

Risk of Dementia among Persons with Diabetes Mellitus: A Population-based Cohort Study

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It is unclear whether persons with diabetes are at increased risk for dementia, including Alzheimer's disease. Existing studies are limited by small sample size, selection bias, and case-control designs. This population-based historical cohort study provides estimates of the risk of dementia and Alzheimer's disease associated with adult onset diabetes mellitus (AODM). The sample included all persons with AODM residing in Rochester, Minnesota, on January 1, 1970, plus all persons diagnosed in Rochester or who moved to Rochester with the diagnosis between January 1, 1970, and December 31, 1984. Individuals were followed through review of their complete medical records from AODM diagnosis until dementia onset, emigration, death, or January 1, 1985. Standardized morbidity ratios for dementia and Alzheimer's disease were calculated, using an expected incidence based on age- and sex-specific rates for the Rochester population. Poisson regression was used to estimate risks for persons with AODM relative to those without. Of the 1,455 cases of AODM followed for 9,981 person-years, 101 developed dementia, including 77 who met criteria for Alzheimer's disease. Persons with AODM exhibited significantly increased risk of all dementia (Poisson regression relative risk (RR) = 1.66, 95% confidence interval (CI) 1.34–2.05). Risk of Alzheimer's disease was also elevated (for men, RR = 2.27, 95% CI 1.55–3.31; for women, RR = 1.37, 95% CI 0.94–2.01). These findings emphasize the importance of AODM prevention and prompt additional investigation of the relation between AODM and dementia. *Am J Epidemiol* 1997;145:301–8.

Alzheimer's disease; amyloid; dementia; diabetes mellitus

A number of diabetic complications and comorbidities (e.g., stroke, hypertension, and depression) (1–3) have been implicated as risk factors for dementia and Alzheimer's disease (4–8). It is also known that adults with diabetes mellitus score lower on certain cognitive tests and subtests than adults without diabetes (9–13). Despite these findings, it is unclear whether adults with diabetes are at increased risk for dementia and Alzheimer's disease. The few studies investigating this issue have yielded conflicting results.

In a cross-sectional study of community residents aged 75, 80, or 85 years, Crosson and Jagger (14) obtained a mental status examination and an oral glucose tolerance test on 239 individuals. Among the 31 persons with diabetes (22 known, nine newly discov-

ered), the proportion with low cognitive function did not differ significantly from that for normal individuals (14). By contrast, Katzman et al. (15) found a significant association between self-reported diabetes and dementia in a nested case-control study of 434 healthy volunteers aged 75–85 years followed over a 5-year period. The proportion with diabetes at baseline was significantly greater among persons who developed vascular or vascular/mixed dementia (5/15) than among those who remained free of dementia (39/350). However, diabetes was present in only two of the 32 persons who developed pure Alzheimer's disease. A study by Mortel et al. (5) also reported that history of diabetes was positively associated with vascular dementia but not Alzheimer's disease. Some case-control studies of Alzheimer's disease found odds ratios less than 1.0 for diabetes (16–19), prompting the suggestion that diabetes is protective for Alzheimer's disease (17). Other case-control studies, however, found a positive association between Alzheimer's disease and impaired glucose regulation (13, 20, 21).

These apparently contradictory findings may be caused in part by study limitations, including small sample size, selection bias, and cross-sectional or case-control designs. The present study addresses

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Abbreviations: AODM, adult onset diabetes mellitus; CI, confidence interval; RR, relative risk; SMR, standardized morbidity ratio.

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these issues using a population-based historical cohort design to estimate the relative risk of dementia and Alzheimer's disease for persons with adult onset diabetes mellitus (AODM).

MATERIALS AND METHODS

The opportunity for population-based historical cohort studies in Rochester, Minnesota, is the result of an unusual set of circumstances. Rochester is relatively isolated from other population centers, and it is the home of the Mayo Clinic, one of the largest tertiary care medical centers in the world. Therefore, since the turn of the twentieth century, Rochester residents have received essentially all of their medical care from a small number of providers. Also, all information from every contact for each patient, including hospital inpatient, hospital outpatient, office visit, emergency room, nursing home, death certificate, and autopsy, is contained within a unit medical record. The diagnoses assigned and surgical procedures performed at each visit are coded and entered into centrally located and continuously updated computer files. With funding from the National Institutes of Health, this indexing system has been expanded to include non-Mayo providers of care to local residents. Under the auspices of the Rochester Epidemiology Project (22), these resources have afforded investigation of the natural history of disease for numerous conditions, including diabetes and dementia. Rochester Epidemiology Project investigations of disease incidence are typically initiated with a computerized listing of all Rochester residents assigned any diagnostic rubric associated with the condition of interest during the study period. The complete community-based medical records for these potential cases are then retrieved and reviewed by trained nurse abstractors who, under the direction of clinical specialists, apply standardized case criteria and assign date of diagnosis.

Identification of the diabetes mellitus cohort

The approach described above was employed in the identification of the Rochester, Minnesota, 1945–1989 diabetes mellitus incidence cohort and the January 1, 1970, 1980, and 1990, prevalence groups (23–25). The diagnostic criteria for diabetes mellitus were those outlined by the National Diabetes Data Group (26). The criteria consisted of two consecutive fasting glucose levels ≥ 140 mg/dl or 1- and 2-hour levels ≥ 200 mg/dl obtained during a standard oral glucose tolerance test. These levels were based on the Auto-Analyzer (Technicon, New York, New York) ferrocyanide reductase technique for plasma, the method used at the Mayo Clinic since May 1972. Glucose

values obtained at other institutions or using earlier laboratory methods were transformed to their post-May 1972 equivalents. Persons who failed to meet the criteria above but for whom there was evidence of oral agents or insulin use for at least 2 weeks or until death also qualified as cases.

Date of diagnosis was the earliest date for which criteria were met. Persons who moved to Rochester with confirmed AODM were assigned the first mentioned date of diagnosis obtained from patient history. Designation as an incidence case required that the individual have been a resident of Rochester for at least 1 year prior to meeting diagnostic criteria. The 1-year residency rule also applied for prevalence cases of January 1, 1970, 1980, or 1990, and was intended to exclude persons who moved to Rochester seeking treatment for diabetes at the Mayo Clinic.

This investigation was limited to adult onset diabetes mellitus, defined as diagnosis at age 20 years or older. This focus on adult onset differs from previous Rochester Epidemiology Project publications that distinguished non-insulin-dependent, insulin-dependent, and secondary types of diabetes using an algorithm based on age, body mass index, treatment type, and evidence of ketosis. With this algorithm, individuals whose ages at diagnosis were ≥ 20 years accounted for 99 percent of all persons with non-insulin-dependent diabetes mellitus; of those who were ≥ 20 years old, >93 percent of the diabetes cases were non-insulin-dependent (25). The decision to avoid classifying participants in this study as insulin- or non-insulin-dependent was prompted by evidence of dramatic changes in treatment over time (23) and is consistent with recommendations in a draft report of the American Diabetes Association Work Group on the diagnosis and classification of diabetes mellitus (P. J. P., Mayo Clinic Foundation, Scottsdale, Arizona, personal communication, April 1996).

Ascertainment of dementia

The complete medical records of each member of the AODM cohort were reviewed by a nurse abstractor (V. A. H.) and evaluated by a neurologist (E. K.) for evidence of dementing illness. Diagnostic criteria for dementia were based on the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (27), adapted for retrospective record review (figure 1). Based on all available clinical, laboratory, and autopsy information, year of onset of symptoms was assigned and cases were classified as Alzheimer's or non-Alzheimer's disease (figure 1). Cases were classified as Alzheimer's disease combined with other types of dementia including cerebrovascular dementia if 1) there was evidence of both Alzheimer's and non-

Diagnostic Criteria for Dementia and Alzheimer's Disease

Dementia diagnostic criteria

Documented evidence of:

- Previously normal intellectual and social function
- Irreversible decline in intellectual and social function
- Dementia as a predominant symptom
- Definite evidence of memory impairment

Documentation of at least two of the following:

(patient must be fully alert)

- Disorientation
 - Decline in personality and/or behavior
 - Dyscalculia
 - Apraxia and/or agnosia
 - Problems with language
 - Impairment in judgment and/or abstract thinking
- and

If diagnosis is based on clinical information only (i.e., without autopsy confirmation), dementia must have been present for 6 months

Clinical diagnosis of Alzheimer's disease

- Dementia as defined above
- Insidious onset
- Slow progression
- Other causes for dementia ruled out

Pathologic diagnosis of Alzheimer's disease

- Dementia as defined above
- Presence of abundant neuritic plaques and/or neurofibrillary tangles in one or more cortical regions other than hippocampus

FIGURE 1. Criteria used in the retrospective record review diagnosis of dementia and Alzheimer's disease among residents of Rochester, Minnesota, 1970–1984.

Alzheimer's disease at autopsy, or 2) if the dementia was characterized by insidious onset and slow progression but was accompanied by preexisting conditions (e.g., stroke, Parkinson's disease, alcoholism) that may have contributed to the dementia. The personnel and the criteria used in this study were the same as those in previous Rochester Epidemiology Project studies describing the incidence and prevalence of dementia and Alzheimer's disease for the Rochester, Minnesota, community (4, 28–32).

Data analysis

The association between diabetes and dementia was estimated using two distinct approaches. The first approach compared observed rates of dementia and Alzheimer's disease among persons with AODM with expected rates, based on published 1970–1984 rates for the Rochester population (29). To provide comparable calendar periods for observed and expected rates, the AODM cohort was limited to the following: January 1, 1970, prevalence cases; plus January 1, 1970,

through December 31, 1984, incidence cases; plus January 1, 1980 or 1990, prevalence cases who were diagnosed elsewhere but moved to Rochester between January 1, 1970, and December 31, 1984. Follow-up began on January 1, 1970, for persons with AODM diagnosed prior to that date; for persons diagnosed after that date and through December 31, 1984, follow-up began with date of diagnosis. Individuals with onset of dementia prior to start of follow-up were excluded from the analysis. Individuals were followed until the earliest of dementia onset, date last seen, death, or January 1, 1985. In the calculation of expected rates, Rochester residents already affected by dementia were removed from the census-derived denominator, and the age group ≥ 85 years was disaggregated into 5-year age-specific categories (29). The effects of age and gender were accounted for in the calculation of observed versus expected incidence using standardized morbidity ratios.

The second statistical approach used Poisson regression to estimate the risks of dementia and Alzheimer's disease for persons with AODM relative to persons

without AODM. Data for these analyses were generated by creating strata defined by all combinations of gender (women, men), year of age, calendar year, and prevalent AODM (no, yes). It is important to note that the dependent variable is the incidence rate within each stratum. As subjects move through strata, they contribute person-years, which provide the denominator for these rates. If subjects were the basis for the analysis, collinearity would be a concern since increasing age is perfectly correlated with increasing calendar year of follow-up. However, the basis for the analysis is person-years accumulated within strata, not individual subjects. When person-years within strata are considered, it is clear that the ages within successive strata will vary: there need not be a close correlation between these two variables. In other words, information about the calendar years for a stratum does not reveal the ages for that stratum.

The observed number of cases and person-years at risk among the AODM strata were calculated as described above. Calculations for non-AODM strata were based on the 1970–1984 Rochester dementia incidence cohort, from which we subtracted Rochester residents who met criteria for AODM prior to dementia onset ($n = 820$ for all dementia; $n = 653$ for Alzheimer's disease). These persons had been identified in a previous study using the same diagnostic criteria employed here for the AODM cohort (23). Person-years for the non-AODM strata were obtained by subtracting the January 1, 1970, 1980, and 1990, AODM prevalence cases from 1970, 1980, and 1990 Rochester census counts, respectively, and interpolating for intercensus years. Rochester residents affected by dementia were also removed from the census-derived denominator (29).

Variables were entered into the regression model in a stepwise fashion. Interaction and polynomial terms

were also assessed and included or not according to the same rules.

RESULTS

The cohort of 1,455 persons with AODM contributed 9,981 person-years of follow-up during the period 1970–1984. Follow-up ranged from zero (one person died at diagnosis of diabetes) to the full 15 years. During follow-up, 101 individuals met criteria for dementia. Seventy-seven of the 101 met criteria for Alzheimer's disease (including Alzheimer's disease combined with other types of dementia). Age- and sex-specific rates for persons with AODM are compared with those for the Rochester population in table 1. The incidence of all dementia and Alzheimer's disease increased with age through 99 years for the Rochester population and through ages 80–89 years for persons with AODM. Rates for ages 90–99 years for persons with AODM were based on very few cases. Among persons with AODM, age-specific rates of dementia and Alzheimer's disease were generally higher for men than for women. The proportions of all dementia classified as non-Alzheimer's, Alzheimer's only, and Alzheimer's combined with other types of dementia did not differ significantly between the AODM cohort (24, 58, and 18 percent, respectively) and the Rochester population (21, 66, and 13 percent, respectively) (30, 31) (Chi-square test, $p = 0.23$).

The number of observed cases of dementia among the AODM cohort was greater than expected based on age- and sex-adjusted rates for the Rochester population. The standardized morbidity ratio (SMR) for both sexes combined was 1.60, 95 percent confidence interval (CI) 1.30–1.95 (for men, SMR = 1.85, 95 percent CI 1.33–2.51; for women, SMR = 1.47, 95 percent CI 1.12–1.89). The incidence of Alzheimer's

TABLE 1. Incidence of dementia and Alzheimer's disease among Rochester, Minnesota, residents with adult onset diabetes mellitus and among the general Rochester, Minnesota, population, 1970–1984

Age (years)	Adult onset diabetes mellitus						Rochester population					
	Men		Women		Total		Men		Women		Total	
	No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
All dementia												
45–59	0	0	0	0	0	0	7	14	6	10	13	12
60–69	5	303	3	189	8	247	43	191	34	107	77	142
70–79	14	1,243	18	1,006	32	1,098	90	687	176	678	266	681
80–89	21	5,129	38	4,091	57	4,420	117	2,449	348	2,689	465	2,624
90–99	1	3,387	3	2,938	4	3,039	21	3,571	68	3,244	89	3,316
Alzheimer's disease												
45–59	0	0	0	0	0	0	1	2	3	5	4	4
60–69	2	122	1	63	3	93	22	98	17	54	39	72
70–79	10	918	16	919	26	919	56	428	153	589	209	535
80–89	17	4,278	28	3,288	45	3,603	87	1,821	303	2,341	390	2,201
90–99	1	3,387	2	2,070	3	2,378	19	3,231	64	3,053	83	3,092

* Incidence per 100,000 person-years.

disease was also greater than expected. The SMR for both sexes combined was 1.59, 95 percent CI 1.25–1.98 (for men, SMR = 2.07, 95 percent CI 1.40–2.96; for women, SMR = 1.38, 95 percent CI 1.02–1.84).

In the second analytical approach, Poisson regression was used to investigate the effects of age, gender, calendar year, and presence of diabetes. The only main effects to contribute significantly to risk of dementia were diabetes and age (table 2). The risk of dementia for persons with AODM was 1.66 times the risk for persons without AODM. The effect of age was not linear; the risk of dementia for a 70-year-old person relative to a 60-year-old person was 7.23; the risk of dementia for a 90-year-old person relative to an 80-year-old person was 2.16. The association between diabetes and dementia did not depend on age ($p = 0.52$ for age by diabetes interaction).

For Alzheimer's disease, the final Poisson regression model included gender and calendar year in addition to age and diabetes (table 2). The effects of age and calendar year were both nonlinear. The significant interaction between age and calendar year indicates that the rise in Alzheimer's disease incidence over time was greater among older age groups. This is consistent with secular trends reported previously for the Rochester population (30). The significant interaction between diabetes and sex indicates that the risk associated with diabetes differed between men and women. For men with diabetes, the risk of Alzheimer's disease was more than twice that for men without diabetes (relative risk (RR) = 2.27; 95 percent CI

1.55–3.31). Although an elevated risk associated with diabetes was observed for women, it did not reach statistical significance (RR = 1.37; 95 percent CI 0.94–2.01). The absence of a diabetes by age interaction ($p = 0.59$) indicates that the risk associated with diabetes did not depend on age. Graphs of the incidence of Alzheimer's disease as a function of age for women and men with and without AODM were drawn using the predicted rates from the Poisson regression model for calendar years 1970 (figure 2, a) and 1984 (figure 2, b).

To test the effect of duration of diabetes, we performed additional analyses in which the AODM strata for the Poisson regression models were subdivided according to duration <5 years versus ≥ 5 years. The 5-year cutoff was selected based on preliminary univariate analyses, which showed that age-specific incidence rates of dementia for persons with diabetes duration of 5–9, 10–19, and ≥ 20 years appeared similar and less than rates for persons with diabetes duration of <5 years. No significant effect for duration of diabetes was observed for either dementia or Alzheimer's disease in the final models, however.

DISCUSSION

This historical cohort study provides the first population-based estimates of the incidence of dementia and Alzheimer's disease among persons with confirmed AODM. The risk of dementia was significantly increased for both men and women with AODM relative to persons without AODM. Although the risk of Alzheimer's disease was elevated for both men and women with AODM relative to those without AODM, it reached significance only for men. The implications of the interaction between diabetes and sex are unclear and await confirmation in further studies.

The associations between AODM and dementia and Alzheimer's disease reported here are consistent with cross-sectional studies showing that persons with diabetes score lower on some tests of cognitive function than persons without diabetes (9–12) and that persons with Alzheimer's disease exhibit impaired glucose regulation compared with normal subjects (20, 21). The findings are also in agreement with a recent cross-sectional study by Ott et al., who found that the odds of both dementia and Alzheimer's disease were significantly increased among persons treated for diabetes (13). By contrast, other case-control studies found Alzheimer's disease odds ratios <1 (15–19), leading some authors to hypothesize a protective effect of diabetes (17). There are serious limitations to this interpretation, however. The difference was significant in only two studies (15, 19); neither study was

TABLE 2. Summary Poisson regression results for risk of dementia and Alzheimer's disease among Rochester, Minnesota, residents, 1970–1984

Variable	Beta	Standard error	<i>p</i> value
All dementia			
Diabetes (0 = no, 1 = yes)	0.507	0.106	<0.001
Age*	-1.020	0.391	0.009
Age ²	0.019	0.005	<0.001
Age ³	-0.000097	0.000023	<0.001
Alzheimer's disease			
Sex (0 = F, 1 = M)	-0.246	0.093	0.008
Diabetes (0 = no, 1 = yes)	0.317	0.153	0.038
Age*	-1.232	0.555	0.027
Year†	0.691	0.366	0.059
Sex* × diabetes	0.501	0.251	0.046
Age* × year	0.003	0.001	0.036
Age ²	0.020	0.007	0.006
Age ³	-0.0001	0.00003	<0.001
Year ²	-0.006	0.002	0.015

* Single year of age.

† Single calendar year.

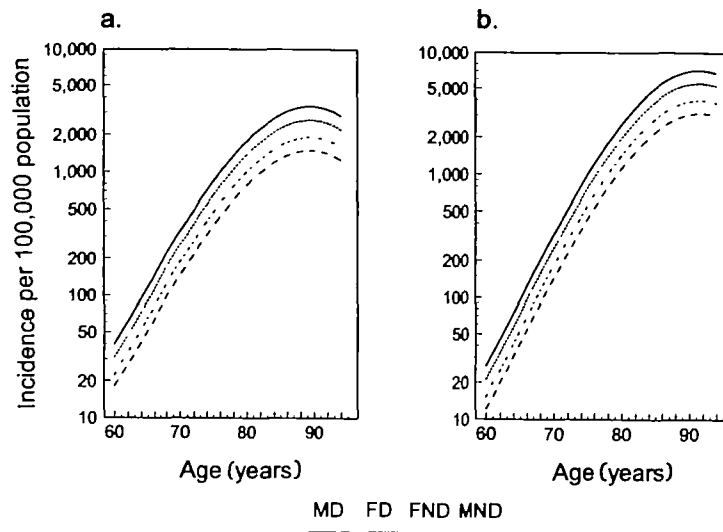


FIGURE 2. The incidence of Alzheimer's disease per 100,000 residents of Rochester, Minnesota, as a function of age for women and men with and without diabetes, with rates drawn on a log scale using the predicted rates from the Poisson regression model for calendar years 1970 (a) and 1984 (b). FD, females with diabetes; FND, females without diabetes; MD, males with diabetes; MND, males without diabetes.

population-based, creating a potential selection bias toward healthy demented cases (32). Some of the studies intentionally excluded persons with cerebrovascular disease from Alzheimer's disease cases (15, 16, 19). Because persons with diabetes are at increased risk of cerebrovascular disease (1), they would be differentially excluded. A lower prevalence of diabetes among persons with Alzheimer's disease in cross-sectional or case-control studies could also be an artifact of the shorter life expectancy for persons with diabetes (23).

A number of these concerns are addressed in this population-based cohort study, which includes both institutionalized and non-institutionalized individuals. This study is not without limitations, however. Confirmation of dementia diagnosis, classification of dementia type, and assignment of year of onset were based on retrospective record review. The progress of all medical conditions and symptoms of dementia over time was assessed with the longitudinal information available within the complete community-based medical records. Cases were often followed until death. Information was accumulated over many years from multiple sources, including autopsy, to reconstruct a clear clinical picture of the dementing illness. However, not all patients underwent neuropsychological or imaging tests, and some were never evaluated by either a neurologist or a psychiatrist. Bias might have occurred if case ascertainment differed between the AODM cohort and the Rochester incidence cohort. Dementia case-finding methodologies were identical with one exception. The medical records of all AODM cases were reviewed for evidence of dementia. By contrast, medical record review for the Rochester pop-

ulation was limited to individuals with at least one of 28 dementia-related diagnostic rubrics in the Rochester Epidemiology Project diagnostic index (28). The consequence of this difference was minimal, however; only one of the 101 cases in the AODM cohort would not have been identified using the diagnostic index.

It is possible that more frequent medical contacts for persons with AODM provided increased opportunity for detection. This did not appear to be the case, as neither mean age at onset nor median time from onset to diagnosis differed between persons with and without AODM (81.3 vs. 81.6 years, Student's *t* test, $p = 0.7$; 10 vs. 14 months, rank sum test, $p = 0.2$). There was no interaction between age and diabetes in the regression analysis.

The potential for bias in the ascertainment of Alzheimer's disease is more problematic. The proportion of cases with autopsy data available did not differ between the AODM (14 percent) and Rochester cohorts (22 percent, $p = 0.07$). Cases with insufficient information in the medical record to assign type were classified as non-Alzheimer's disease dementia in both cohorts, and the proportion classified as non-Alzheimer's disease was similar between cohorts. Although the proportion of Alzheimer's disease cases classified as Alzheimer's combined with other types of dementia including cerebrovascular dementia did not differ significantly, it was greater in the AODM cohort than in the Rochester cohort (see Results). Given that persons with diabetes are at elevated risk for vascular dementia, it is possible that vascular dementia was differentially misclassified as Alzheimer's combined with other types of dementia including cerebrovascular dementia among persons with AODM. Unfortu-

nately, the neuroimaging techniques employed to operationally define vascular dementia were generally unavailable until after the study period (33). The possibility of differential misclassification was investigated by excluding all 18 cases of Alzheimer's disease combined with other types of dementia including cerebrovascular dementia in the AODM cohort, under the assumption that they were really non-Alzheimer's disease cases. The remaining 59 observed cases of Alzheimer's disease were compared with the 48 cases expected, under the assumption that cases of Alzheimer's disease and Alzheimer's combined with other types of dementia including cerebrovascular dementia in the Rochester population were all correctly classified. Although no longer significant, the SMR remained elevated (SMR = 1.22, 95 percent CI 0.93–1.57). It is therefore unlikely that the increased incidence of Alzheimer's disease among persons with AODM found in this study was due entirely to differential misclassification. However, such a possibility cannot be completely dismissed.

In summary, this study revealed an increased risk of dementia for persons with AODM and refuted the hypothesis that AODM is protective for Alzheimer's disease. The associations could be causal (20) or could result from shared risk factors (1–8), including common genetic predispositions (34, 35). The prevention and treatment of both dementia and diabetes will benefit from further investigation of this association.

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