Diabetes and risk of physical disability in adults: a systematic review and meta-analysis

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Summary

Background According to previous reports, the risk of disability as a result of diabetes varies from none to double. Disability is an important measure of health and an estimate of the risk of disability as a result of diabetes is crucial in view of the global diabetes epidemic. We did a systematic review and meta-analysis to estimate this risk.

Methods We searched Ovid, Medline, Embase, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature up to Aug 8, 2012. We included studies of adults that compared the risk of disability—as measured by activities of daily living (ADL), instrumental activities of daily living (IADL), or mobility—in people with and without any type of diabetes. We excluded studies of subpopulations with specific illnesses or of people in nursing homes. From the studies, we recorded population characteristics, how diabetes was diagnosed (by doctor or self-reported), domain and definition of disability, and risk estimates for disability. We calculated pooled estimates by disability type and type of risk estimate (odds ratio [OR] or risk ratio [RR]).

Results Our systematic review returned 3224 results, from which 26 studies were included in our meta-analyses. Diabetes increased the risk of mobility disability (15 studies; OR 1·71, 95% CI 1·53–1·91; RR 1·51, 95% CI 1·38–1·64), of IADL disability (ten studies; OR 1·65, 95% CI 1·55–1·74), and of ADL disability (16 studies; OR 1·82, 95% CI 1·63–2·04; RR 1·82, 95% CI 1·40–2·36).

Interpretation Diabetes is associated with a strong increase in the risk of physical disability. Efforts to promote healthy ageing should account for this risk through prevention and management of diabetes.

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Introduction

The prevalence of diabetes worldwide has more than doubled over the past three decades, with an estimated 347 million adults living with diabetes in 2008.[1,2] Diabetes increases the risk of disabling disorders including cardiovascular disease,[3] retinopathy,[4] renal failure,[5] and peripheral vascular disease.[4] Physical disability[6] is a useful measure of the overall effect of diabetes on health. Disability can be defined in several ways, including difficulties with activities of daily living (ADL), difficulties with instrumental activities of daily living (IADL), and mobility limitations.[7] In 2004, the worldwide direct costs of all disability to individuals was between 11% and 69% of income and costs to the governments of countries in the Organisation for Economic Co-operation and Development accounted for roughly 10% of public social spending.[8]

The risk of disability associated with diabetes has been studied previously[9–12] with results ranging from no association to a doubling of risk. Epidemiological studies have varied in design, how diabetes was assessed (eg, by doctor or self-reported), definition of disability, and length of follow-up. Few studies have analysed the moderating effects of diabetes duration or glycaemic control and little is known of the risk of disability associated with measures of prediabetes—ie, impaired glucose tolerance or impaired fasting glucose. Although two reviews[6,13] have qualitatively summarised the evidence of a relation between diabetes and disability, no meta-analysis has pooled estimates of this risk. Accurate estimation of the risk of disability associated with diabetes is pivotal to understanding the health needs of the ageing population.

We did a systematic review and meta-analysis to estimate the magnitude of the relation between diabetes and prediabetes and the risk of disability, and to analyse the potential moderating factors of this association, particularly sex, duration of diabetes, and glycaemic control.

Methods

Systematic review

The protocol for this systematic review and meta-analysis has been published previously.[14] This study was done in accordance with the PRISMA[15] and MOOSE[16] guidelines. We searched Ovid, Medline, Embase, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature up to Aug 8, 2012 for reports published in English. We searched for "diabetes", "glucose intolerance", "diabet*", "glucose intoleran*", and "impaired glucose toleran*" as medical subject headings and keyword terms in the title, abstract, and text, combined with the operator "OR". We included all types of diabetes irrespective of cause,

which includes gestational, type 1, type 2, insulin-dependent, insulin-requiring, and insulin-depleted diabetes. We then combined diabetes terms with the operator "AND" for disability terms: "activities of daily living", "disabled persons", "mobility limitation", as well as keyword terms "disabl*", "disabiliti*", "limit*", "impair*", "mobili*", "ambulat*", "activit*", and "function*". All disability terms were combined with the operator "OR". The search was limited to case-control, cohort, and cross-sectional studies, and clinical trials of adults older than 19 years. We also searched the reference lists of included studies and reviews for relevant reports.

Two investigators independently reviewed the retrieved articles in two stages; first assessing relevance from the title and abstract and if relevance was still unclear, the full text was read. Any disagreement about inclusion was referred to a third reviewer and resolved by discussion.

We only included studies published in peer-reviewed journals that reported diabetes status, disability, and an estimate of risk for the association between diabetes and disability compared with no diabetes. Measures of disability included single and composite measures of disability based on ADL, IADL, or mobility.

We excluded studies of subgroups of patients with specific illnesses, or undergoing specific medical or surgical procedures, and studies of nursing home residents. We excluded disability measures that were defined by disturbances in cognitive function because our aim was to study physical disability. We also excluded studies reporting disability as a continuous measure.

When studies analysed the same population, we excluded the study with the weaker study design—ie, cohort studies were preferred to cross-sectional studies. If two cohort studies used the same baseline population, we included the study with the longer follow-up.

Data collection

Data from each study were independently extracted by two reviewers and cross-checked by EW. We recorded study design, baseline study year, length of follow-up, sample size, response rate, study characteristics, mean age, proportion of men, method used to ascertain diabetes and disability status, disability incidence, confounders, and effect size with 95% CIs of the association between diabetes and disability. If information was missing, we contacted the authors. We extracted sex-specific risk estimates when available. We preferentially extracted the risk estimates from models that adjusted for age, sex, education, and smoking but not for chronic diseases that might be part of the causal pathway.

Statistical analysis

We pooled risk estimates according to assessment of disability (ADL, IADL, or mobility) and the type of risk estimate reported (odds ratio [OR] or risk ratio [RR]). Generally, studies dichotomised disability at the level of at least some difficulty in at least one activity. Because definitions of severity of disability varied between studies, we analysed severity of disability according to the following hierarchy (least to most disabled):[17] mobility disability preceding IADL disability, and IADL preceding ADL disability. As a conservative approach, when a risk estimate was reported for a composite measure of disability, we included it in the analysis following the same hierarchy—eg, if a composite measure included a mobility measure, the study was analysed as mobility disability because mobility disability is first in the hierarchy.

We were unable to combine ORs and RRs because we assumed that disability is a common outcome and therefore the OR and RR will not approximate each other.[18] We subdivided the pooled ORs by study design. We calculated the log of the OR or RR, with standard errors, for all point estimates and 95% CIs using the generic inverse variance method. We used a random effect model because we expected the data to be heterogeneous across studies.

We compared pooled ORs for different study designs with the test for subgroup differences in Review Manager (version 5.2). If study designs did not differ significantly, we reported the final pooled effect size of all studies combined, irrespective of design. We assessed the proportion of variance in pooled estimates because of heterogeneity by χ^2 and I^2. A p value of less than 0·1 was deemed significant. I^2 less than 25% was considered low heterogeneity, 25–75% was considered medium heterogeneity, and ≥75% was considered high hetero-

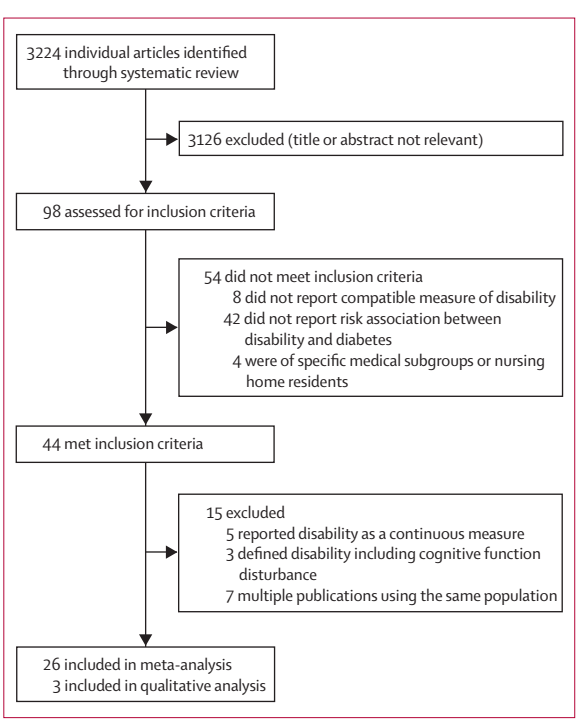

Figure 1: **Study selection**

geneity.[19] We did sensitivity analyses by systematically excluding one study at a time and assessing any change in pooled effect size. If data were available, we analysed the moderating effects of sex, duration of diabetes, and control of diabetes on the association between diabetes and risk of disability.

	Study	Baseline year	Sample size	Sex	Population characteristics	Domain of disability studied	Adjustments (model used in this meta-analysis)
Cross-sectional studies							
Bruce (2000)[40]	Aboriginal Peoples Survey	1991	3062	Men and women	Metis population, Canada	ADL, mobility (walk 350 m, flight of stairs, one room to another, stand 20 min)	Age, sex, chronic health conditions (arthritis, hypertension, heart problems, and emphysema)
Chau et al (2011)[41]	Elderly Health Centres	1998–2001	66 813	Men and women	Elderly people from Hong Kong enrolled in elderly health centres	IADL	Age, sex, education
Gregg et al (2000)[42]	Third National Health and Nutrition Examination Survey	1988–94	6588	Men and women	Non-institutionalised people aged 60 years and older	Mobility (walk 0·25 miles, climb 10 steps, housework), objective mobility test (walking speed, chair stands, tandem stands)	Age, ethnic origin, education, BMI
Hiltunen et al (1996)[43]	NA	1991–92	369	Men and women	Non-institutionalised people born before 1921, in Finland	ADL, IADL, mobility (moving outdoors, walking indoors, walk 400 m, stairs)	Age, sex, coronary heart disease, BMI, impaired glucose tolerance
Kalyani et al (2010)[44]	National Health and Nutrition Examination Survey	1999–2006	6097	Men and women	Non-institutionalised people aged 60 years and older	ADL, IADL, mobility (walk 0·25 miles, 10 steps)	Age, sex, education, race, ethnic origin, smoking
Kishimoto et al (1998)[45]	NA	1994–95	7303	Men and women	Aged over 60 years, from five towns in Japan	ADL	Age
Kriegsman et al (1997)[46]	NA	1992–93	2805	Men and women	Age 55–85 years from population registries, the Netherlands	Mobility (walk up or down 15 steps, using public transport, cutting toenails)	Age, sex, other chronic diseases
Maggi et al (2004)[47]	The Italian Longitudinal Study on Aging	1992	4768	Men and women	Elderly Italians	ADL	Age, education, BMI
Malhotra et al (2012)[48]	Social Isolation, Health and Lifestyle Survey	2009	5000	Men and women	Community-dwelling Singaporeans aged 60 years and older	ADL	Age, sex, ethnic origin, type of housing, marital status, all other self-reported health conditions
Martinez-Huedo et al (2011)[49]	National Health Survey, Spain	2000–07	7835	Men and women	Elderly Spanish people	ADL, IADL, mobility (10 steps)	Age and sex (unclear)
McLaughlin et al (2011)[50]	Australian Longitudinal Study on Women's Health and Perth Health in Me Study	2008	3493	Men and women	National sample, Australia	Mobility (climbing one or several flights of stairs)	Sex, marital status, doctor-diagnosed chronic disorders
Nourhashemi et al (2001)[51]	Epidemiologie de l'ostéoporose	1992–94	7364	Women only	People aged over 75 years, France	IADL	Age, cognition, vision and hearing disorders, fear of falling, self-rated health, social network, education, income, chronic diseases, fat mass, total bone mineral density
Odding et al (2001)[52]	Rotterdam Study	1989–92	3075	Men and women	Residents aged 55 years and older, the Netherlands	Mobility (climbing, walking, getting in and out of bed or car, bending, rising from chair)	Age
Patel et al (2006)[53]	Mexican Health and Aging Study	2001	4872	Men and women	Elderly Mexican people	ADL	Age, sex, education
Sinclair et al (2008)[54]	Case-control		403 cases, 403 controls	Men and women	Cases: known to have diabetes, aged 65 and older, controls: non-diabetics matched for age, sex, and general practice, Wales	Mobility (use of aids)	Mobility limitation: adjusted for age, hypertension, cerebrovascular disease, COPD, cancer, osteoarthritis, dementia
Tucker et al (2000)[55]	NA	1992–97	472	Men and women	Hispanic elderly Puerto Ricans, USA	ADL, IADL, mobility (walk 0·25 miles, 10 steps)	Age
Valderrama-Gama et al (2002)[56]	NA	1994–95	772	Men and women	Non-institutionalised people, aged 65 years and older, Spain	ADL	Age, sex
Wu et al (2003)[57]	Sacramento Area Latino Study on Aging	1998–99	1789	Men and women	Hispanic Americans aged 60 years and older	ADL, IADL	Age, sex, BMI, waist-to-hip ratio, household income, depression score, hypertension, history of stroke
Wu et al (2010)[12]	Social Environment and Biomarkers of Aging Study	1989	652	Men and women	Nationally representative sample aged 60 years and older, Taiwan	ADL, IADL, mobility (walk 200–300 m, two to three flights of stairs, getting out of bed, heavy housework)	Sex, age, education

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	Study	Baseline year	Sample size	Sex	Population characteristics	Domain of disability studied	Adjustments (model used in this meta-analysis)
(Continued from previous page)							
Longitudinal studies							
Al Snih et al (2005)[9]	Hispanic Established Populations for the Epidemiologic Study of the Elderly	1993–94; follow-up of 7 years	1835	Men and women	Mexican Americans aged 65 years or older	ADL, mobility (stairs, walk 0·5 miles), timed 8-foot walk	Age, sex, chronic diseases (hypertension, myocardial infarction, stroke, cancer, hip fracture), vision function, MMSE score, obesity at baseline
Gregg et al (2002)[10]	Osteoporotic Fractures study	1986–88; follow-up of 9 years	6971	Women only	Community-dwelling white women	Mobility (walk two to three blocks, ten steps, housework)	Age, BMI, education, physical activity, oestrogen use, marital status, baseline functional status (level of reported difficulty)
Penninx et al (2009)[58]	Health, Aging, and Body Composition study	1997–98; follow-up of 5 years	2920	Men and women	Well-functioning, white and black people aged 70–79 years, USA	Mobility (walk 0·25 mile, climb 10 steps)	Age, sex, race, site, education, smoking, alcohol use, lung disease, heart disease, stroke, cancer, arthritis.
Reynolds et al (2003)[59]	Asset and Health Dynamics Among the Oldest Old and Health and Retirement surveys	1993, 1995, 1998	4228	Men and women	70 years or older, USA	ADL, IADL	Age, sex, ethnic origin, family network, household assets, chronic diseases
Spiers et al (2005)[60]	Medical Research Council Cognitive Function and Ageing Study	1991–94; follow-up of 2 years	10 582	Men and women	65 years and older, UK	IADL	Age, sex, chronic disorders, education, living status, smoking
Volpato et al (2003)[61]	Women's Health and Aging Study	1991; follow-up of 3 years	729	Women only	Patients aged 65 years and older with mild-moderate disability at baseline, USA	ADL, mobility (walk 0·25 miles, climb stairs), objective mobility test (4 m walking speed, chair stand, balance)	Age, race, smoking
Woo et al (1998)[11]	NA	Baseline year not reported; follow-up of 18 months	1334	Men and women	Aged 70 years and older, Hong Kong	ADL	Age, sex

ADL=activities of daily living. IADL=instrumental activities of daily living. BMI=body-mass index. MMSE=mini mental state examination. COPD=chronic obstructive pulmonary disease. NA=not available.

Table: **Studies included in meta-analysis**

We assessed quality according to the Newcastle-Ottawa Scale with highest quality assessed as: (1) longitudinal study design; (2) disability-free cohort at baseline; (3) measured glucose or physician-diagnosed diabetes; and (4) models adjusted for appropriate confounders including age, sex, smoking, and education, and excluding chronic diseases that might be part of the pathway from diabetes to disability. For studies reporting risk of mobility disability, objectively measured mobility was an additional quality criterion. Studies that met all quality domains were classified as high quality.[20] We assessed publication and selective reporting bias by the symmetry of the funnel plot.[21]

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our initial search yielded 3224 articles, 98 of which had relevant titles and abstracts. After reading the full text, 44 met our inclusion criteria (figure 1). 15 of these were excluded at the stage of data extraction (figure 1).[22–36] A further three[37–39] did not report CIs and were not available on request but the reported point estimates of the association between diabetes and disability were included in the qualitative review.

Thus, 26 studies were included in our meta-analysis; 22 reported ORs and four reported RRs. Most studies were cross-sectional, nine were longitudinal, and one was a case-control study (table). Although the study of Wu and colleagues[12] was longitudinal, we only included the results from their cross-sectional analysis of their baseline data because their longitudinal data reported change in disability status over time, not the risk of incident disability from diabetes.[57] Length of follow-up in the longitudinal studies ranged from 18 months[11] to 9 years.[10]

The 26 studies included 30 populations with sample sizes between 369 and 66 813.[41,43] Study populations included ten from North America with five studies of specific ethnic groups[9,38,53,55,57] and one of an Indigenous population;[40] five studies were done in Asia;[11,12,41,45,48] nine in Europe;[43,46,47,49,51,52,54,56,60] and one in Australia.[50] Three study populations included only women[10,51,61] and all studies were of populations with a mean baseline age of more than 55 years, with most older than 65 years. No

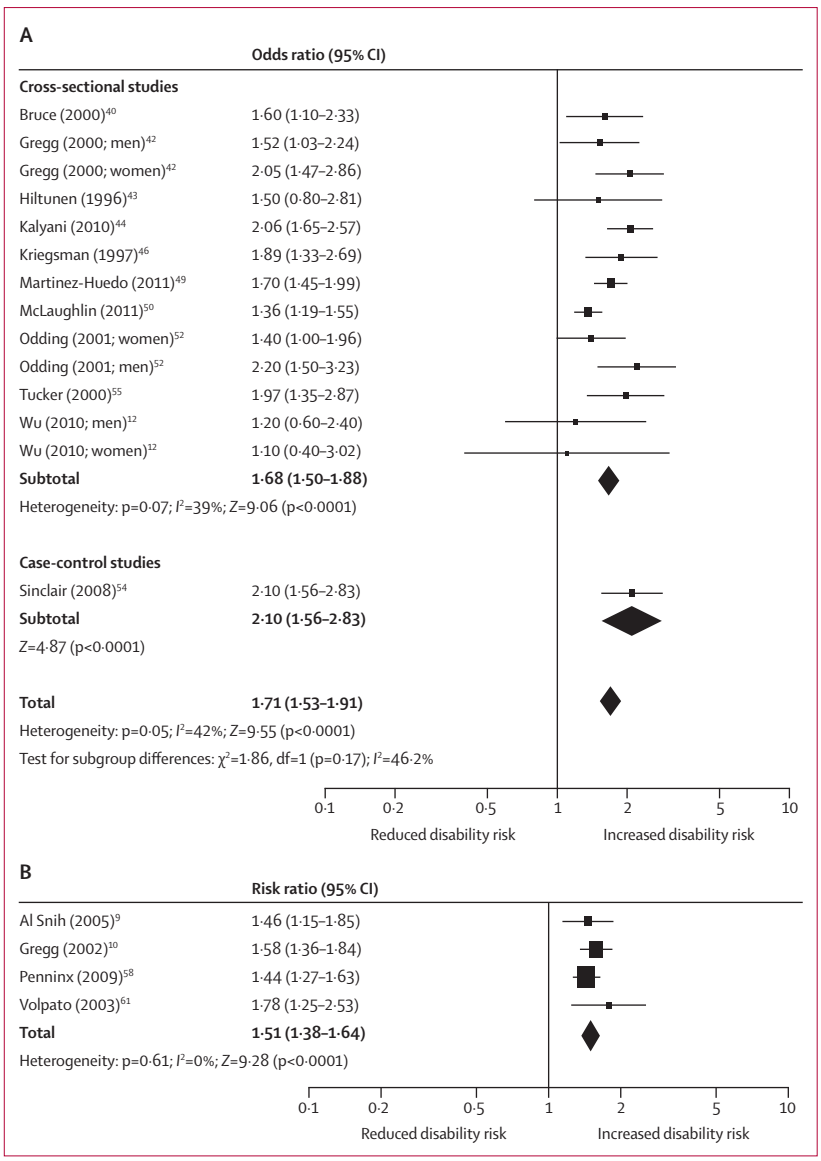

Figure 2: **Association between diabetes and mobility disability**
Assessed by odds ratio (A) and risk ratio (B).

studies defined the type or cause of diabetes. Two studies[10,57] further analysed the role of duration of diabetes in disability. Two others[39,43] analysed the association between impaired glucose tolerance and disability.

Measures of ADL included bathing, dressing, eating, walking across a room, transferring from a bed or chair, and using the toilet. Measures of IADL included using the phone, shopping, and using transport. Impaired mobility was assessed by self-reported limitations in walking 0·25–0·5 miles or walking up and down stairs. Mobility was also objectively measured by physical performance tests such as walking speed, chair stands, and balance tests.

16 studies analysed 20 populations for the association between diabetes and mobility disability. Of these 16, four objectively measured mobility.[9,42,47,61] Al Snih and colleagues and Gregg and colleagues reported effect sizes for both self-reported and objectively measured mobility limitation; only those relating to the objective measures were used in our meta-analysis. Maggi and coworkers[47] reported effect sizes for outcomes of several physical performance tests but no risk association for a dichotomised mobility disability outcome, therefore we could not include their findings in our meta-analysis. Of the 15 included studies, 11 were cross-sectional, four longitudinal (all reported RRs), and one case-control. Two included women only.[10,61] Maggi and coworkers[47] reported ORs for varying severity of disability ranging from 1·39 (95% CI 0·98–1·98) to 2·16 (95% CI 1·25–3·73) in women with diabetes and 1·07 (95% CI 0·72–1·58) to 2·81 (95% CI 1·44–5·41) in men with diabetes.

Pooled ORs from cross-sectional studies showed that diabetes was associated with an increased odds of mobility disability compared with no diabetes (OR 1·68, 95% CI 1·50–1·88; figure 2A). The case-control study reported an OR of 2·10 (95% CI 1·56–2·83). All together, the OR was 1·71 (95% CI 1·53–1·91). Meta-analysis of longitudinal studies reporting RRs showed that people with diabetes were more likely to report incident mobility disability than those without diabetes (pooled RR 1·51, 95% CI 1·38–1·64; figure 2B).

Our meta-analysis of the association between diabetes and IADL included ten studies, all of which reported ORs. Pooled point estimates from cross-sectional studies showed an increased risk of IADL disability with diabetes compared with no diabetes (OR 1·67, 95% CI 1·57–1·77; figure 3). Pooled estimates did not differ significantly between cross-sectional and longitudinal studies (p=0·17) and overall heterogeneity when cross-sectional and longitudinal studies were pooled was not significant (p=0·24; I^2=21%). The pooled OR from combining cross-sectional and longitudinal studies was 1·65 (95% CI 1·55–1·74).

We analysed the risk of ADL disability associated with diabetes from 16 studies, representing 19 populations. 14 studies reported effect sizes as ORs (12 cross-sectional, two longitudinal) and two longitudinal studies reported RRs (figure 4A). Pooled ORs from cross-sectional studies showed that having diabetes was associated with an increased odds of difficulties with ADL compared with no diabetes (OR 1·87; 95% CI 1·66–2·10). The pooled risk estimate from longitudinal studies was 1·48 (95% CI 1·12–1·94), which is not significantly different from the pooled estimate from cross-sectional studies (p=0·12). All together, the OR was 1·82 (95% CI 1·63–2·04). Pooled estimates from all studies reporting RRs for ADL disability showed an increase in the risk of disability if the person had diabetes (RR 1·82; 95% CI 1·40–2·36; figure 4B).

We report significant, but low heterogeneity between cross-sectional studies reporting the association between

diabetes and ADL (p=0·06; I^2 39%) and mobility disability (p=0·07; I^2 39%). Studies reporting risk of IADL disability did not have significant heterogeneity (I^2 39%; p=0·29).

Systematic exclusion of some individual studies from the analyses resulted in changes to heterogeneity and the effect size in the analysis of cross-sectional studies addressing the association between diabetes and mobility disability, although we could not test whether these changes were significant (data not shown). Exclusion of point estimates from the study of McLaughlin and colleagues[50] decreased the overall heterogeneity to 0% (p=0·56) and slightly increased the pooled OR for mobility disability to 1·80 (95% CI 1·65–1·96) from 1·71 (1·53–1·91). None of the other studies on mobility disability reporting ORs or RRs affected heterogeneity or the pooled effect size after exclusion from our analysis (data not shown). Likewise, no significant changes occurred to the heterogeneity or pooled estimates when any of the studies reporting risks of IADL disability were excluded (data not shown).

Exclusion of the study by Kalyani and colleagues[44] from the meta-analysis of ADL disability decreased the overall heterogeneity from 37% to 17% (p=0·26). The pooled effect size decreased from 1·82 (95% CI 1·63–2·04) to 1·76 (1·59–1·94). Exclusion of the point estimate for men in the study by Maggi and coworkers[47] also decreased heterogeneity to non-significance (I^2=26%; p=0·16). Exclusion of the other studies of ADL that reported ORs did not substantially affect heterogeneity. Only two studies in the meta-analysis of longitudinal studies of ADL disability reported RRs and heterogeneity was not significant (figure 4).

Meta-analyses of studies that did not adjust for chronic diseases that might be in the pathway from diabetes to disability did not substantially alter the pooled effect sizes. None of the studies met all of our quality criteria (appendix).

We also assessed the association between diabetes and disability in studies that met our inclusion criteria but were not compatible for meta-analysis. Three studies reported effect sizes without CIs. Clark and coworkers[37] reported an OR of 1·27 for mobility disability within 2 years (adjusted for sociodemographic, economic, and lifestyle factors, and multiple chronic diseases) in a population aged 51–61 years, though it was not significant (p>0·05). In a cross-sectional study of physical function (measured by the physical function component in the Medical Outcomes Study 36-item questionnaire) in people aged 60–70 years, Sayer and colleagues[39] reported an OR of 2·73 (p<0·001) for people with diabetes compared with those with normal glucose tolerance. Rodriguez-Saldana and coworkers[38] assessed the relation between diabetes and disability in a population in Mexico City from repeated surveys over 10 years. They reported RRs of 2·46 for ADL disability and 3·11 for IADL disability in people with diabetes compared with those without diabetes.

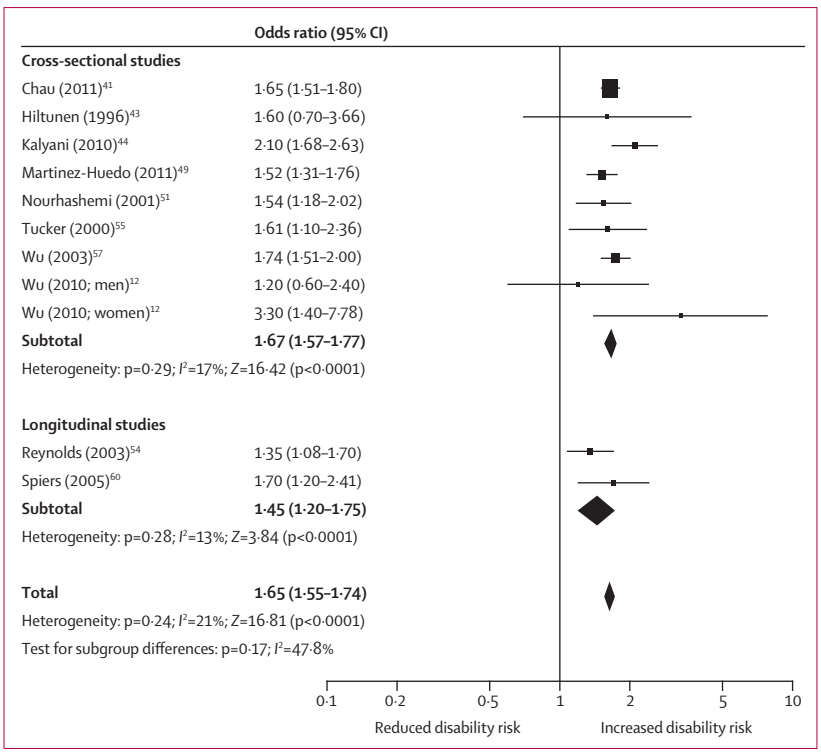

Figure 3: **Association between diabetes and instrumental activities of daily living**

With regards to impaired glucose tolerance and risk of disability, Hiltunen and colleagues[43] reported an OR of 1·12 for poorer function in people with impaired glucose tolerance compared with those with normal glucose tolerance, after adjustment for age and sex. Sayer and coworkers[39] reported an OR of 1·62 (p=0·03). We could not pool these estimates because of incompatible data.

In our assessment of moderating factors, we detected no difference between sexes for odds of ADL or mobility disability in cross-sectional studies (data not shown). Our data were insufficient to analyse sex differences in the relation between diabetes and disability risk from longitudinal studies. We were unable to analyse the roles of duration of diabetes or degree of glycaemic control in the association between diabetes and disability. Although two studies[10,57] investigated the effect of diabetes duration, the categorisations of diabetes duration were not comparable. All funnel plots looked symmetrical (appendix); however, some analyses included only a small number of studies.

See Online for appendix

Discussion

This study is the first meta-analysis to estimate the magnitude of the association between diabetes and disability and shows a roughly 50–80% increased risk of disability for people with diabetes compared to people without diabetes. This risk accords with previous reviews and large longitudinal studies.[6,10,13] Although ORs were the primary measure of risk, differences in absolute risk

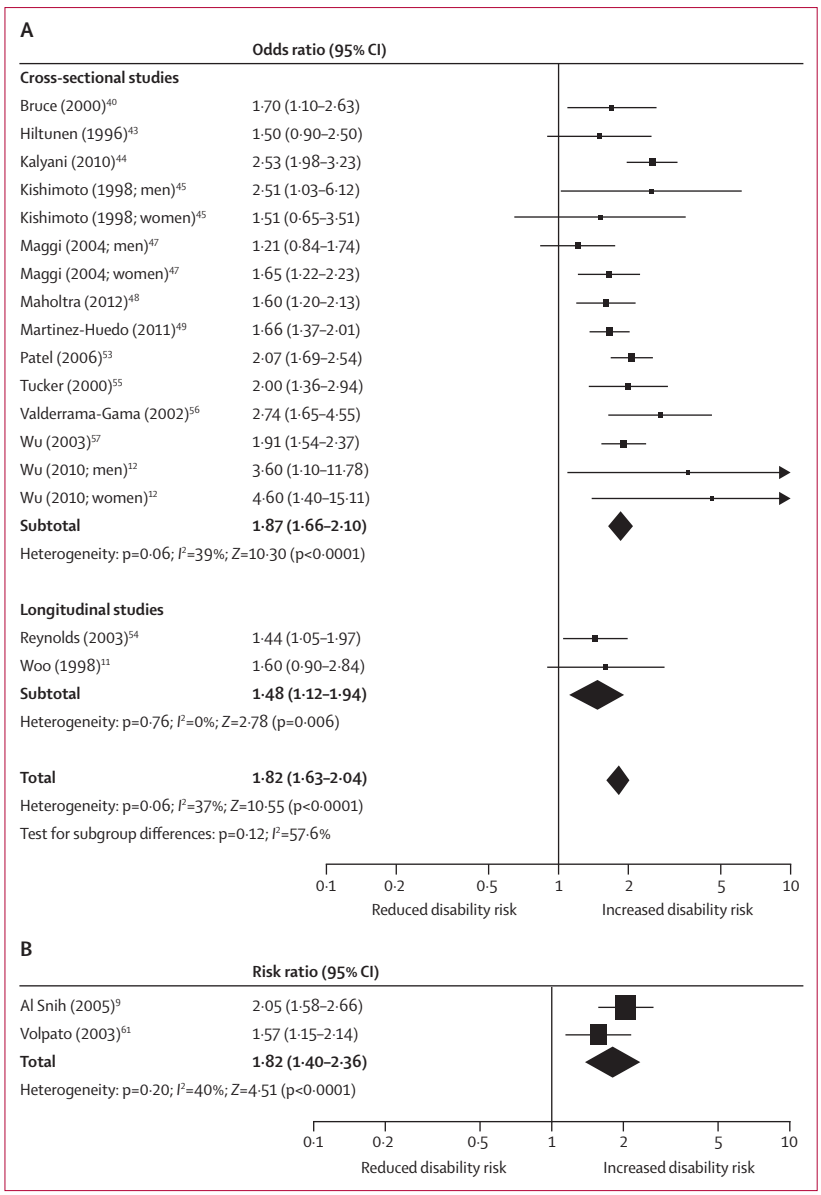

Figure 4: **Association between diabetes and activities of daily living**
Assessed by odds ratio (A) and risk ratio (B).

offer another perspective on the implications of diabetes and its effect on disability. For example, in a longitudinal study[62] of 8344 women aged older than 65 years, the yearly incidence of disability in those with diabetes was roughly 10% compared with less than 5% in those without diabetes.

The major strength of our study was the inclusion of a large number of studies with risk estimates for different domains of disability. We showed a consistent association across ADL, IADL, and mobility. All but one longitudinal study analysed incident disability in a population free of disability at baseline. The consistency of our results between longitudinal and cross-sectional studies suggests little effect of reverse causation. Furthermore, heterogeneity between studies was low or zero for all analyses. No studies met all our quality criteria, but Volpato and colleagues[61] met all but one and reported an RR consistent with the pooled point estimates.

Misclassification of diabetes status could dilute the strength of association between diabetes and disability. Self-reported diabetes status might underestimate the true prevalence of diabetes, as shown in a previous large study in which only half of patients with diabetes knew their diagnosis.[63] Furthermore, in longitudinal studies in which diabetes status is ascertained at baseline, longer follow-up is likely to be associated with misclassification of no diabetes, with new cases of diabetes occurring during follow-up. We did not analyse modification of risk by length of follow-up because of the small number of studies. However, the consistency of our results across studies with and without diabetes diagnosed by blood glucose analysis by a doctor suggests that this effect is not a major limitation.

No information was included about type or cause of diabetes—some studies might have included various types of diabetes. However, in elderly people, type 2 diabetes is predominant. Thus, we cannot establish whether the association between diabetes and disability differs by cause of diabetes. Furthermore, the magnitude of associations between diabetes and disability might not be generalisable to all definitions of disability, but the consistency of effect sizes across the three disability types (ADL, IADL, and mobility) suggests that this limitation is not substantial.

The mechanisms by which hyperglycaemia leads to disability are still unclear. High concentrations of glucose might lead to systemic, chronic inflammation, which is part of a multifactorial process eventually resulting in disability.[6,13] Some studies[64,65] have also shown that diabetes is associated with rapid loss of skeletal muscle strength and quality, worsening with increased duration of diabetes and poor glycaemic control. The increased risk of disability from diabetes might be moderated by duration of diabetes and glycaemic control such as that measured by HbA_{1C}. Wu and colleagues[57] suggested that the longer the duration of diabetes, the greater the risk of disability, although this finding was not supported by Gregg and coworkers.[10] Poor glycaemic control and long duration of diabetes increase the risk of diabetic complications—eg, cardiovascular disease, stroke, peripheral vascular disease, renal disease, peripheral neuropathy, and retinopathy.[4,66–68] All these complications can result in disability. No studies included in our meta-analysis investigated the effect of duration of diabetes or glycaemic control.

Some studies[39,43] suggest that patients with impaired glucose tolerance have an increased risk of disability, even before progression to diabetes. Our ability to investigate this possibility was limited by the scarcity of reports analysing prediabetes. The possibility that the

risk of disability increases in a graded manner from impaired glucose tolerance to diabetes and might be moderated by duration of diabetes further emphasises the need for more effective prevention of diabetes, particularly in middle-aged people. A large longitudinal study that measures fasting glucose, oral glucose tolerance test, HbA_{1c} at baseline, and multiple domains of disability over time is needed to fill the gaps in our understanding of the moderators of the association between diabetes, as well as the link between prediabetes and disability.

As the world's population ages, diabetes will become more common, increasing the need for disability-related health resources. Costs will be both direct (eg, for health services, assistive devices, nursing home costs) and indirect (loss of productivity both from individuals and their carers).

Contributors

EW formulated the research question, designed the study, searched the published work, extracted and selected articles, extracted and analysed data, and drafted and revised the report. KB and AP helped to formulate the research question, designed the study, selected articles, extracted and interpreted data, and commented on drafts. EG extracted and selected articles, extracted data, and commented on drafts. JH, RF-P, and CS selected articles, extracted data, and commented on drafts.

Conflicts of interest

We declare that we have no conflicts of interest.

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