Published in final edited form as:

Lancet Child Adolesc Health. 2019 January ; 3(1): 35–43. doi:10.1016/S2352-4642(18)30309-2.

Co-occurrence of early diabetes-related complications in adolescents and young adults with type 1 diabetes: the SEARCH for Diabetes in Youth study

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Author Contributions. KAS, JMS, RBD, and DD designed the present research question, developed the analysis plan, and drafted the manuscript. EMD, ETJ, LD, JML, CP, SM, RBD, and DD supervised data collection. JMS and RD conducted the analyses. All authors interpreted the results, critically reviewed the manuscript for intellectual content, and approved the final manuscript. KAS takes responsibility for the contents of the manuscript.

Duality of Interest. Dr. D'Agostino Jr reports personal fees from Amgen and KCI outside the submitted work. Dr. Marcovina reports consulting for Denka Seiken and MedTest Dx outside the submitted work. The other authors declared no conflicts of interest.

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Abstract

Background.—One in three adolescents and young adults with type 1 diabetes have at least one early diabetes-related complication/comorbidity. However, the prevalence, patterning, and risk factors for co-occurring complications in this population are not well understood.

Methods.—The SEARCH for Diabetes in Youth observational cohort study includes 1327 individuals diagnosed with type 1 diabetes before 20 years of age from 5 United States locations. Sociodemographic and metabolic risk factors were assessed at baseline (mean diabetes duration = 0·8 years, mean age = 10·9 years) and follow-up (mean diabetes duration = 7.8 years, mean age = 18·0 years). Early diabetes complications (diabetic kidney disease, diabetic retinopathy, peripheral neuropathy, cardiovascular autonomic neuropathy, and arterial stiffness) were assessed at follow-up. We aimed to describe co-occurrence of complications and examine differences in co-occurrence within demographic and metabolic risk factor clusters identified using cluster analysis.

Findings.—Overall, co-occurrence of any ≥2 complications was observed in 5·9% of all participants, more frequently than expected by chance alone (4·4%, p=0·015). Specifically, retinopathy and diabetic kidney disease, retinopathy and arterial stiffness, and arterial stiffness and cardiac autonomic neuropathy all co-occurred more frequently than expected (all p<0·05). The cluster analysis produced four unique clusters characterized by progressively worsening metabolic risk factor profiles (longer duration; higher A1c, non-HDL cholesterol, and waist to height ratio) and differences in sociodemographic characteristics (race/ethnicity, household income, type of health insurance). Prevalence of ≥2 complications progressively increased with worsening metabolic profiles (from 2·3% to 20·8%, p<0·001).

Interpretation.—We report that early complications co-occur in adolescents and young adults with type 1 diabetes more frequently than expected after an average of less than eight years of diabetes duration. A cluster of high risk factors identifies groups that may benefit most from interventions to reduce complications.

INTRODUCTION

The burden of type 1 diabetes is continuing to increase worldwide.[1] In the United States, the incidence of type 1 diabetes among youth <20 years of age increased by 1.4% per year from 2002 to 2012,[2] and the prevalence increased more than 20% from 2001 to 2009,[3] resulting in a growing number of individuals living with diabetes from youth onward. The presence of diabetes-related early complications and comorbidities in this population is substantial, with one in three individuals exhibiting early signs of any one complication/comorbidity after just eight years of average diabetes duration.[4] As the duration of diabetes increases, the prevalence of each complication/comorbidity is expected to rise, particularly when accompanied by suboptimal glycemic control.[5] Several studies have also reported that microvascular complications (retinopathy, neuropathy, nephropathy) tend to co-occur in individuals with type 1 diabetes, although this work has largely been conducted among adults aged 30 years or older with at least 15 years of diabetes duration.[6–9]

In younger populations, there is limited understanding of the co-occurrence of early complications and comorbidities within a relatively short duration of type 1 diabetes. In a Danish study of 339 participants aged 12–24 years, individuals with microalbuminuria at baseline were more likely to have both nephropathy and neuropathy, but not retinopathy, six years later.[10] In contrast, a study of 80 Swedish participants aged 7–22 years reported that individuals with neuropathy were not more likely to simultaneously exhibit nephropathy or retinopathy compared to those without.[11] Our group previously reported that type 1 diabetes participants who had cardiac autonomic neuropathy were significantly more likely to concurrently exhibit increased arterial stiffness at an average age of 18·6 years and 10·1 years of diabetes duration.[12] While other studies have reported on prevalence of complications/comorbidities in younger populations with type 1 diabetes,[13,14] these studies did not examine the prevalence of co-occurring complications, or the risk factors that are associated with co-occurring complications. Since co-occurring complications are associated with increased personal and societal burden,[9,15] this knowledge can help identify youth at highest risk who may need early intensive intervention.

Thus, the purpose of this study was to examine the co-occurrence of diabetes-related early complications/comorbidities in a large, diverse sample of adolescents and young adults with type 1 diabetes. We examined co-occurrence by number and type, as well as by demographic characteristic and metabolic risk factor groups identified using cluster analysis. We hypothesized that there would be non-random co-occurrence of complications/comorbidities among participants that differed in their demographic characteristics and metabolic risk factors.

METHODS

Participants.

The present study includes data from a subset of individuals participating in the SEARCH for Diabetes in Youth Study. SEARCH identifies individuals diagnosed with any type of diabetes before 20 years of age through a population-based registry network at 5 sites in the United States (South Carolina; Cincinnati, Ohio and surrounding counties; Colorado with southwestern American Indian sites; Seattle, Washington, and surrounding counties; and Kaiser Permanente Southern California membership in 7 counties). Individuals who received a new diagnosis of type 1 or type 2 diabetes in 2002–2006 or 2008 were invited to complete a baseline SEARCH visit to measure risk factors for diabetes complications; by design, individuals diagnosed in 2007 were not invited to participate in baseline interviews. In 2011–2015, participants with ≥5 years diabetes duration, who had previously completed a baseline visit, were invited to participate in a follow-up visit, at which diabetes risk factors and early diabetes-related complications and comorbidities were assessed. This follow-up visit was completed by 2777 participants at a mean age of 17·9 years (SD 4·8) and mean diabetes duration of 8·0 years (SD 2·0). The distribution of demographic, metabolic, and socioeconomic characteristics of participants who completed the follow-up visit were similar to that of the larger SEARCH registry population.[4] The study was approved by the institutional review boards with jurisdiction in each study location. All participants provided

consent or assent as age-appropriate, and parents also provided consent for those aged <18 years.

Demographic, anthropometric, and metabolic assessments.

Trained research staff conducted the in-person baseline and follow-up research visits. Participants (or parents, for younger participants) self-reported date of birth, sex, race, ethnicity, highest parental education, annual household income, and type of health insurance. Date of diagnosis had been obtained from medical records as part of the registry study, and was used to calculate age of diagnosis and diabetes duration at each visit. Height and weight were measured in light indoor clothing without shoes and used to calculate body mass index (BMI, kg/m^2) and age- and sex-specific BMI z-scores.[16] Circumference at the natural waist was measured and used to calculate waist-to-height ratio. Blood pressure was measured after 5 minutes of seated rest, with the mean of three readings taken 1 minute apart used for analysis. Mean arterial pressure was calculated as 1/3 systolic + 2/3 diastolic. Participants were instructed to fast overnight for ≥8 hours and abstain from medications (including short-acting insulin) on the morning of the visit. Blood samples were obtained and analyzed for hemoglobin A1c, glucose, lipids, creatinine, and cystatin C at the central laboratory (Northwest Lipid Metabolism and Diabetes Research, Seattle, WA). Participants were asked to bring a first morning urine void to the follow-up visit; if not done, a spot urine specimen was collected at the time of the visit (~8% of participants). Urine samples were analyzed for albumin and creatinine at the central laboratory.

Diabetes classification.

Baseline blood specimens were analyzed for glutamic acid decarboxylase-65 antibodies and insulinoma-associated-2 antibodies at the central laboratory,[17] and for zinc-T8 autoantibody at the Eisenbarth Laboratory (University of Colorado, Denver, CO).[18] Insulin sensitivity at baseline was estimated using a validated equation that included waist circumference, hemoglobin A1c, and triglyceride levels.[19] Etiologic type 1 diabetes was defined as ≥1 positive antibody result (regardless of insulin sensitivity) or no positive antibody results and insulin sensitivity (score ≥8·15).[20]

Diabetes-related complication/comorbidity assessments.

Diabetic kidney disease was defined as the presence of albuminuria (≥30 μg/mg of creatinine) or low glomerular filtration rate (≥60 mL/min/1·73m^2 as estimated by the CKD-EPI equations with serum creatinine and cystatin C).[21] Diabetic retinopathy was assessed with 45° color digital fundus images taken with a nonmydriatic camera (Visucam Pro N, Carl Zeiss Meditech) and centered on the disc and macula of both eyes. Photos masked to all clinical characteristics were graded by the Wisconsin Ocular Epidemiology Reading Center. Diabetic retinopathy was defined as mild, moderate, or proliferative retinopathy in at least one eye.[22] Our threshold for diagnosing retinopathy was set higher than typically used clinically in order to distinguish diabetic retinopathy from milder forms that are possibly related to etiologies other than diabetes retinopathy. Peripheral neuropathy was defined as a score >2 on the Michigan Neuropathy Screening Instrument.[23] Cardiovascular autonomic neuropathy was assessed by heart rate variability using the SphygmoCor-Vx device (AtCor Medical). Electrocardiographic R-R intervals measured in a supine position for 10 minutes

were used to estimate five heart rate variability indices: the SD of the intervals, root mean square differences of successive intervals, normalized high-frequency power, normalized low-frequency power, and the low-to-high frequency ratio. Cardiovascular autonomic neuropathy was defined as abnormalities in three or more of the five indices, based on ≥5th or ≥95th percentile (as appropriate) observed in age- and sex-matched control participants of the SEARCH Cardiovascular Disease (CVD) ancillary study.[12] Arterial stiffness was measured with the SphgymoCor-Vx device, and defined as a carotid-femoral pulse wave velocity ≥90th percentile compared to control participants of the SEARCH CVD study.[12]

Statistical analyses.

Analyses were conducted in two parts. First, a frequency analysis was used to examine the difference in observed versus expected prevalence of co-occurring complications/comorbidities. Second, a cluster analysis (Ward minimum variance method) was used to identify unique clusters of participants based on demographic characteristics and metabolic risk factors, between whom the prevalence of co-occurring complications/comorbidities was compared. A sensitivity analysis was performed for the cluster analysis by winsorizing the data by limiting the extreme values to 3 standard deviations within the mean value in order to reduce the potential impact of outliers on the Ward method for cluster analysis. Results were compared between these different approaches. All analyses were conducted in SAS v9·4 (Cary, NC) with statistical significance set at 0·05.

The frequency analysis included 1327 SEARCH participants who had etiologic type 1 diabetes, were age ≥ 10 years, reported using insulin and had complete data on all five complications/comorbidities of interest at the follow-up visit (Figure 1). For these participants, we classified prevalence of co-occurring complications/comorbidities in multiple ways: a) discrete number of complications/comorbidities for each participant (0–5), b) mutually exclusive numerical category of co-occurring complications (none, only one, any 2 or more), c) type of complication/comorbidity occurring singly (e.g., retinopathy and no others), and d) all possible pairs of co-occurring complications/comorbidities (e.g., retinopathy + diabetic kidney disease, regardless of the presence or absence of other complications/comorbidities). For each classification, we used exact binomial tests to determine if the observed prevalence significantly differed from the prevalence expected by chance alone.[24] Expected cell counts were calculated by examining the overall contingency table of all possible combinations of complications/comorbidities and using this table to calculate the individual expected cell counts (proportions) assuming independence across all cells. These expected cell counts (proportions) allowed us to construct specific exact binomial tests to determine whether the observed proportions were different from the expected proportions. The advantage of using exact binomial tests for comparing observed to expected proportions is that this approach is appropriate for each comparison regardless of the cell count observed within any particular cell of the table.

The cluster analysis was restricted to 1142 of the above participants with type 1 diabetes who had complete data for sex, race/ethnicity, age at the follow-up visit, and the following metabolic risk factor variables from both the baseline and follow-up visits: duration of diabetes, hemoglobin A1c, waist to height ratio, mean arterial pressure, HDL cholesterol,

and non-HDL cholesterol (Figure 1). We used cluster analysis to identify unique clusters of participants based on these characteristics. We compared demographics, metabolic characteristics, and numerical category of co-occurring complications/comorbidities between clusters using the Chi-Square test for categorical variables or Kruskal-Wallis tests for continuous variables. Although ANOVA models would be valid to compare most continuous variables, the Kruskal-Wallis test was used to allow the same test to be used for all variables even if the assumption of normality were not met for all variables.

RESULTS

Participant characteristics are reported in Table 1. On average, participants were 10·1 years old at the time of type 1 diabetes diagnosis, completed their baseline visit at 10·9 years of age (0·8 years diabetes duration), and completed their follow-up visit at 18·0 years of age (7·8 years diabetes duration). The majority of participants (76·6%) were non-Hispanic white. At baseline, the majority of participants had parents with a high school education or more (95·9%), lived in households with annual incomes ≥$50,000 (59·9%), and had private health insurance (80·3%). The average hemoglobin A1c was 7·6% (60.0 mmol/mol) at baseline and 9·2% (76.8 mmol/mol) at the follow-up visit. In general, blood pressure and lipid levels were higher at the follow-up visit compared to the baseline visit.

The prevalence and co-occurrence of early type 1 diabetes-related complications/comorbidities is reported in Table 2. Overall, 70·9% of participants had no complications/comorbidities, which was not significantly different than what was expected by chance alone (68·4%, p=0·053). Fewer participants than expected had one and only one complication/comorbidity (23·2% versus 27·2%, p=0·0011), while more participants than expected had any two or more (5·9% versus 4·4%, p=0·015). Only two participants had four complications/comorbidities, and none of the participants had all five. The prevalence of each complication/comorbidity occurring in isolation was lower from that expected by chance, although this was statistically significant only for retinopathy (1·8% versus 2·9%, p=0·016). Pair-wise comparisons showed that retinopathy + diabetic kidney disease, retinopathy + arterial stiffness, and arterial stiffness + cardiovascular autonomic neuropathy each co-occurred more frequently than expected (all p<0·05). The remaining pair-wise comparisons also reflected cooccurrence more frequently than expected, although they did not reach statistical significance.

The cluster analysis identified four unique participant clusters of varying sizes, which were labeled according to the severity of metabolic risk factors (low risk n=261, mid risk n=509, high risk n=348, highest risk n=24; Table 3). The sensitivity analysis using the winsorized data (i.e., data limited to within 3 standard deviations of the mean) also generated four clusters with 1120 out of 1142 participants being classified into the same clusters using either method. The 22 participants who were re-classified were all in the third (high) cluster in the original analyses, with nine being considered in the mid-risk cluster and 13 being considered in the higher-risk cluster. Since the cluster analysis results are very similar using both methods, we present the main results below using the non-winsorized data since it represented the actual observed data for the participants; the results using the winsorized data are presented in the Appendix.

As expected, the clusters significantly differed for nearly all the variables used to derive them (sex, race/ethnicity, age at follow-up visit, hemoglobin A1c at follow-up visit, baseline and follow-up values of duration of diabetes, waist to height ratio, mean arterial pressure, HDL cholesterol, and non-HDL cholesterol; all p<0·05). The comparison of baseline hemoglobin A1c did not reach statistical significance (p=0·088), although the point estimates suggest that the participants in the higher risk clusters had the highest A1c. They also differed significantly in the proportion of participants who had private health insurance and household incomes ≥$50,000 annually. Moving across clusters from lowest to highest risk, there were significant increases in diabetes duration (baseline p=0·018, follow-up p=0·0028), hemoglobin A1c (follow-up p<0·0001), waist to height ratio (baseline and follow-up p<0·0001), and non-HDL cholesterol (baseline and follow-up p<0·0001). For both mean arterial pressure and HDL cholesterol at baseline, values worsened from low to mid to high risk (p=0·0051 and p<0·0001, respectively); however the highest risk cluster had the lowest mean arterial pressure and highest HDL cholesterol of all the clusters at baseline. At the follow-up visit, however, mean arterial pressure increased and HDL cholesterol decreased from the low to highest risk clusters (all p<0·001). Although these comparisons are not a *priori*, per se, since they are made conditional on the specific result of the cluster analysis, we note that of the 15 variables that we compared across clusters, twelve had p-values that were less than 0.01 and eight of these were less than 0·001, indicating that the differences are quite strong, and the notable difference in means across clusters were substantial, indicating the effects are quite large (e.g., A1c at follow-up of 8·5 versus 11·8 in the low and highest risk clusters, respectively). The clusters notably differed in terms of the number of co-occurring complications/comorbidities (p<0·001; Figure 2). There was a decrease across clusters in the proportion of participants with no complications/ comorbidities ((78·9%, 69·5%, 66·1%, and 41·7%), and an increase in the proportion with any 2 or more(2·3%, 6·3%, 8·0%, 20·8%).

DISCUSSION

In this cohort of adolescents and young adults with type 1 diabetes, we observed a higher than expected co-occurrence of any two or more early diabetes-related complications at a relatively young age and short duration of diabetes. Complications occurring in isolation were observed less frequently than expected, indicating that adolescents and young adults with type 1 diabetes who develop any complication are likely to have concurrent complications. Individuals with high-risk profiles at baseline and after eight years of follow-up were ten times more likely to develop multiple complications than individuals with less adverse profiles. These data suggest that there are subgroups of young people with type 1 diabetes, identifiable within the first few years of diabetes duration, for whom efforts to prevent diabetes-related complications beginning soon after diagnosis may be particularly needed.

Co-occurring complications are not uncommon among older adults with a longer duration of type 1 diabetes: there have been reports of an increased prevalence of retinopathy with neuropathy,[6–8] retinopathy with nephropathy,[6,23]and neuropathy with nephropathy,[7] as well as the “triopathy”.[25] Increased arterial stiffness and/or cardiovascular autonomic neuropathy have also been observed at higher frequencies among adults also exhibiting retinopathy,[26]

neuropathy,[8,12] or nephropathy.[26] In adolescent and young adult populations with type 1 diabetes, a higher prevalence of retinopathy with nephropathy[14] and cardiovascular autonomic neuropathy with arterial stiffness[12] have been reported. Our study confirms these latter adolescent and young adult results, and provides new evidence that retinopathy is likely to co-occur with arterial stiffness in this population. We also showed that retinopathy was significantly less likely to occur individually, as just 24 of the 54 participants had retinopathy only. Our data suggest that adolescent and young adult patients who screen positive even for early stages of diabetic retinopathy are likely to have another complication, emphasizing the importance of regular screening for complications in line with current recommendations.[27]

Our study provides novel evidence of the higher than expected burden of any two or more co-occurring complications in adolescents and young adults with type 1 diabetes. This is likely due to common or overlapping etiologies for the complications. The clusters that we identified using demographic and metabolic characteristics at baseline and after eight years of follow-up demonstrated that there are early and persistent risk factors that can distinguish between individuals who are significantly more or less likely to develop multiple complications after a relatively short disease duration. Compared to participants with the least adverse metabolic risk factor profile, those with the most adverse metabolic risk profile were half as likely to be free of complications at follow-up and ten times as likely to develop any two or more complications. There was a consistent trend of worsening characteristics across clusters for most risk factors that was evident at both baseline and follow-up. The change in risk factors over time was also disparate between clusters: in the lowest risk cluster, metabolic risk factors changed little from baseline to follow-up, while the highest risk cluster exhibited substantial increases in hemoglobin A1c, mean arterial pressure, and non-HDL cholesterol, and decreases in HDL cholesterol. These data are consistent with prior studies that report metabolic risk factors for complications in type 1 diabetes, including suboptimal glycemic control,[5,10,13] hypertension,[6,8,21] and dyslipidemia.[4] The relatively high A1c levels we observed at the follow-up visit (average of 9.2%) are particularly worrisome and serve as a call to action to improve glycemic control of adolescents and young adults with type 1 type 1 diabetes in the United States. In line with current clinical recommendations,[27] our data indicate that intensive management of cardiometabolic risk factors among individuals with type 1 diabetes, in addition to improving glycemic control, could be vital to preventing early onset of multiple complications. Moreover, our cluster analysis suggests heterogeneity in the population of individuals with type 1 diabetes with a substantial proportion (32·6% of our sample) disproportionately at risk for co-occurring complications.

The clusters also differed according to sex, race/ethnicity, type of health insurance, and household income. The proportion of females increased from the lowest to highest risk cluster, suggesting that co-occurring complications are more likely to occur in girls and young women. Prior studies of co-occurring complications in type 1 diabetes have not reported on sex differences,[6–8,10,11,14] although studies of individual complications have reported either a higher prevalence among males,[6,10,28] or females,[29] or no sex differences.[7,13,14] Despite lower incidence and prevalence of type 1 diabetes in Hispanic, non-Hispanic black, Asian/Pacific Islander, or American Indian youth compared to non-Hispanic white

youth,[2,3] the clusters with the fewest non-Hispanic white youth had a higher prevalence of co-occurring complications. Prior studies have documented racial/ethnic disparities in microvascular complications of type 1 diabetes, which have been attributed to biological, behavioral, social, environmental, and healthcare factors.[30] The clusters with a lower proportion of private health insurance and annual household income also exhibited a greater prevalence of co-occurring complications, even though these variables were not included in the analysis used to generate the clusters. These data collectively suggest that non-white youth from low-resource environments who have adverse metabolic profiles are more likely to develop co-occurring early complications. However, it is notable that some participants (2·3%) in the low risk cluster did develop ≥2 complications by follow-up, while over 40% in the high risk cluster did not develop any complications by follow-up. Further research is needed to understand the factors operating in the participants with high risk profiles that may protect from the development of co-occurring complications, as well as the factors that contribute to the manifestation of co-occurring complications among youth with apparently low risk profiles.

This study has strengths and limitations. We used a large, racially and ethnically diverse sample that is clinically and demographically representative of the overall population of adolescents and young adults with type 1 diabetes in the United States.[4] Longitudinal measurements of sociodemographic and metabolic risk factors are a strength, while a single assessment of early diabetes complications without confirmatory testing is a limitation. The number of participants with co-occurring complications was small for some combinations, including those with three or more complications, which prevented a more detailed examination of co-occurring frequencies and patterns. Lastly, our results may have limited generalizability to populations with other degrees of glycemic control, with different sociodemographic characteristics, or differences in clinical management of type 1 diabetes.

In conclusion, we report that early diabetes complications/comorbidities co-occur more frequently than expected among adolescents and young adults with type 1 diabetes at a relatively short diabetes duration. A cluster of high-risk factors identifies groups that could potentially be targeted by behavioral or medical interventions to reduce the early development of life-long debilitating diabetes-related morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

The SEARCH for Diabetes in Youth Study is indebted to the many youth and their families, and their health care providers, whose participation made this study possible.

The authors wish to acknowledge the involvement of the South Carolina Clinical & Translational Research Institute, at the Medical University of South Carolina, NIH/National Center for Advancing Translational Sciences (NCATS) grant number UL1 TR000062; Seattle Children's Hospital and the University of Washington, NIH/NCATS grant number UL1 TR00423; University of Colorado Pediatric Clinical and Translational Research Center, NIH/NCATS grant Number UL1 TR000154; the Barbara Davis Center at the University of Colorado at Denver (DERC NIH grant number P30 DK57516); the University of Cincinnati, NIH/NCATS grant number UL1 TR000077; and the Children with Medical Handicaps program managed by the Ohio Department of Health. This

study includes data provided by the Ohio Department of Health, which should not be considered an endorsement of this study or its conclusions.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the National Institute of Diabetes and Digestive and Kidney Diseases.

Funding. Grant Support: SEARCH for Diabetes in Youth is funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05–069, and DP-10–001) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases.

Site Contract Numbers: Kaiser Permanente Southern California (U48/CCU919219, U01 DP000246, and U18DP002714), University of Colorado Denver (U48/CCU819241–3, U01 DP000247, and U18DP000247–06A1), Children's Hospital Medical Center (Cincinnati) (U48/CCU519239, U01 DP000248, and 1U18DP002709), University of North Carolina at Chapel Hill (U48/CCU419249, U01 DP000254, and U18DP002708), University of Washington School of Medicine (U58/CCU019235–4, U01 DP000244, and U18DP002710–01), Wake Forest University School of Medicine (U48/CCU919219, U01 DP000250, and 200–2010-35171).

Role of the Sponsors. Dr. Saydah (CDC) is a participating member of the study Steering Committee and the Writing Group for this manuscript because of the cooperative funding agreement. She was involved in the design of the study but not the conduct of the study; she was not involved in the collection, management, and analysis of the data, but was involved in interpretation of the data; she was involved in the preparation, review, and approval of the manuscript and the decision to submit the manuscript for publication.

Funding. Centers for Disease Control and Prevention, National Institutes of Health

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Research in context

Evidence before this study

In November 2017, we searched PubMed for English language publications with no date limitations using the following terms alone and in combination: type 1 diabetes, complications, co-occurrence, multiple, retinopathy, neuropathy, nephropathy, kidney disease, arterial stiffness, heart rate variability, pulse wave velocity, youth, children, and adolescents. We also reviewed reference lists of identified original and review articles. We found that studies examining diabetes-related complications/comorbidities among youth and young adults with type 1 diabetes, including our recent analysis (Dabelea et al, JAMA 2017), largely examined complications individually, and did not report whether complications/comorbidities were likely to co-occur, or the risk factors related to such co-occurrence.

Added value of this study

We evaluated the co-occurrence and related risk factors of multiple diabetes-related complications and comorbidities among youth and young adults with type 1 diabetes across five sites in the United States. We observed a higher than expected co-occurrence of any two or more early diabetes-related complications at a relatively young age and at only eight years of diabetes duration. Individuals with the highest risk profile at baseline and after eight years of follow-up were ten times more likely to develop multiple complications than individuals with less adverse profiles.

Implications of all the available evidence

One in three adolescents and young adults with type 1 diabetes have at least one early diabetes-related complication/comorbidity, and complications/comorbidities co-occur more frequently than expected by chance alone at a relatively short diabetes duration. A cluster of high risk factors identifies groups that may be targeted by interventions to reduce the early development of life-long debilitating diabetes-related morbidity.

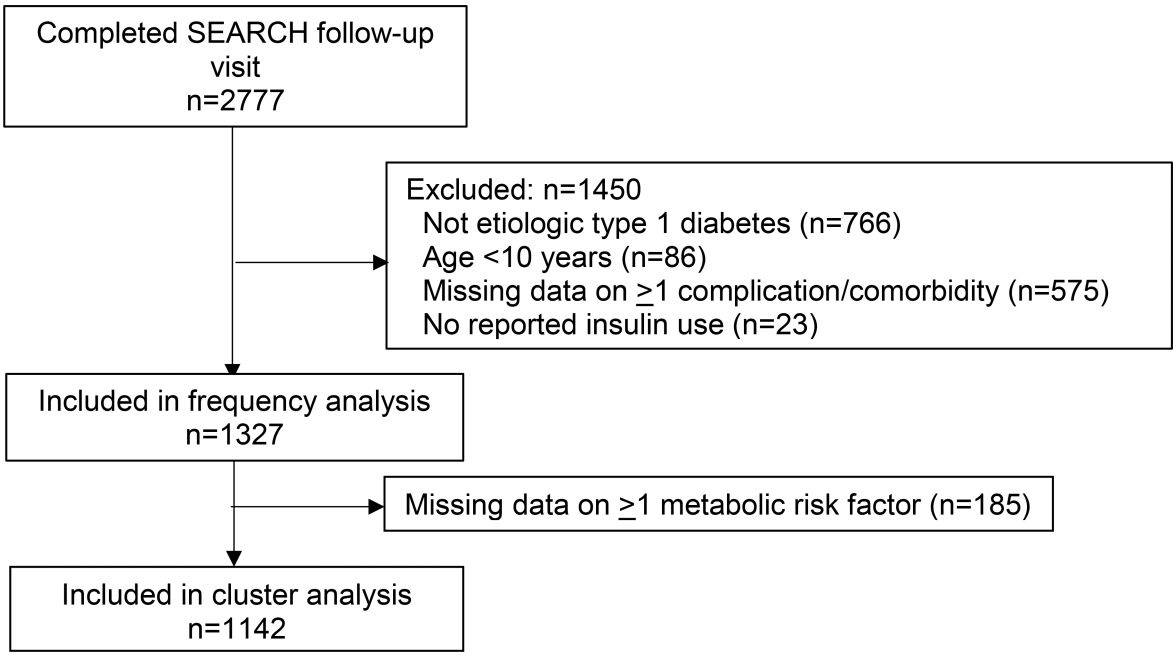

Figure 1.

Flow diagram of participants in the SEARCH for Diabetes in Youth Study at the time of the follow-up visit (2010–2015)

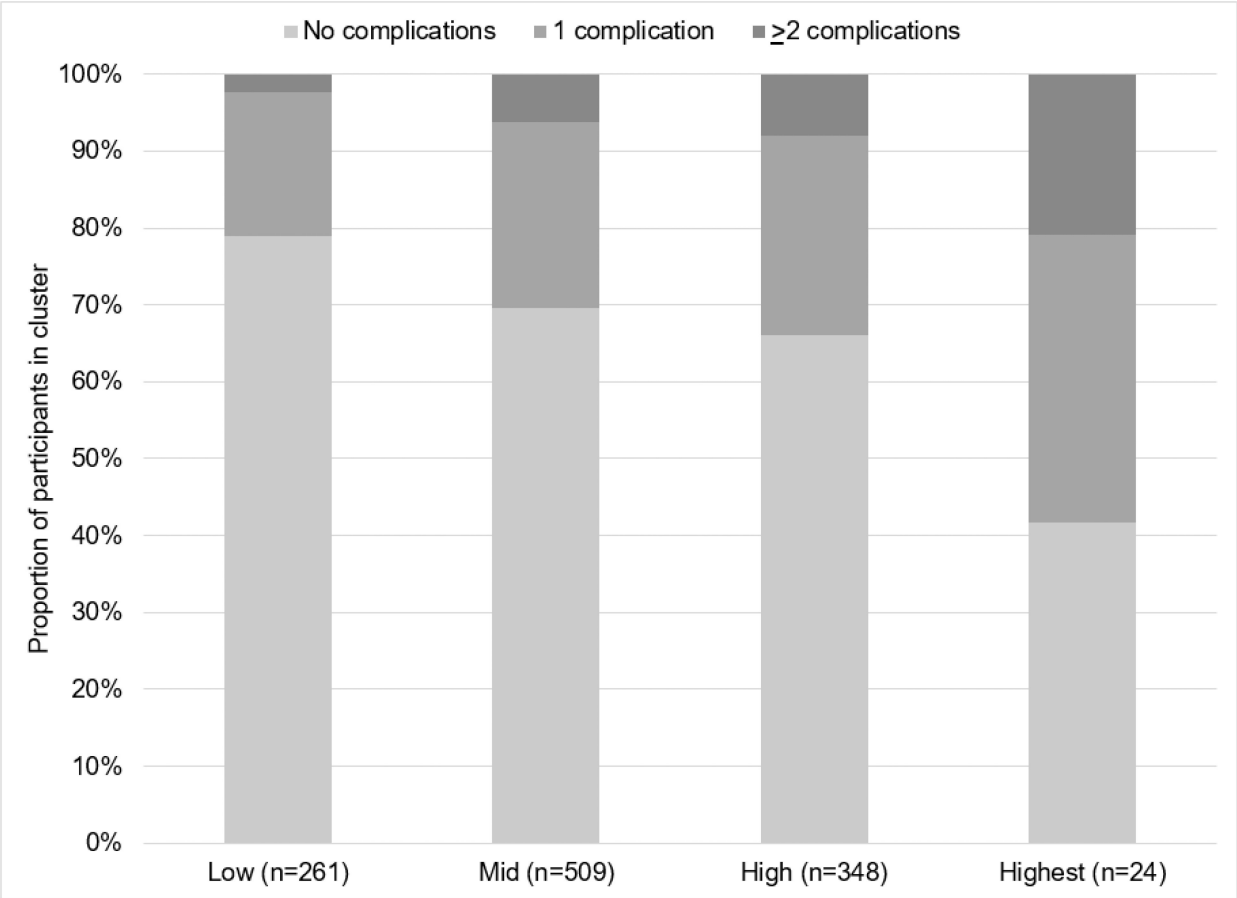

Figure 2.

Frequency of co-occurring diabetes-related complications/comorbidities among risk factor clusters of 1,142 participants with type 1 diabetes in the SEARCH for Diabetes in Youth study (2010–2015). Clusters were derived using a cluster analysis and the following variables: sex; race/ethnicity; age at the follow-up visit; baseline and follow-up duration of diabetes, hemoglobin A1c, waist to height ratio, mean arterial pressure, HDL cholesterol, and non-HDL cholesterol. Chi-Square $p<0.001$ for difference in frequency of co-occurring complications between clusters.

Table 1.

Characteristics of 1,327 participants in the SEARCH for Diabetes in Youth Study at their baseline (2001–2009) and follow-up (2010–2015) visits

	Baseline visit		Follow up visit	
	n	**Mean ± SD or count (%)**	**n**	**Mean ± SD or count (%)**
Female (n)	1327	599 (45·1)		---
Non-Hispanic white (n)	1327	1017 (76·6)		---
Age at diagnosis (years)	1327	10·1 (3·9)		---
Age at visit (years)	1327	10·9 (3·9)	1327	18·0 (4·1)
Diabetes duration (years)	1327	0·8 (0·5)	1327	7·8 (1·9)
Parental education (n)	1311		1309	
<High school graduate		54 (4·1)		56 (4·3)
High school graduate or higher		1257 (95·9)		1253 (95·7)
Annual household income (n)	1309		1323	
<$25,000		163 (12·5)		195 (14·7)
$25,000 - $49,999		264 (20·2)		216 (16·3)
$50,000 - $74,999		247 (18·9)		206 (15·6)
>$75,000		537 (41·0)		494 (37·3)
Do not know/refused		98 (7·5)		212 (16·0)
Health insurance (n)	1314		1322	
Private		1055 (80·3)		961 (72·3)
Medicare/Medicaid		206 (15·7)		250 (18·9)
Other		33 (2·5)		65 (4·9)
None		20 (1·5)		46 (3·5)
Hemoglobin A1c (%)	1318	7·6 (1·5)	1326	9·2 (1·8)
mmol/mol		60·0 (16·1)		76·8 (20·1)
BMI z-score	1310	0·5 (1·0)	1327	0·6 (1·0)
Waist circumference (cm)	1296	65·9 (11·4)	1327	77·9 (11·7)
Waist to height ratio	1219	0·45 (0·05)	1327	0·46 (0·06)
Systolic blood pressure (mmHg)	1292	99·8 (11·5)	1327	106·7 (11·0)
Diastolic blood pressure (mmHg)	1291	62·8 (10·1)	1327	69·0 (8·7)
Mean arterial pressure (mmHg)	1291	75·1 (9·6)	1327	81·6 (8·6)
Total cholesterol (mg/dl)	1275	159·8 (26·9)	1325	170·0 (35·6)
LDL cholesterol (mg/dl)	1275	91·4 (22·6)	1324	96·5 (28·7)
HDL cholesterol (mg/dl)	1275	55·6 (12·7)	1324	54·9 (13·4)
Triglycerides (mg/dl) [median (Q1, Q3]	1275	55 (43, 73)	1325	74 (55, 105)
Non-HDL cholesterol (mg/dl)	1275	104·1 (25·0)	1324	115·0 (35·5)

Data are mean ± standard deviation, median (Q1, Q3) [continuous], or n (%) [categorical].

Table 2.

Frequency of diabetes-related complications and comorbidities among 1,327 participants in the SEARCH for Diabetes in Youth study at an average of 7.8 years after type 1 diabetes diagnosis (2010–2015)

	Observed		Expected	
	n	%	%	p-value*
Number of diabetes-related complications 0	941	70·9	68.4	0·053
1	308	23·2	27.2	0·0011
2	62	4·7	4.1	0·34
3	14	1·1	0.3	0·0001
4	2	0·2	0.0	<0·0001
5	0	0·0	0.0	---
Any 2 or more	78	5·9	4.4	0·015
Individually occurring complications†				
Retinopathy	24	1·8	2.9	0·016
Diabetic kidney disease	51	3·8	4.2	0·62
Peripheral neuropathy	50	3·8	4.2	0·47
Arterial stiffness	69	5·2	6.3	0·10
Cardiovascular autonomic neuropathy	114	8·6	9.6	0·24
Co-occurring complications†				
Retinopathy + diabetic kidney disease	11	0·8	0.2	0·0007
Retinopathy + peripheral neuropathy	7	0·5	0.2	0·087
Retinopathy + arterial stiffness	13	1·0	0.3	0·0016
Retinopathy + cardiovascular autonomic neuropathy	11	0·8	0.5	0·15
Diabetic kidney disease + peripheral neuropathy	5	0·4	0.3	0·89
Diabetic kidney disease + arterial stiffness	12	0·9	0.5	0·059
Diabetic kidney disease + cardiovascular autonomic neuropathy	10	0·8	0.7	0·90
Peripheral neuropathy + arterial stiffness	8	0·6	0.5	0·65
Peripheral neuropathy + cardiovascular autonomic neuropathy	15	1·1	0.7	0·11
Arterial stiffness + cardiovascular autonomic neuropathy	24	1·8	1.0	0·015

*P-values reflect exact tests.

†Individual complications are mutually-exclusive; only the complication listed is present. Co-occurring complications are not mutually-exclusive; other complications may be present in addition to the listed pairs.

Table 3.

Characteristics of risk factor clusters among 1,142 participants with type 1 diabetes in the SEARCH for Diabetes in Youth study

	Low	Mid	High	Highest	p-value*
Size of cluster (n)†	261 (22·9)	509 (44·6)	348 (30·5)	24 (2·1)	
Female (n)	100 (38·3)	218 (42·8)	175 (50·3)	10 (41·7)	0·0064
Non-Hispanic white (n)	217 (83·1)	395 (77·6)	257 (73·9)	15 (62·5)	0·0017
Age at diagnosis (years)	10·5 (3·7)	10·5 (3·6)	10·9 (3·6)	9·7 (2·6)	0·30‡
Baseline visit (2001–2009)					
Age (years)	11·3 (3·7)	11·4 (3·5)	11·7 (3·6)	10·9 (2·7)	0·47‡
Diabetes duration (years)	0·7 (0·5)	0·8 (0·6)	0·8 (0·5)	1·1 (0·9)	0·018
Hemoglobin A1c (%)	7·4 (1·3)	7·7 (1·5)	7·7 (1·7)	8·1 (1·8)	0·088
mmol/mol	57·6 (13·7)	60·3 (16·0)	60·8 (18·4)	64·8 (20·0)	0·088
Waist to height ratio	0·44 (0·04)	0·45 (0·05)	0·47 (0·06)	0·47 (0·05)	<0·0001
Mean arterial pressure (mmHg)	74·8 (9·2)	76·0 (9·6)	76·5 (9·1)	70·3 (11·2)	0·0051
HDL cholesterol (mg/dl)	58·6 (13·2)	56·5 (12·4)	52·2 (12·4)	58·4 (14·9)	<0·0001
Non-HDL cholesterol (mg/dl)	78·4 (12·6)	104·5 (16·9)	120·6 (26·1)	125·6 (23·9)	<0·0001
Follow-up visit (2010–2015)					
Age (years)	18·0 (4·2)	18·4 (3·9)	18·9 (3·8)	17·8 (2·9)	0·021
Diabetes duration (years)	7·4 (1·9)	7·8 (1·9)	8·0 (1·9)	8·0 (2·0)	0·0028
Hemoglobin A1c (%)	8·5 (1·5)	9·0 (1·7)	9·7 (1·9)	11·8 (2·0)	<0·0001
mmol/mol	69·8 (16·7)	74·6 (18·5)	82·8 (21·2)	105·2 (21·7)	<0·0001
Waist to height ratio	0·44 (0·05)	0·46 (0·06)	0·49 (0·07)	0·50 (0·05)	<0·0001
Mean arterial pressure (mmHg)	80·0 (8·0)	82·6 (8·6)	82·4 (8·4)	84·4 (10·1)	0·0003
HDL cholesterol (mg/dl)	58·7 (12·8)	54·4 (13·1)	51·4 (12·3)	50·4 (12·4)	<0·0001
Non-HDL cholesterol (mg/dl)	79·0 (12·9)	105·7 (12·2)	147·9 (21·5)	245·5 (33·5)	<0·0001
Health insurance (n)					<0·0001‡
Private	211 (80·8)	386 (76·1)	222 (64·2)	9 (37·5)	
Medicare/Medicaid	34 (13·0)	87 (17·2)	83 (24·0)	11 (45·8)	
Other	10 (3·8)	23 (4·5)	19 (5·5)	1 (4·2)	
None	6 (2·3)	11 (2·2)	22 (6·4)	3 (12·5)	
Parental education (n)					0·057‡
<High school graduate	6 (2·3)	24 (4·8)	20 (5·8)	1 (5·0)	
High school graduate or higher	253 (97·7)	476 (95·2)	326 (94·2)	19 (95·0)	
Annual household income (n)					0·0020‡
<$25,000	26 (10·0)	73 (14·4)	69 (19·9)	6 (25·0)	
$25,000 - $49,999	41 (15·8)	72 (14·2)	66 (19·0)	5 (20·8)	
$50,000 - $74,999	36 (13·8)	85 (16·7)	44 (12·7)	2 (8·3)	
>$75,000	125 (48·1)	185 (36·4)	111 (32·0)	5 (20·8)	
Do not know/refused	32 (12·3)	93 (18·3)	57 (16·4)	6 (25·0)	

Data are n (%) or mean (SD). Clusters were derived using a cluster analysis and the following variables: sex; race/ethnicity; age at the follow-up visit; baseline and follow-up duration of diabetes, hemoglobin A1c, waist to height ratio, mean arterial pressure, HDL cholesterol, and non-HDL cholesterol

*P-values reflect Chi-Square tests (categorical) or Kruskal-Wallis tests (continuous).

†Percentages reflect the proportion of the full sample (n=1,142); all other percentages reflect the proportion of the cluster.

‡Age at diagnosis, age at baseline visit, health insurance, parental education, and annual household income were not used to define the clusters. Sample sizes for health insurance, parental education, and annual household income varied (1138, 1125, and 1139, respectively).