Increased Cardiovascular Disease, Resource Use, and Costs Before the Clinical Diagnosis of Diabetes in Veterans in the Southeastern U.S.

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IMPORTANCE: Screening for diabetes might be more widespread if adverse associations with cardiovascular disease (CVD), resource use, and costs were known to occur earlier than conventional clinical diagnosis.

OBJECTIVE: The purpose of this study was to determine whether adverse effects associated with diabetes begin prior to clinical diagnosis.

DESIGN: Veterans with diabetes were matched 1:2 with controls by follow-up, age, race/ethnicity, gender, and VA facility. CVD was obtained from ICD-9 codes, and resource use and costs from VA datasets.

SETTING: VA facilities in SC, GA, and AL.

PARTICIPANTS: Patients with and without diagnosed diabetes.

MAIN OUTCOME MEASURES: Diagnosed CVD, resource use, and costs.

RESULTS: In this study, the 2,062 diabetic patients and 4,124 controls were 63 years old on average, 99 % male, and 29 % black; BMI was 30.8 in diabetic patients vs. 27.8 in controls ($p<0.001$). CVD prevalence was higher and there were more outpatient visits in Year -4 before diagnosis through Year +4 after diagnosis among diabetic vs. control patients (all $p<0.01$); in Year -2, CVD prevalence was 31 % vs. 24 %, and outpatient visits were 22 vs. 19 per year, respectively. Total VA costs/year/veteran were higher in diabetic than control patients from Year -4 (\$4,083 vs. \$2,754) through Year +5 (\$8,347 vs. \$5,700) ($p<0.003$) for each, reflecting underlying increases in outpatient, inpatient, and pharmacy costs

($p<0.05$ for each). Regression analysis showed that diabetes contributed an average of \$1,748/year to costs, independent of CVD ($p<0.001$).

CONCLUSIONS AND RELEVANCE: VA costs per veteran are higher—over \$1,000/year before and \$2,000/year after diagnosis of diabetes—due to underlying increases in outpatient, inpatient, and pharmacy costs, greater number of outpatient visits, and increased CVD. Moreover, adverse associations with veterans' health and the VA healthcare system occur early in the natural history of the disease, several years before diabetes is diagnosed. Since adverse associations begin before diabetes is recognized, greater consideration should be given to systematic screening in order to permit earlier detection and initiation of preventive management. Keeping frequency of CVD and marginal costs in line with those of patients before diabetes is currently diagnosed has the potential to save up to \$2 billion a year.

KEY WORDS: diabetes; health care cost; cardiovascular disease; prediabetes.

ABBREVIATIONS

A1c	Hemoglobin A1c
CAD	Coronary artery disease
CBD	Cerebrovascular disease
CDW	Corporate Data Warehouse
CVD	Cardiovascular disease
DPP	United States Diabetes Prevention Program
GEE	Generalized Estimating Equations
HERC	Health Economics Resource Center
KPNW	Kaiser Permanente Northwest
MEPS	Medical Expenditure Panel Survey
NGT	Normal glucose-tolerant (on an OGTT)
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance test
PVD	Peripheral vascular disease

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INTRODUCTION

The Veterans Health Administration (VA) oversees the largest integrated healthcare system in the U.S., and diabetes is a common and costly problem for the VA. The veteran population is rich in minorities and older patients—groups at higher risk of developing diabetes—and in 2000, close to 20 % of VA outpatients had diabetes.¹ The result is increased morbidity and mortality for VA patients, and increased resource use and costs for the VA. In 1998, VA diabetes costs were estimated at \$1.67 billion, 3.9 % of total VA expenditures,² and in 2000, 28 % of pharmacy costs were attributed to diabetes.³ Since that time, total direct medical expenditures attributable to diabetes in the U.S. have increased from approximately \$92 billion in 2002⁴ to \$116 billion in 2007⁵ and \$176 billion in 2012⁶; average annual medical expenditures for a person with diagnosed diabetes were estimated to be \$11,744 in 2007⁵ and \$13,700 in 2012.⁶

Veterans with diabetes often have multiple health problems, and CVD is a complication in approximately 50 % of cases.⁷ Moreover, while metabolic control in veterans tends to be better than in non-veterans,^{8,9} studies show that many veterans have elevated A1c levels,¹⁰ even after adjusting for comorbidity and life expectancy.^{10,11} In particular, despite evidence-based guidelines showing “a strong case for intensive control among patients free, or nearly free, of diabetic microvascular disease”¹² early in their natural histories, many veterans do not have good diabetes control.

Making the diagnosis early allows a sustained benefit from medications such as metformin.¹³ However, we found the initial diagnosis of diabetes to be delayed in veterans in the southeastern U.S., with delays averaging 1–2 years after two occurrences of hyperglycemia; the diagnosis was often based on nonstandard criteria, although it was usually correct.¹⁴ While access to care is more uniform in the VA than in the U.S. in general, we also found disparities in how the diagnosis was made, since A1c levels at diagnosis were higher in black than in white veterans (7.8 % vs. 7.1 %), a difference too great to be explained by differences in age, sex, BMI, and the glucose-independent associations between race and A1c.^{15,16} Disparities can be alleviated when care is guided by uniform algorithms for management, as we have shown at Grady Hospital in Atlanta.¹⁷ We further found that A1c levels would be substantially lower if unrecognized diabetes were identified

by screening with oral glucose tolerance tests (OGTTs). A1c levels averaged 6.2 % in OGTT-detected diabetes.¹⁸

Since diabetes is asymptomatic early in its natural history, earlier diagnosis would require screening. However, systematic screening to identify patients with previously undiagnosed diabetes is uncommon both in the VA and in other healthcare systems.¹⁹ While national and international diabetes associations call for screening of most adults over the age of 40–50 years and screening of all adults with risk factors,^{20–22} other agencies recommend testing only in the setting of hypertension,^{23,24} hyperlipidemia,²³ or as part of risk evaluation in patients with CVD.^{25,26}

Screening might be more common in large healthcare systems if adverse associations with diabetes, such as increased healthcare costs, were widely recognized to occur early in the natural history of the disease, at a time when adverse effects might be forestalled with preventive management. Higher rates of CVD, increased healthcare resource use, and higher costs have been reported before a clinical diagnosis of diabetes in data from the Nurses' Health Study, primary care clinics in the United Kingdom, and Kaiser Permanente Northwest (KPNW), respectively,^{27–31} but there has been no coordinated study of the time course of adverse associations with early diabetes within a single healthcare system. We sought to determine when the adverse associations with diabetes could be detected, using CVD as a measure of impact on health, and resource use and cost as measures of impact on the healthcare system, in veterans in the southeastern U.S. who received care through the VA. We demonstrated that CVD, resource use, and costs were all significantly and substantially increased four years prior to clinical diagnosis, and that costs rose further after the diagnosis was made.

METHODS

Design

We conducted a case–control analysis, similar to reports in the literature,^{27,28,31} using Corporate Data Warehouse (CDW) information on veterans in SC, GA, and AL receiving healthcare through Veterans Integrated Service Network (VISN) 7. This study was approved by the Institutional Review Board at Emory University.

For each patient, CDW outpatient “visits” included data associated with a given patient on outpatient visit days, even if an outpatient visit occurred on the day of hospitalization, an inpatient day, or the day of discharge. These outpatient data captured the date of each visit, all available information regarding the type of visit (emergency room, primary care, etc., using both stop codes and location description), and all associated ICD-9 codes. Inpatient “days” included data associated with the day of hospitalization and all hospital days as well as the day of discharge. For each day, data included

the date, all available information regarding the type of hospital day (medicine, surgery, etc.), and all associated ICD-9 codes. Outpatient visits and inpatient days were sorted into one-year units before and after the index year (the year of initial diagnosis of diabetes, see below). The years prior to the index year were designated years -1, -2, etc., and the years after the index year were designated years +1, +2, etc. (see online Appendix, Fig. 1).

Subjects

We first selected patients with an initial diagnosis of diabetes on or after 10/1/2002, which provided at least four years for data to populate the CDW. The diagnosis was defined as previously validated^{10,14,15} by either a single use of the diabetes ICD-9 code 250.xx in association with a primary care outpatient visit, any use of the code twice, or any prescription of a diabetes drug, following no use of the code, or use of a diabetes drug in the prior three years. We then restricted the analysis to diabetic patients receiving continuous primary care, defined as ≥ 5 visits over ≥ 4 fiscal years (FY) before and ≥ 4 visits over ≥ 3 FY after the “index” FY in which the diagnosis was made. In order to limit bias, diabetic patients were matched 1:2 with controls who had similar follow-up, age, race/ethnicity (including “unknown” if race was not identified), gender, and VA facility where care was provided, but no use of the diabetes ICD-9 code. The “index” FY for each control was assigned as the FY providing four years with at least five visits before the index year, and three years with at least four visits after the index year. Cases and controls thus had similar continuity of primary care, but neither cases nor controls were required to have visits and laboratory tests during each FY before, during, and after the index FY, which led to some variation in the number of cases and controls with the data during each FY. From 10/1/2002 through 11/25/2009, 381,898 patients without a diagnosis of diabetes and 92,514 patients with a diagnosis of diabetes (19.5 %) had at least one primary care visit in VISN 7, and from these, application of the criteria described above resulted in 6,244 potential diabetic patients and 9,550 potential control patients. Application of the matching criteria then resulted in 2,062 diabetic patients and 4,124 matched control patients.

Based on our previous studies showing that the diagnosis of diabetes in veterans in the southeastern U.S. is commonly delayed by about two years after hyperglycemia is present,¹⁴ years 1 and 2 prior to the index year of diagnosis could be considered as “undiagnosed diabetes,” and years 3 and 4 prior to the year of diagnosis as “prediabetes” (see Appendix, Fig. 1).

Identification of CVD

CVD was captured by association of outpatient contacts and inpatient days with ICD-9 diagnostic and procedure codes typically used in the literature (see Appendix, Table 1),

including coronary artery disease (CAD), cerebrovascular disease (CBD), and/or peripheral vascular disease (PVD), with and without inclusion of heart failure.

VA Healthcare System Resource Use and Costs

These were obtained from the patient-level dataset PLCOSTXX maintained by the VA's Health Economics Resource Center (<http://www.herc.research.va.gov/research/default.asp>, HERC). This dataset includes VA costs per veteran per FY, including costs for inpatient care, outpatient care, and pharmacy, along with inpatient days and outpatient visits. The VA does not usually generate bills for individual patients, and HERC costing is based on estimated average costs for outpatient encounters and inpatient stays that have the same demographic and discharge characteristics. All costs were expressed as 2007 dollars.

Analysis

Demographic characteristics of diabetes and control patients were compared using t tests. T tests were also used to compare CVD prevalence, number of days of inpatient care, number of outpatient visits, and total inpatient, outpatient, and pharmacy costs for diabetes and control patients for comparable FYs prior to, during, and after the index FY. To assess trends over time, generalized estimating equation (GEE) methods were used, including group (diabetes or control) and year as independent variables, with and without adjustment for CVD and BMI. Clustering (according to care in different VA facilities) was also accounted for in GEE. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

At the time of diabetes diagnosis (or matched time point for controls), the groups of 2,062 diabetic patients and 4,124 matched controls had similar demographic characteristics: average age 63 years, 99 % male, 28.7 % black, 38.6 % white, and 32.7 % unknown race (all $p = \text{ns}$). The average BMI in diabetic patients was 30.8 kg/m² and in controls was 27.8 ($p < 0.001$). Other diagnoses such as hypertension or dyslipidemia, smoking, levels of risk factors such as LDL cholesterol, and family history were not included in the data query for this study. Cases and controls had similar continuity of primary care, but neither was required to have visits or laboratory tests during each FY before, during, and after the index FY, which led to some variation in the number of cases and controls with data during each FY.

Prevalence of CVD

Fig. 1 shows that prevalence of CVD in the diabetic patients was significantly higher than in the controls, both before and

Fig. 1. Prevalence of CVD (according to use of ICD-9 codes, as in "Methods," excluding CHF) in diabetic and control patients across the years before and after the year of initial diagnosis (or matched time point in controls). Shown in the tables under the figure are numbers of patients for whom data were available in each year ($p < 0.001$ all years). Data shown are mean and 95 % CI.

after diagnosis of diabetes ($p < 0.001$ for each year, in year -4 prior to the index year of diagnosis through year +4 after diagnosis). There were fewer subjects in years -4 and -3 prior to diagnosis (Fig. 1 and subsequent figures show the number of subjects in each group with data in each year), so the precision was lower at those time points, but the trend was consistent. Patterns were similar with or without inclusion of heart failure along with CVD, and for assessment of coronary artery disease both alone and with or without heart failure (not shown). We did not determine the relative contribution of each diagnostic and procedure code to total CVD.

Annual VA Healthcare System Resource Use

Fig. 2 shows that there was increased resource use (outpatient contacts per subject per year) for patients with diabetes that began before diagnosis and continued in the years following diagnosis. The differences in the number of contacts per year were significant in year -4 prior to the year of diagnosis ($p < 0.01$) through year +4 after the year of diagnosis ($p < 0.001$, all other included years). A similar trend was also seen for increased inpatient days in subjects with diabetes compared to controls, although the numbers of inpatient days were smaller and the differences were statistically significant ($p < 0.05$) only in years -3, 0, and +1 (data not shown).

Annual VA Healthcare System Costs, Component Costs, and Cost Differences

Total VA costs per veteran per year in 2007 dollars are shown in Fig. 3. As expected, costs tended to increase over time in both diabetic and control groups as patients aged. Differences in total annual costs in diabetic vs. control groups were

Fig. 2. Total annual VA outpatient visits per patient (obtained from HERC databases, as in "Methods") in diabetic and control patients across the years before and after the year of initial diagnosis. Data shown are mean and SEM for each year. The table below shows the number of subjects with visits during each year ($p < 0.01$ at FY-4; all other years, $p < 0.001$).

significant beginning in year -4 (\$4,083 vs. \$2,754) through year +5 (\$8,347 vs. \$5,700) ($p < 0.003$ for all of these years). Thus, the difference in total VA costs was over \$1,000 per year before diabetes was diagnosed, and rose to over \$2,000 per year after diabetes was diagnosed. The pattern was similar for outpatient costs ($p < 0.007$ for each of years -4 through +4), inpatient costs ($p < 0.05$ for most of years -4 through +5), and pharmacy costs ($p < 0.001$ for years -4 through +5) (absolute values not shown, but cost differences shown in Table 1). Since there were fewer subjects with data available in the earliest and latest years of the study, we repeated the analyses

Fig. 3. Total annual VA costs per patient (obtained from HERC databases, as in "Methods") in diabetic and control patients across the years before and after the year of initial diagnosis. Tabulated values are the number of subjects during each year with cost data, including only diabetic subjects that had at least two matched control subjects during the index year; some control subjects were matched to more than one diabetic subject for this analysis. Data shown are mean and SEM ($p < 0.007$ at all years).

Table 1. Increased cost associated with diabetes in the 4 years before and after the diagnosis of diabetes

Costs	Year	−4	−3	−2	−1	0	+1	+2	+3	+4
Total	Diabetes-Control (\$)	1329	1491	1454	1429	1968	2463	2079	2258	1703
	SE	488	288	282	297	311	295	307	357	316
	P	0.0026	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	trend $p=0.045$, increase by \$101 per year									
N	Diabetes (n)	560	2043	2008	2008	2024	2061	2046	2038	1996
	Control (n)	298	4070	3972	3917	3839	4105	4046	4021	3962
Outpatient	Diabetes-Control (\$)	456	503	523	579	742	1236	1025	859	794
	SE	184	95	101	108	131	105	150	128	127
	P	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	trend $p=0.033$, increase by \$68 per year									
Inpatient	Diabetes-Control (\$)	529	747	671	547	915	761	620	899	409
	SE	372	239	223	236	244	240	223	291	246
	P	0.12	0.004	0.004	0.04	0.002	<0.001	0.008	0.009	0.118
	trend $p=ns$									
Pharmacy	Diabetes-Control (\$)	344	241	260	303	311	466	434	500	500
	SE	84	46	72	91	67	49	48	46	64
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	trend $p=0.004$, increase by \$32 per year									

Average marginal costs in 2007 dollars for patients with diabetes compared to control patients, shown as the difference (cost of diabetic group – cost of control group) in total costs, outpatient costs, inpatient costs, and pharmacy costs, for fiscal years (FY) 4 years prior to the index year when diabetes was initially diagnosed (FY 0), and 4 years after diabetes was diagnosed. Shown are p values for t tests comparing the costs in the two groups for each year, and p values for trends assessed by GEE over time in the marginal costs. The values of n are the numbers of patients for whom data were available in each given year (not all subjects had cost data available in every year, including the index year for some data). Based on our previous studies showing that the diagnosis of diabetes in veterans in the southeastern U.S. is commonly delayed by about two years after hyperglycemia is present, years 1 and 2 prior to the index year of diagnosis could be considered as “undiagnosed diabetes”, and years 3 and 4 prior to the year of diagnosis as “prediabetes” (outlined also in Appendix, Fig. 1).

and obtained similar results using only diabetic subjects that had data available from two matched control subjects within a given year (Appendix, Fig. 2), and with diabetic and control subjects who had data available every year, which limited the analysis to FY −3 to +4 (Appendix, Fig. 3).

Component costs for the diabetic vs. control groups are shown in Fig. 4 of the appendix, and cost differences are shown in Table 1 (without adjustment for CVD and BMI). Differences in total costs averaged \$1,329 in year −4 and \$1,703 in year +4, and rose an average of \$101 per year over this time period ($p=0.045$). Although inpatient costs tended to be higher in the diabetic group compared to the controls, the difference was not significant in all years examined, and there was no significant trend for differences in inpatient costs. Differences in outpatient costs were significant in each year, and rose by an average of \$68 per subject per year ($p=0.033$). Pharmacy cost differences were also significant in each year, and rose by an average of \$32 per subject per year ($p=0.004$).

Table 2. VA cost per diabetic patient adjusted for year, BMI, time, and CVD using GEE model

Parameter	Estimate	SE	95 % CI	p
Intercept	\$4845	554	3759, 5931	<0.0001
Year	\$42	30	−17, 101	0.16
BMI	−24	19	−62, 15	0.23
Group Diabetes	\$1748	256	1247, 2249	<0.0001
Year*Group Diabetes	\$148	71	9, 287	0.037
CVD	\$2485	192	2109, 2862	<0.0001

Analysis using GEE of contributions to total VA costs in 2007 dollars in the groups of diabetic compared to control patients, with adjustments for the FY for which data was available, BMI, trends in costs over time (year*group), and costs related to CVD, as outlined in “Methods”. Analysis included patients who had data each FY from −3 to +3; CVD included heart failure.

The trends tended to be similar with adjustments for CVD and BMI (not shown).

Independent Impact of Diabetes on Costs

Since the diabetic and control groups differed in BMI and prevalence of CVD, we used GEE to evaluate the impact of diabetes on total VA costs per veteran per year in 2007 dollars, independent of such factors. Table 2 shows that from years −3 before the diagnosis of diabetes to +3 after the diagnosis, the contributions of BMI were not significant (shown as a continuous variable in Table 2 and categorical in Appendix, Table 2), and that costs did not rise significantly over this time period (i.e., with increasing age) once CVD and diabetes were taken into account. CVD (including heart failure) contributed \$2,485 to costs ($p<0.0001$), diabetes contributed \$1,748 to costs independent of CVD ($p<0.0001$), and the costs attributable to diabetes rose by an average of \$148 per year ($p=0.037$).

Additional analyses were conducted to further confirm the lack of effect of obesity, and sought to identify any risk factors that might contribute to the CVD cost. With this dataset, we were able to assess the role of elevated LDL cholesterol (LDL >130 mg/dl) as a categorical value that contributed to the cost, but less than diabetes or CVD, and did not diminish the effects of diabetes or CVD on costs (Appendix, Table 2).

DISCUSSION

We used information in VA databases to examine the time course of the adverse associations of diabetes with veterans’ health and the VA healthcare system. We selected patients who had continuity of care, and diabetic patients were matched 1:2

with controls similar in age, gender, race/ethnicity, and facility where they received care. Compared to the control patients, the diabetic patients had higher BMI, higher prevalence of CVD, more outpatient visits, and higher annual total costs, inpatient costs, outpatient costs, and pharmacy costs. The association of diabetes with increased total costs per veteran per year persisted after adjusting for differences in BMI and prevalence of CVD, and rose by an average of \$148 per year. The differences in CVD, healthcare system resource use, and healthcare system costs between diabetic patients and controls began four years before diabetes was diagnosed, and were statistically significant. The differences in total healthcare system costs were also clinically significant, averaging over \$2,000 per year after diabetes was diagnosed and closer to \$1,000 per year before diabetes was diagnosed. While differences after diagnosis might be due in part to the bias of providers who approach patients with diagnosed diabetes differently from controls, differences prior to diagnosis are more likely to be due to the disease itself: undiagnosed diabetes and prediabetes, with associated comorbidities.

The novelty of the current study is (a) the examination of a substantial number of patients with diabetes compared to carefully matched controls, all of whom received continuous primary care for an extended period of time within the largest integrated healthcare system in the U.S., where diabetes management has been shown to be superior to that of conventional managed care,⁹ and where disease, resource use, and cost information were all available; and (b) the demonstration of statistically significant and clinically meaningful adverse associations of diabetes with both patients' health (CVD) and the healthcare system (resource use and costs), which began at least four years prior to the clinical diagnosis of diabetes. Since the period four years prior to the clinical diagnosis in this population has previously been shown to include both 1–2 years of undiagnosed diabetes and a prior period of prediabetes¹⁴—asymptomatic conditions—these findings suggest that earlier identification in order to permit preventive management will require screening.

However, while many patients have some measurement of glucose levels,^{32–35} directed screening is presently infrequent even in high-risk populations such as those with coronary artery disease³⁶ or prior gestational diabetes.³⁷ In a Canadian population, glucose was measured in 37 % of patients within one year and 63 % within three years, but less than 1 % had sensitive testing with an OGTT, and even the rate of A1c measurement was low.^{34,38} Screening allows for the identification of prediabetes and early diabetes, which enables the use of non-pharmacologic or pharmacologic treatment that can improve glycemic control and reduce progression of dysglycemia,³⁹ although there is no evidence at this time that population screening can improve outcomes.⁴⁰ Current recommendations are based largely on consensus,^{20,41} and emphasize screening of patients who are at higher risk, where screening and early treatment are more likely to be cost-effective.⁴²

The natural history of diabetes frequently involves a longer period of gradually increasing glucose levels, followed by a

shorter period with a more rapid rise shortly before diabetes is diagnosed.^{43,44} Thus, in most patients with clinically diagnosed diabetes, the years just prior to diagnosis likely involve a combination of prediabetes and undiagnosed diabetes. In one meta-analysis, the duration of prediabetes was estimated at 8–10 years.⁴⁵ Such a duration is thought to be long enough to justify a screening program, if interventions aimed at prediabetes were cost-effective⁴⁵, as they have been shown to be in the U.S. Diabetes Prevention Program (DPP, see below).

The period prior to the clinical diagnosis of diabetes has previously been associated with adverse effects on both health and healthcare systems. Such adverse effects have included increased CVD,^{28,46} greater utilization of primary care,^{27,47} and higher costs.^{29–31,48} In patients at KPNW who had impaired fasting glucose (IFG, with fasting plasma glucose levels 100–125 mg/dl), marginal costs in patients with fasting glucose 110–125 mg/dl were \$1,308 more per year in 2007 dollars compared to patients who had normal fasting plasma glucose and were matched for age, sex, and year of fasting plasma glucose, and marginal costs were \$881 in patients with fasting glucose 100–109 mg/dl.³⁰ The Medical Expenditure Panel Survey (MEPS) found marginal costs for a 50-year-old patient with new-onset diabetes to be higher by \$4,431/year in 2007 U.S. dollars, after adjusting for age, race/ethnicity, sex, and a variety of other variables, but not BMI.⁴⁹ The marginal costs for KPNW patients with IFG are similar to our findings of VA marginal costs prior to the diagnosis of diabetes (\$1,329 to \$1,491 per year over the four years prior to the year of diagnosis). Both groups may have included some patients with undiagnosed early diabetes, but the largely employed KPNW population was slightly younger (60 vs. 63 years of age on average) and about half female, and may have had a lower disease burden than the VA population. The MEPS marginal costs for initially diagnosed diabetes were higher than the VA costs (\$1,708 to \$2,463 per year over the four years after the year of diagnosis); the American Diabetes Association estimate for marginal costs of diabetes of \$6,649 in 2007⁵ were higher as well. These studies also attributed a greater proportion of costs to inpatient hospitalization than the present analyses, which may reflect differences in the patient populations and/or healthcare systems or methods of data collection.

It is difficult to separate adverse effects attributable to prediabetes vs. undiagnosed diabetes in analyses of administrative databases, but one modeling approach estimated that isolated impaired glucose tolerance (IGT) was associated with greater costs than isolated IFG.²⁹ The Norfolk study⁵⁰ and a recent meta-analysis⁵¹ also provide evidence that sub-diabetic levels of glucose and A1c confer increased risk of CVD. However, we are not aware of previous reports of the adverse impact of prediabetes and early diabetes on costs independent of associated CVD.

The DPP and other studies aimed at prediabetes have demonstrated that lifestyle change and the use of medications can reduce progression to diabetes³⁹ and the development of microvascular complications⁵². In patients with prediabetes,

there may be particular benefit from achieving regression to normal glucose tolerance.⁵³ A 10-year analysis of costs in the DPP indicated that lifestyle change may be cost-effective and the use of metformin marginally cost-saving,⁵⁴ and we have also projected that screening to detect prediabetes and early diabetes, combined with lifestyle change or treatment with metformin, may be cost-saving, particularly in high-risk groups.^{42,55} Our present findings demonstrating early adverse associations involving both health and the healthcare system prior to the diagnosis of diabetes are consistent with earlier observations, and suggest that screening and appropriate management may improve both the health of individuals and healthcare systems.

Strengths of this study include a substantial number of patients, a high percentage of minority patients, rigorous design, the use of a well-validated metric for the diagnosis of diabetes, and assessment of impact on health (CVD), resource use, and costs within an integrated healthcare system in which the quality of care is generally good compared to general U.S. managed care.⁹ Limitations include a predominantly male population, restriction to veterans (who tend to be older, sicker, and poorer than the general population), and restriction to the southeastern U.S. Although our findings may not apply in other settings, the consistency with earlier, less extensive studies supports generalizability. While the diabetic patients were each matched with two control patients, not all patients had analyzable data in each study year. However, the findings were unchanged when analyses included only diabetic patients who had two matched control patients with data at the same time point at any time during the study (Appendix, Fig. 2), and diabetes and control patients who all had data at each FY (could be evaluated only from FY -3 through +4, Appendix, Fig. 3). While diabetic and control patients were matched according to care in individual VA hospital facilities, residual potential bias may exist due to care in different clinics or from different providers, and such potential clustering should be considered in further research. Another potential limitation is that underlying risk factors for diabetes and CVD may not be independent, and could contribute to increased costs. We were able to determine that obesity and increased LDL cholesterol appeared to contribute little to the diabetes-related increase in costs, but future studies should also examine the contributions of differences in blood pressure, glucose control, and other factors that were beyond the scope of this study. While we were also unable to assess CVD, resource use, and costs incurred when veterans received care outside the VA, the selection of patients who received primary care within the VA for an extended period of time renders it likely that the great majority of their care was, indeed, provided through the VA, and that inclusion of their non-VA care would not have had a substantial impact on the study findings.

This study shows that diabetes has adverse effects on health (CVD) and the healthcare system (resource use and costs) *before the diagnosis is made* when patients have undiagnosed prediabetes and early diabetes. Systematic screening to detect these disorders earlier and permit prompt preventive management, therefore, may benefit both the health of patients and our

healthcare systems. Since close to 2 million people are now diagnosed with diabetes each year in the U.S.,⁵⁶ prevention measures that could keep their marginal costs in line with those of patients with prediabetes have the potential to save up to \$2 billion a year.

Since this manuscript was submitted, it has been shown that lifestyle change in patients with prediabetes is associated with a longterm decrease in both cardiovascular and all-cause mortality,¹ and the United States Preventive Services Task Force (USPSTF) has issued draft recommendations for much broader screening for diabetes and prediabetes - such as adults who are aged 45 years and above, and those who are younger but have risk factors² (see Additional Reference List).

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Conflict of Interest: The authors each declare that they have no conflict of interest.

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