Prior Presentation. Parts of this study were presented in abstract form at the Israeli Diabetes, Hypertension, Obesity & Stroke Conference 2020, Tel Aviv, Israel, 26 February 2020.

References

1. Leiba A, Fishman B, Twig G, et al. Association of adolescent hypertension with future end-stage renal disease. JAMA Intern Med 2019; 179:517–523

2. Twig G, Zucker I, Afek A, et al. Adolescent obesity and early-onset type 2 diabetes. Diabetes Care 2020;43:1487–1495

3. Flynn JT, Kaelber DC, Baker-Smith CM, et al.; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140: e20171904

4. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol 2018;6:69–80

5. Climie RE, van Sloten TT, Bruno RM, et al. Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. Hypertension 2019;73: 1138–1149