Complications in Young Adults With Early-Onset Type 2 Diabetes

Losing the relative protection of youth

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OBJECTIVE — To determine whether adults diagnosed with type 2 diabetes from age 18 to 44 years more aggressively develop clinical complications after diagnosis than adults diagnosed at ≥45 years of age.

RESEARCH DESIGN AND METHODS — We compared outcomes among 7,844 adults in a health maintenance organization who were newly diagnosed with type 2 diabetes between 1996 and 1998. We abstracted clinical data from electronic medical, laboratory, and pharmacy records. To adjust for length of follow-up and sex, we used proportional hazards models to compare incident complication rates through 2001 between onset groups (mean follow-up 3.9 years). To adjust for the increasing prevalence of macrovascular disease with advancing age, onset groups were matched by age and sex to control subjects without diabetes for macrovascular outcomes.

RESULTS — Adults with early-onset type 2 diabetes were 80% more likely to begin insulin therapy than those with usual-onset type 2 diabetes (hazards ratio [HR] 1.8, 95% CI 1.5–2.0), despite a similar average time to requiring insulin (~2.2 years). Although the combined risk of microvascular complications did not differ overall, microalbuminuria was more likely in early-onset type 2 diabetes than usual-onset type 2 diabetes (HR 1.2, 95% CI 1.1–1.4). The hazard of any macrovascular complication in early-onset type 2 diabetic patients compared with control subjects was twice as high in usual-onset type 2 diabetic patients compared with control subjects (HR 7.9 vs. 3.8, respectively). Myocardial infarction (MI) was the most common macrovascular complication, and the hazard of developing an MI in early-onset type 2 diabetic patients was 14-fold higher than in control subjects (HR 14.0, 95% CI 6.2–31.4). In contrast, adults with usual-onset type 2 diabetes had less than four times the risk of developing an MI compared with control subjects (HR 3.7, $P < 0.001$).

CONCLUSIONS — Early-onset type 2 diabetes appears to be a more aggressive disease from a cardiovascular standpoint. Although the absolute rate of cardiovascular disease (CVD) is higher in older adults, young adults with early-onset type 2 diabetes have a much higher risk of CVD relative to age-matched control subjects.

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We are experiencing an escalating epidemic of type 2 diabetes, largely attributable to the fattening of modern society (1–4). Obesity has increased by 70% in adults aged 18–29 years, and type 2 diabetes has increased in parallel by 70% in adults aged 30–39 years over the last decade, making young adults the fasting growing adult group for both obesity and type 2 diabetes (1,3). Despite this rapidly changing demographic trend, little is known about outcomes in this age-group.

To our knowledge, no study has evaluated incident complications in a population newly diagnosed with type 2 diabetes or how these complications may differ with age of onset. Our underlying hypothesis was that adults diagnosed with early-onset type 2 diabetes may represent a distinct, and more aggressive, phenotype. This study sought to determine if clinical outcomes differ in adults with early-onset type 2 diabetes (age 18–44 years) compared with usual-onset of type 2 diabetes at ≥45 years in a population of adults with incident type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The study subjects were members of a long-established, nonprofit, prepaid group model health maintenance organization (HMO), Kaiser Permanente Northwest (KPNW). More than 750 primary care and specialty physicians provided comprehensive, prepaid group coverage to ~20% (almost 450,000 people) of the Portland, Oregon, metropolitan area. Subscribers' demographics are similar to the area population as a whole, with non-Hispanic whites representing ~90% of the population and the remainder comprising African Americans, Asians/Pacific Islanders, Native Americans, and individuals of Hispanic descent (5,6). KPNW has 18.5% Medicare-eligible members (>64 years of age) and ~8% Medicaid members through the Oregon Health Plan, which provides medical coverage for Oregon residents below the poverty level (7).

All KPNW members have access to medically necessary services by, or on referral from, their primary care physician. KPNW maintains administrative and clinical electronic databases on inpatient admissions, pharmacy dispenses, outpatient visits, laboratory tests, and outside claims/referrals. All databases are linked

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HMO, health maintenance organization; KPNW Kaiser Permanente Northwest; MI, myocardial infarction; WHO, World Health Organization.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

through each member's unique health record number.

The KPNW Diabetes Registry maintains a continuous census of >50,000 members diagnosed since 1 January 1987. The methods used to create the registry are described elsewhere (8). Validation studies show the registry to be >99% sensitive and 99% specific for diagnosed diabetes. In addition, it is a very stable population, with annual disenrollment rates among people with diabetes consistently lower than the general membership (3.4% from 1987 to 1996) (9).

We studied adults newly diagnosed with type 2 diabetes from 1996 to 1998, and followed them for incident complications through 31 December 2001 (average follow-up 3.9 years). Recognizing that the type of diabetes is hardest to classify in the first year of diagnosis, we conservatively defined type 2 diabetes as consistent type 2 diabetes diagnosis (ICD-9 code 250.x2) (10) by all physicians treating the patient during that first year. To ensure that the subjects were newly diagnosed (incident), they needed at least 1 full year of plan membership before diabetes diagnosis to be included in the study. To adequately compare macrovascular complications, which are not unique to diabetes and would also be expected to increase in prevalence by age, we selected a random sample of age- and sex-matched control subjects with the same membership eligibility during the study period for comparison.

Age at diagnosis was calculated by the entry date into KPNW's diabetes registry. Subjects were classified as early onset if they were diagnosed at <45 years of age (early-onset type 2 diabetes), and were considered usual-onset if diagnosed at ≥45 years of age. We defined ≥45 years as usual-onset because virtually all adults diagnosed at >45 years have type 2 diabetes (11); also, 45 years is the age the American Diabetes Association currently recommends for type 2 diabetes screening in adults (12).

Measurement of subject characteristics

We reviewed data from electronic outpatient and inpatient medical records and centralized laboratory and pharmacy data to ascertain clinical outcomes. Microvascular disease was defined as presence of any of these: background diabetic retinopathy (362.01 and 250.5x) (10); proliferative diabetic retinopathy (362.02, 361.0x, 361.2, 362.81, 362.83, 362.84, 379.23, 361.9, 362.56, 363.32, and 369.4) (10); microalbuminuria (either ICD-9 codes 250.4x or urine microalbumin >30 mg/l on at least two occasions) (13); nephropathy (either ICD-9 codes 583-6, 582.9, or 791.0 or any of the following lab measurements on at least two occasions: urine microalbumin >300 mg/l (13), quantitated 24-h protein >165 mg/l, serum creatinine >1.6 mg/dl, or creatinine clearance <15 ml/min); or end-stage renal disease (requiring dialysis or transplant).

Macrovascular disease was defined as the presence of myocardial infarction (MI) (410–412.99 and 414.xx) (10,14); cerebrovascular disease (430–437.1 and 38.12) (10); coronary artery bypass graft (36.10–36.16 and 36.2–36.9) (10); percutaneous transluminal coronary angioplasty (36–36.02 and 36.05) (10); or peripheral vascular disease (443–444.xx, 250.7x, or procedure codes 39.29, 39.25, 39.59, and 84.10–84.17) (10). Although the American Heart Association standard for defining MI as an outcome is ICD-9 codes 410–414 (10,14), we excluded code 413 (angina) in our definition because angina is a "softer" end point that may be mistakenly coded for noncardiac chest pain and because people with diabetes may have an atypical presentation of cardiac disease without classic anginal symptoms (15).

Because screening tests are ordered at the time of diabetes diagnosis, discovery of associated complications present at diagnosis may lag somewhat. Thus, we defined prevalent complications as any micro- or macrovascular complication within 3 months of diagnosis. Incident complications were defined as development of a complication ≥3 months after diabetes diagnosis in a person without prevalent complications.

Initiation of insulin was ascertained by dispense of insulin from the day of diagnosis. We can reasonably estimate insulin use because ~97% of our members receive all or most of their insulin from KPNW pharmacies (based on a survey to 11,331 KPNW members with diabetes, 58.5% of whom responded) (16). We also ascertained average glycemic control both at diagnosis and during follow-up in the two onset groups. During the study period, KPNW measured long-term glucose control using HbA_{1c} or fructosamine. HbA_{1c} was more commonly used. To facilitate analysis, we converted fructosamine results (bG21 colorimetric assay; Boehringer Mannheim, Indianapolis, IN) to their HbA_{1c} equivalents (Diamat HPLC assay; Bio-Rad, Hercules, CA) using the following formula: fructosamine/40 = HbA_{1c}. This formula closely approximates the actual relationship observed within the HMO (16).

Statistical analyses

We conducted all statistical analyses using the SAS version 6.12 (SAS Institute, Cary, NC). We used Pearson χ^2 tests or Fisher's exact tests for comparing proportions and *t* tests for comparing mean differences. Cox proportional hazard models (17) were used to identify differences in incident complications after adjusting for follow-up period and sex. Relative risks were calculated to compare adjusted risk of macrovascular outcomes in people with diabetes compared with age- and sex-matched control subjects. Adjusted hazards ratios (HRs) and CIs are obtained from the proportional hazards analyses. Wald CIs for the odds ratios are based on the asymptotic normality of the parameter estimates (18). All the statistical tests that we report are two-sided, and the term statistically significant implies a *P* value <0.05.

RESULTS

A total of 8,198 individuals (≥18 years of age) were newly diagnosed with type 2 diabetes between 1996 and 1998 by their physician. We excluded 354 patients in which diabetes type was coded as both type 1 and type 2 by treating physician(s) during the first year after diagnosis, leaving a final study population of 7,844 (1,600 early-onset and 6,244 usual-onset subjects). Though both groups were on average obese (i.e., BMI >30 kg/m^2) (19,20), the younger-onset group was significantly more obese (37 vs. 33 kg/m^2, $P < 0.001$) (Table 1).

The average time to insulin treatment was no different by age of type 2 diabetes onset in adults (~2.2 years after diagnosis) (Table 1). However, a much higher proportion of young adults with type 2 diabetes required insulin treatment (18 vs. 11%, $P < 0.001$) (Table 1). Furthermore, the mean HbA_{1c} of young adults with early onset was higher at diagnosis than in adults with usual onset (8.7 vs. 8.1%, $P < 0.001$), and average HbA_{1c} was

Table 1—*Comparison of outcomes in early-onset versus usual-onset type 2 diabetes*

Variable	Early onset	Usual onset	*P* value	HR (95% CI)*
n	1,600	6,244		
Age at diagnosis (years)	37.6 ± 5.7	60 ± 10.1	<0.001	
Female sex	832 (52)	2,872 (46)	<0.001	
BMI at diagnosis (kg/m^2)‡	37.2 ± 8.6	33.3 ± 7.0	<0.001	
HbA_{1c} at diagnosis (%)§	8.7 ± 2.4	8.1 ± 2.2	<0.001	
Change in HbA_{1c} (%)‖	−0.4 ± 2.7	−0.6 ± 2.3	<0.001	
Required insulin therapy (%)	289 (18.1)	696 (11.2)	<0.001	
Time to insulin use after diagnosis (years)¶	2.3 ± 1.8	2.2 ± 1.8	0.722	1.8 (1.5–2.0)
BDR pre/at diagnosis	8 (0.5)	71 (1.1)		
BDR after diagnosis	61 (3.8)	404 (6.5)	0.016	0.7 (0.5–0.9)
PDR pre/at diagnosis	1 (0.1)	30 (0.5)		
PDR after diagnosis	25 (1.6)	322 (5.2)	<0.001	0.4 (0.2–0.6)
Microalbuminuria pre/at diagnosis	20 (1.3)	105 (1.7)		
Microalbuminuria after diagnosis	421 (26.3)	1,615 (25.9)	<0.001	1.2 (1.1–1.4)
Nephropathy pre/at diagnosis	36 (2.3)	248 (4.0)		
Nephropathy after diagnosis	233 (14.6)	1,008 (16.1)	0.297	1.1 (0.9–1.3)
ESRD pre/at diagnosis	6 (0.4)	26 (0.4)		
ESRD after diagnosis	22 (1.4)	97 (1.6)	0.665	0.9 (0.6–1.4)
Any microvascular complication# pre/at diagnosis	56 (3.5)	408 (6.5)		
Any microvascular# after diagnosis	531 (33.2)	2,305 (36.9)	0.132	1.1 (1.0–1.2)

Data are means ± SD or *n* (%). *HR is obtained from Cox proportional hazards model and adjusted for sex and length of follow-up. Only subjects who did not have the complication at diagnosis are included in the analyses. ‡BMI calculated on those with measured height in addition to weight within 3 months of diagnosis: 925 early onset, 4,130 usual onset. §Calculated for those who had measured HbA_{1c} at diagnosis: 1,570 early onset, 6,125 usual onset. ‖Calculation is determined from HbA_{1c} measurement at diagnosis to last measurement in follow-up period. Only subjects with both measurements are included: 1,416 early onset, 5,799 usual onset. ¶Applies only to those requiring insulin therapy. #Any microvascular complication includes background diabetic retinopathy (BDR), proliferative diabetic retinopathy (PDR), microalbuminuria, macroalbuminuria, or end-stage renal disease (ESRD).

slightly less improved (−0.4 vs. −0.6%, $P < 0.001$) despite a higher proportion requiring insulin treatment (Table 1). After adjustment for sex and length of follow-up, adults with early onset had a 80% higher hazard of requiring insulin treatment for their type 2 diabetes than adults with usual onset at ≥45 years of age (HR 1.8, 95% CI 1.5–2.0) (Table 1).

Overall, adults with early-onset type 2 diabetes had a similar risk of developing microvascular eye and renal complications (Table 1). Adults with early-onset type 2 diabetes had a slightly lower hazard of developing new background or proliferative retinopathy (Table 1). About one in four adults developed incident microalbuminuria during follow-up (Table 1). After adjustment for sex and length of follow-up, adults with early-onset type 2 diabetes had a 20% increased hazard of developing microalbuminuria compared with usual-onset type 2 diabetes (HR 1.2, 95% CI 1.1–1.4) (Table 1).

Because detection of early asymptomatic incident microvascular complications depends on screening, we evaluated screening rates in both onset groups to assess for any potential differential bias. For the eye exam, adults with early-onset type 2 diabetes had slightly lower rates of screening than those with usual-onset type 2 diabetes (77 vs. 87%), and thus it is possible that we underestimated incident retinopathy in the early-onset group. Furthermore, as only 11% of either onset group had an eye exam within the first 3 months of diagnosis, it is possible that the incident cases of background or proliferative retinopathy were actually present at diagnosis. In contrast, both groups had similarly high rates of screening for microalbuminuria during follow-up (94 vs. 96%). Likewise, both groups had high screening rates for microalbuminuria within 3 months of diagnosis (71 vs. 73%), so we are confident that the majority of new cases of microalbuminuria were truly incident.

Macrovascular complications such as MI and stroke are much more prevalent with type 2 diabetes in older adults and account for over half the mortality in older adults with type 2 diabetes (21). However, cardiovascular disease (CVD) generally also increases in prevalence with aging in people without diabetes. Therefore, to evaluate the impact of diabetes on macrovascular complications based on age of diabetes onset separately from the expected increase with aging, we matched all people with diabetes with age- and sex-matched nondiabetic control subjects. We found that, relative to matched control subjects, both onset groups had a twofold higher proportion of macrovascular disease and MI in particular, even by the time of diabetes diagnosis (Table 2), although the absolute rates of CVD were higher in both older adult cases and control subjects, as would be expected with older age. Importantly, after controlling for length of follow-up (which was variable primarily due to differing dates of diabetes diagnosis within the study period), younger adults with type 2 diabetes had a eightfold higher overall hazard of developing any macrovascular disease relative to control subjects (HR 7.9, 95% CI 4.8–13.0) compared with only a fourfold increased hazard in the usual-onset type 2 diabetic group (HR 3.8, 95% CI 3.4–4.2) (Table 2). Furthermore, young adults had a

Table 2—*Macrovascular outcomes in early- and usual-onset type 2 diabetic patients and in age- and sex-matched control subjects*

	Early-onset			Usual onset		
Variable	Type 2 diabetic patients	Control subjects	HR (95% CI)*	Type 2 diabetic patients	Control subjects	HR (95% CI)*
n	1,600	1,600		6,244	6,244	
MI pre/at diagnosis (%)	0.8	0.4		13.0	7.3	
MI after diagnosis (%)†	4.6	1.2	14.0 (6.2–31.4)	23.4	12.2	3.7 (3.2–4.2)
Stroke pre/at diagnosis (%)	0.3	0.3		3.7	2.3	
Stroke after diagnosis (%)†	1.6	0.6	30.1 (6.0–152.1)	11.1	6.5	3.1 (2.7–3.7)
CABG pre/at diagnosis (%)	0	0		0.5	0.5	
CABG after diagnosis (%)	0.8	0.2	‡	3.8	2.0	3.1 (2.5–4.0)
PTCA pre/at diagnosis (%)	0.1	0		0.3	0.1	
PTCA after diagnosis (%)	1.0	0.3	6.5 (2.1–20.3)	1.9	1.1	3.5 (2.5–5.0)
PVD pre/at diagnosis (%)	0.3	0.1		2.1	1.3	
PVD after diagnosis (%)	1.6	0.8	3.6 (1.7–7.9)	9.1	4.0	4.2 (3.5–5.1)
Any macrovascular complication§ pre/at diagnosis (%)	1.3	0.7		16.2	9.5	
Any macrovascular complication§ after diagnosis (%)†	7.0	2.5	7.9 (4.8–13.0)	34.3	18.5	3.8 (3.4–4.2)

*HRs are obtained from Cox proportional hazards model and adjusted for sex and length of follow-up. Only subjects who did not have the complication at diagnosis are included in the analyses. †95% CIs do not overlap between early- and usual-onset groups. ‡Due to small number of CABG events in control subjects, HR can not be calculated. §Any macrovascular event is any of the above complications.

higher hazard of developing incident macrovascular diseases compared with control subjects in every cardiovascular category, except for peripheral vascular disease (Table 2). It is important to note that peripheral vascular disease is really a mix of both macro- and microvascular disease, as it included peripheral revascularization procedures and lower extremity amputations that often result from neuropathy.

Adults with early-onset type 2 diabetes had a 14-fold hazard of MI compared with age- and sex-matched control subjects (HR 14.0, 95% CI 6.2–31.4), whereas usual-onset type 2 diabetes had only an ~4-fold MI hazard (Table 2). Similarly, adults with early-onset type 2 diabetes had an ~30-fold hazard of cerebrovascular disease compared with control subjects (HR 30, 95% CI 6.0–152.1), whereas adults with usual-onset type 2 diabetes had only an ~3-fold hazard compared with control subjects (HR 3.1, 95% CI 2.7–3.7). The absolute value for the hazard ratio for early-onset cerebrovascular disease should be interpreted with caution because of the wide CIs, but clearly the hazard for cerebrovascular disease is increased in the early-onset compared with usual-onset group relative to control subjects, as 95% CIs do not overlap. Furthermore, the reason why the CIs are wide, as well as why we could not formally test for an interaction between age and diabetes in the combined group, was for exactly the same reason as our findings: events are not occurring in young control subjects. However, because the 95% CIs for the HR do not overlap between early- and usual-onset groups with incident MI, stroke, or overall macrovascular disease, we are confident that there are significant differences between the two onset groups for these outcomes (Table 2).

To determine if there was a general pattern among the older adults for MI risk based on age of diabetes onset, we stratified by age-groups for MI (the most common macrovascular complication) and found that adults aged 45–54 years at type 2 diabetes onset had a sixfold risk of MI compared with control subjects (HR 6.1, 95% CI 4.5–8.4), whereas adults age 55–64, 65–74, and >75 years had a similar hazard of only three times the risk of age- and sex-matched control subjects (data not shown). We were not able to stratify MI outcomes further within the younger-onset group (HR 14.0) (Table 2), as even in our large population the events were so rare in young control subjects that estimates would not be accurate. However, it is interesting to note that the threefold increased relative hazard of MI in adults age >55 years is highly consistent with the two- to threefold increased risk of incident coronary heart disease (CHD) in people with diabetes observed in several prior population studies of primarily older adults, including groups with impaired glucose tolerance or diabetes by self-report (22–25).

To determine sex differences in macrovascular risk by age of onset, we stratified incident macrovascular complications. Interestingly, the marked increased in relative MI risk compared with control subjects occurred almost entirely among women (Fig. 1). Surprisingly, the relative risk of cerebrovascular disease in

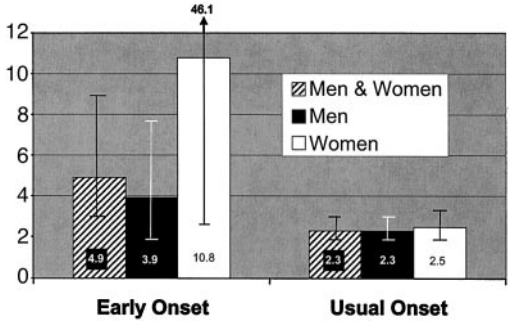

Figure 1—*Relative risk of myocardial infarction with diabetes compared with age- and sex-matched control subjects. Relative risks, which do not account for length of follow-up, are used to demonstrate where the effect of incident MI is occurring (young women) because hazard ratios (HRs) could not be calculated after stratification by sex due to a small number of events in young control subjects.*

the early-onset group was twofold higher in young men than young women (data not shown), but again the CIs are very wide as cerebrovascular events are rare in the young control subjects, so interpretation requires caution. The only other significant category that relative risk could be calculated with stratification was peripheral vascular disease, and young men also had a much greater relative risk compared with young women (data not shown).

CONCLUSIONS — In this population-based study of 7,844 patients newly diagnosed with type 2 diabetes, adults with early-onset type 2 diabetes had an 80% increased risk of requiring insulin therapy compared with adults with usual-onset type 2 diabetes, despite no difference in average time to insulin therapy (~2.2 years). Adults with early-onset type 2 diabetes were also 20% more likely to develop microalbuminuria than those with usual-onset type 2 diabetes. Most importantly, although the absolute risk of CVD was higher in older adults with and without diabetes, young adults with early-onset type 2 diabetes had a much higher relative hazard of developing CVD compared with age-matched control subjects. This increased relative risk was most striking with MI, in which young adults, and especially young women, had an ~14-fold increased risk compared with matched control subjects.

To our knowledge, no study has comprehensively evaluated a population newly diagnosed with type 2 diabetes to determine how the well-described complications of type 2 diabetes differ by age at onset. Most striking is the relative increased risk of CVD, and especially MI, in young adults compared with age- and sex-matched control subjects. Stratification by sex further demonstrated that essentially all of this increased risk occurred in young women with type 2 diabetes. This is particularly alarming in the context of known sex-based differences in mortality after MI, where women with diabetes, and especially young women, have a much higher mortality associated with an MI than men (22,26–28).

In the context of our findings of a 14-fold increased relative MI risk, it is also striking that young adults with early-onset type 2 diabetes also have a 20% increased risk of developing microalbuminuria compared with adults with usual-onset type 2 diabetes. Microalbuminuria is a strong risk factor for CHD (22) and is one of the diagnostic criteria, along with diabetes, of the newly defined World Health Organization (WHO) metabolic syndrome (29). This syndrome is a constellation of cardiovascular risk factors such as microalbuminuria, hypertension, central obesity, and abnormal lipids that tend to cluster in people with diabetes and increase CHD risk more than would be expected from these risk factors alone (29).

In addition to the increased risk of microalbuminuria in adults with early-onset type 2 diabetes, we found a similarly high rate of metabolic syndrome components in a prior study comparing baseline characteristics of adults with incident type 2 diabetes by age of diabetes onset in our HMO population (4). In that study, we found an inverse relationship with increasing obesity and age of type 2 diabetes onset. We also found that among the early-onset group, 82% had abnormal lipids and half (49%) had hypertension (>130/85 mmHg) at the time of diagnosis.

Our prior results, combined with the current study, suggest that the metabolic syndrome is present at diabetes diagnosis in most young adults and is an important contributor to the marked increased risk of CVD detected in this study. Unfortunately, we cannot determine the relative contribution of these components or classic cardiovascular risk factors, such as smoking, in the present study. Because screening rates for cholesterol are much more infrequent among healthy young control subjects, we were concerned that the potential differential biases, either from selecting an unhealthy control sample required to have measured lipids or by restricting the multivariate analysis to those control subjects with measured lipids, would skew accurate assessment of the relative contribution of lipids. Further research on the potential mechanisms and relative contributions of these mechanisms to the increased risk of CVD in young adults with early-onset type 2 diabetes is needed.

Our study has several important strengths. Our cases of physician-diagnosed diabetes are in a large community-based population with extensive longitudinal electronic medical records. Furthermore, these cases are followed in a diabetes registry in which the validated diagnosis of diabetes is >99% sensitive and specific for diabetes. Another unique strength of the study is our ability to randomly match by age/sex for an appropriate control group. Furthermore, matching by eligibility time period to allow the control subjects to have the same opportunity to be similarly diagnosed with macrovascular complications is another strength. KPNW uses comprehensive evidence-based guidelines for diabetes management that are consistent for both younger- and older-onset groups.

In our large community-based population, as in other clinical settings, the diagnosis of type 2 diabetes is based on the best clinical judgment of the treating physician(s). We fully recognize that distinguishing type 1 from type 2 diabetes is increasingly more challenging for clinicians with incidence of type 2 diabetes dramatically rising in young adults and children. Some of these younger patients with type 2 diabetes present with diabetic ketoacidosis, and, as the general population fattens, many people with type 1 diabetes are also obese (1,2,30–33). Because distinguishing diabetes type is most difficult in the first several months after diagnosis, we conservatively classified physician-diagnosed type 2 diabetes by excluding the 354 cases (4% of potential type 2 cases) in which the physician(s) caring for the patient coded both type 1 and 2 diabetes during the first year following diagnosis to reduce the potential of misclassification bias. By excluding these more severe cases, we may underestimate the full impact of type 2 diabetes on risk of incident complications but can be more confident we are distinguishing differences among adults diagnosed with type 2 diabetes, which was our primary aim. The fact that the average time course for insulin therapy initiation in both onset groups was similar (~2.2 years) strongly argues that our definition of type 2 diabetes is consistent for both onset groups.

Finally, although the clinical diagnosis of diabetes type will likely evolve in the future and may include testing for insulin antibodies and/or or C-peptide levels, currently these measures are not routinely done in clinical practice and similarly were not routinely measured in our population. In the future, we hope the pathophysiology explaining both the differences and similarities between what we currently categorize as latent autoimmune diabetes of young adults (34) compared with type 2 diabetes in young

adults, in which up to one-third may have positive GAD antibodies (≥20 units/l) (35), is better understood. For now, our current study of young adults with type 2 diabetes who were clinically diagnosed by their physicians demonstrates that these young adults have a much higher risk of macrovascular complications, and particularly MI, compared with control subjects.

In summary, among a population newly diagnosed with type 2 diabetes, we found that young adults are more likely to require insulin therapy, have similar overall risk of microvascular complications (but a greater risk of microalbuminuria in particular), and have a marked increased relative risk of macrovascular cardiovascular complications compared with control subjects. More research is clearly needed to understand how the pathophysiology and clinical course of type 2 diabetes differs by age of onset. This is particularly important to our society because young adults, who are increasingly obese and developing type 2 diabetes, will soon increasingly be developing the morbidity and premature mortality associated with CVD several decades earlier in life.

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