Diabetes, Inflammation, and Functional Decline in Older Adults

Findings from the Health, Aging and Body Composition (ABC) study

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OBJECTIVE — Age, diabetes, and elevated inflammatory markers independently increase the risk of functional decline. We examined the effect of C-reactive protein (CRP) and interleukin-6 (IL-6) on the incident mobility limitation in older adults with and without diabetes.

RESEARCH DESIGN AND METHODS — We analyzed data from a cohort of 2,895 well-functioning adults aged 70–79 years, followed for development of persistent functional limitation over 3.5 years. Participants were assessed for the presence of diabetes according to fasting glucose and/or hypoglycemic medication use and were divided into three equal groups (tertiles) according to level of CRP or IL-6. Persistent functional limitation was defined as difficulty climbing 10 steps or walking one-quarter mile on two consecutive semiannual assessments.

RESULTS — At baseline, 702 participants (24%) had diabetes. CRP values were (median ± SD) 2.8 ± 4.4 versus 3.7 ± 5.4 for those with normal glucose and diabetes, respectively ($P < 0.001$). The unadjusted incidence of functional limitation associated with increased levels of CRP and IL-6 was greater among participants with diabetes. After adjusting for clinical and demographic covariates, persistent functional limitation for the highest tertile was greater compared with that for the lowest tertile of CRP or IL-6 for those with and without diabetes. CRP hazard ratios (HRs) were 1.7 (95% CI 1.2–2.3) versus 1.4 (1.1–1.6), respectively. IL-6 HRs were 1.8 (1.3–2.5) versus 1.6 (1.4–2.0), respectively.

CONCLUSIONS — In initially high-functioning older adults, those with diabetes and higher inflammatory burden had an increased risk of functional decline. Interventions at early stages to reduce inflammation may preserve function in these individuals.

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Identifying individuals at high risk for disability is a critical concern in primary care. This is especially important because early intervention is more likely to be beneficial. Chronic diseases such as diabetes are associated with a higher incidence of disability among the elderly (1–9). Older adults with diabetes are often obese, which further predisposes them to disability (10,11). In addition, diabetes-related factors such as neuropathy and vasculopathy can also contribute to disability (12–14). Many of these complications are difficult to remediate, making early detection particularly important. The presence of inflammation probably poses additional independent risk of functional limitation in these high-risk populations (15–17).

Poor health outcomes in older adults are associated with an elevation in inflammatory markers (6,18–21). Concentrations of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen are increased with coronary disease, disability, and poorer self-reported mobility (22–25). Elevated levels of CRP are observed in the elderly, in smokers, in those who exhibit glucose intolerance, and in the obese (26–30). In general, those with type 2 diabetes are noted to have higher CRP levels (31–33), although not consistently (19). CRP levels >3.0 mg/l add prognostic information to traditional risk factors of future cardiovascular risk (34–36).

The purpose of this study was to explore the links between diabetes, inflammation, and disability in a cohort of older adults with and without diabetes. It is unclear whether diabetes itself or the associated elevated inflammation and obesity underlie the increased risk for functional decline. Older adults with diabetes and increased inflammation, as measured by high CRP or IL-6 levels, may have increased relative risk of disability compared with those who do not have elevated markers of inflammation or with individuals without glucose abnormalities. We prospectively evaluated the association between type 2 diabetes and levels of inflammation as measured by CRP or IL-6 for the prediction of future risk of mobility limitation. Because obesity is associated with diabetes, functional decline, and inflammatory marker levels, we also examined the impact of obesity on incident functional limitation among those with and without diabetes in the presence of elevated inflammation markers.

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Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; IL-6, interleukin-6; PVD, peripheral vascular disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESEARCH DESIGN AND METHODS

— We used data from the Health, Aging and Body Composition (Health ABC) study, a prospective cohort ($n = 3,075$) assessed in 1997–1998 from community-dwelling older adults between 70 and 79 years of age, living in designated zip code areas surrounding the Pittsburgh, Pennsylvania, and Memphis, Tennessee, clinical centers. Study participants were selected from a sample of white Medicare beneficiaries and all age-eligible community-dwelling black residents. Participants were eligible if they reported no difficulty walking for one-quarter mile, walking up 10 steps, or performing basic activities of daily living. We excluded those participants missing inflammatory marker levels or glucose determinations, leaving 2,895 participants for this analysis. All participants gave informed consent. The institutional review boards at each study site approved all protocols.

Baseline assessments

Questionnaire variables obtained at the baseline visit included comorbid conditions, including diabetes, peripheral vascular disease (PVD), coronary artery disease (CAD), heart failure, lung disease, and arthritis. These diagnoses were based on a combination of self-report, medication use, and clinic evaluation. Sociodemographic variables included race, age, education, and personal habits such as cigarette smoking, alcohol use, and usual physical activity. In addition, history of hydroxymethylglutaryl-CoA reductase inhibitor (statin), estrogen replacement, corticosteroid, and nonsteroidal anti-inflammatory use were obtained using a 2-week medication inventory of prescription and over-the-counter preparations brought to the clinic by the participant. Anthropomorphic measures such as height and weight were also directly obtained. During the baseline visit, blood samples were also drawn after an overnight fast.

Diabetes assessment

Each participant had HbA_{1c} (A1C) measured (Bio-Rad, Hercules, CA). Participants also had a fasting glucose measured and received an oral glucose tolerance test if they were not currently taking medication for diabetes at baseline. Thus, the diagnosis of diabetes was based on their self-report of the diagnosis and use of oral hypoglycemic medications or insulin or measured fasting glucose ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl at the study baseline (37). Participants without a diagnosis of diabetes who met the criteria based on fasting levels or oral glucose tolerance test results were considered to have newly diagnosed diabetes.

Mobility limitation

Mobility limitations were assessed at baseline using several methods, which were combined into a final score. Participants were asked to perform several physical performance tests including repeated chair stands, standing balance (semitandem, full-tandem, and single-leg stands), a 6-m walk at the usual pace, and a narrow 6-m walk. All tests were timed, and test times were converted to rates. Participants who were unable to do a test successfully were assigned a score of 0. Lastly, ratio scores were created for each test (see Simonsick et al. [38] for more detail) and were summed to get a continuous scale ranging from 0 to 4. This approach was designed to minimize ceiling effects and maximize overall dispersion on each measure. Persistent functional limitation was determined on the basis of interviewer-administered questionnaires given every 6 months during follow-up. Participants were defined as having persistent lower extremity functional limitation if they reported any difficulty walking one-quarter mile or walking up 10 steps for two consecutive semiannual assessments. This requirement of two consecutive instances of limitation permitted a more reliable indicator of a clinically significant decline.

Inflammatory markers

Inflammatory biomarkers, CRP and IL-6, were measured in blood samples. Serum levels were determined from frozen fasting blood samples at the University of Vermont at Burlington. CRP was measured using an enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA) with a sensitivity of 0.08 μg/ml and an interassay coefficient of variation of 8.0%. The detectable limit for IL-6 (by HS600 Quantikine kit) was 0.10 pg/ml, and the interassay coefficient of variation was 10.3%. Values were measured in duplicate, and the average was reported for both assays.

Statistical analyses

Baseline characteristics were compared among participants with and without type 2 diabetes. We used χ^2 tests for comparing proportions, Kruskal-Wallis tests for skewed continuous variables, and *t* tests for normally distributed variables. We used accepted cutoff values for variables such as BMI (normal <25 kg/m^2, overweight 25–29 kg/m^2, and obese ≥30 kg/m^2) and diabetes (37). Our main independent variables, CRP and IL-6, were divided into three equal groups (tertiles), with the lowest tertile serving as the referent category. To evaluate the relationship between inflammatory marker status and incident persistent functional limitation, we constructed Cox proportional hazard models to estimate the unadjusted and adjusted hazard ratios (HRs) of mobility limitation according to tertile of inflammation (PHREG in SAS version 8.1). These analyses were performed among all participants, and results were also stratified by the presence or absence of diabetes. An interaction between CRP or IL-6 and diabetes was assessed using a cross-product term in the Cox regression model. Those who survived without disability were censored on the date of last follow-up; those who died before disability were censored at the time of their death. We also conducted an analysis of functional limitation by obesity status, separating BMI into normal (<25 kg/m^2), overweight (25–29 kg/m^2), and obese (≥30 kg/m^2).

Covariates chosen a priori and included in the multivariable Cox regression model were PVD, heart failure, CAD, fasting glucose, and impaired fasting glucose for those without a diagnosis of diabetes. We also examined several sociodemographic, health status, and comorbidity variables based on previously reported associations with elevated CRP and functional limitation (39–41). These factors, collected at baseline, were age, sex, race, walking and exercise category, baseline performance score, BMI, assessed coronary disease, statin use, and estrogen replacement. In addition, we entered baseline anti-inflammatory use and smoking status into the model. For all analyses, SAS version 8.2 (SAS Institute, Cary, NC) was used.

RESULTS

Baseline characteristics

The mean age for the study cohort was 73.6 ± 2.9 years; 702 individuals, 24% of the sample, had diabetes. Forty-eight percent of all participants were male, and 42% were black. Diabetes was more prevalent among those who were obese, black, and male ($P < 0.05$). Table 1 displays the distribution of demographic and clinical

Table 1—*Baseline clinical characteristics by diabetes status*

Measurement	Diabetes status		
	No diabetes	Diabetes	*P* values
n	2,193	702	
Age (years)	73.6 ± 2.9	73.8 ± 2.9	0.489
Sex (% female)	116 (53)	319 (45)	<0.001
Black	821 (37)	369 (53)	<0.001
Completed years of education			
Less than high school	502 (23)	223 (32)	<0.001
High school graduate	718 (33)	228 (33)	<0.001
Postsecondary	963 (44)	238 (38)	<0.001
Smoking status			
Current	228 (10)	61 (9)	0.06
Former	978 (45)	342 (49)	0.07
BMI (kg/m^2)	27 ± 4.7	29 ± 4.9	<0.001
Performance score (0–4)	2.2 (±0.0.5)	2.0 (±0.0.8)	<0.001
CRP	2.8 (±4.4)	3.7 (±5.4)	<0.001
IL-6	2.3 (±1.9)	2.8 (±2.1)	<0.001
A1C (%)	6.0 (±0.5)	7.6 (±1.5)	<0.001
Conditions associated with diabetes			
PVD	314 (14)	157 (22)	<0.001
Heart failure	50 (2)	40 (6)	<0.001
CAD	425 (19)	205 (29)	<0.001
Knee osteoarthritis	127 (6)	32 (6)	0.4
COPD	196 (9)	56 (8)	0.43
Oral estrogen among women	270 (12)	65 (9)	0.03
HMG-CoA reductase inhibitor	266 (12)	103 (15)	0.08
Current use of NSAIDs	498 (23)	141 (20)	0.15

Data are *n* (%), mean ± SD, or median (±SD). COPD, chronic obstructive pulmonary disease; HMG, hydroxymethylglutaryl; NSAID, nonsteroidal anti-inflammatory drug.

variables of the 2,895 participants by diabetes status. Participants with diabetes were more likely to have PVD, CAD, and heart failure ($P < 0.001$). Although no one reported difficulty walking one-quarter mile or up 10 steps as a function of study eligibility requirements, those with diabetes were less active and had lower mean baseline performance scores compared with those without diabetes ($P < 0.001$). CRP and IL-6 levels were also higher among those with diabetes than those without ([median ± SD] 2.8 ± 4.4 vs. 3.7 ± 5.4 and 2.3 ± 1.9 vs. 2.8 ± 2.1, respectively). CRP and IL-6 levels were significantly higher in those who smoked ($P < 0.02$) and in women who used hormone replacement ($P < 0.001$) (data not shown in Table 1).

Incident functional limitation

Among the 2,895 participants, 1,195 experienced persistent functional limitation during 3.5 years of follow-up; the total follow-up time was 9,411 person-years. The incidence of functional limitation was 17.6 per 100 person-years among those with diabetes and 11.4 per 100 person-years among those without diabetes. The unadjusted HR (95% CI) of functional limitation for participants with diabetes to those without diabetes was 1.5 (1.3–1.7).

Figure 1 shows the unadjusted incidence rate of functional limitation among participants with or without diabetes by CRP and IL-6 tertiles. When levels of inflammation were low, participants with and without diabetes had a similarly low incidence of functional limitation. At increasing levels of both makers, the incidence of functional limitation increased for both participants with and without diabetes. After adjusting for several demographic and clinical factors (age, race, sex, performance score at baseline, use of anti-inflammatory drugs, current smoking status, PVD, heart failure, CAD, BMI, current estrogen use, and statin use), the observed effect of diabetes on functional limitation did not remain statistically significant.

HRs for the development of persistent

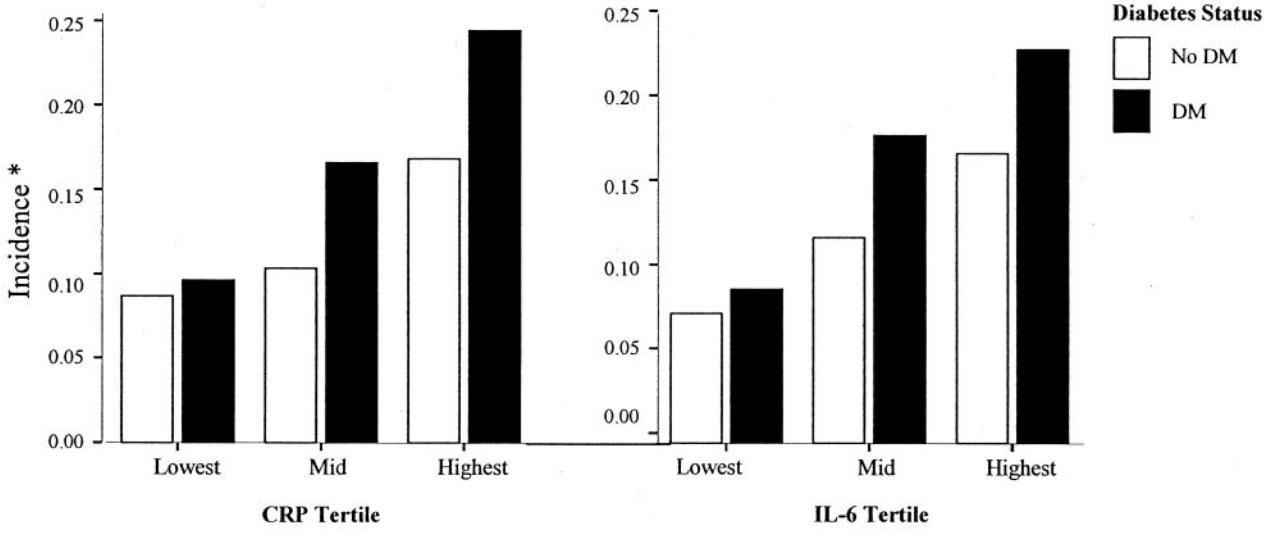

Figure 1—*Functional limitation with and without diabetes (DM) by inflammation status. *Unadjusted incidence of functional limitation in person-years; those with BMI <18.5 kg/m^2 were excluded from the analysis.*

Table 2—*Crude and adjusted HRs of functional limitation according to baseline CRP and IL-6 among all participants and according to diabetes status*

	Tertile of CRP (mg/l)			
	1	2	3	*P* for trend
All participants				
Unadjusted HR (95% CI)	1.0	1.3 (1.1–1.5)	2.1 (1.8–2.4)	<0.0001
Adjusted HR*	1.0	1.1 (0.9–1.3)	1.5 (1.2–1.6)	<0.0001
With diabetes				
Unadjusted HR (95% CI)	1.0	1.59 (1.16–2.16)	2.3 (1.7–3.0)	<0.0001
Adjusted HR†	1.0	1.52 (1.09–2.12)	1.7 (1.2–2.3)	0.0033
Without diabetes				
Unadjusted HR (95% CI)	1.0	1.2 (0.99–1.4)	1.9 (1.6–2.3)	<0.0001
Adjusted HR‡	1.0	0.97 (0.81–1.17)	1.4 (1.1–1.6)	0.0010
	Tertile of IL-6 (mg/l)			
	1	2	3	*P* for trend
All participants				
Unadjusted HR (95% CI)	1.0	1.6 (1.4–1.8)	2.2 (1.9–2.5)	<0.0001
Adjusted HR*	1.0	1.4 (1.2–1.6)§	1.7 (1.4–2.0)	<0.0001
With diabetes				
Unadjusted HR (95% CI)		1.6 (1.2–2.2)	2.1 (1.6–2.7)	<0.0001
Adjusted HR†	1.0	1.6 (1.2–2.2)	1.8 (1.3–2.5)	0.0021
Without diabetes				
Unadjusted HR (95% CI)	1.0	1.5 (1.3–1.8)	2.1 (1.7–2.5)	<0.0001
Adjusted HR‡	1.0	1.4 (1.1–1.6)	1.6 (1.4–2.0)	<0.0001

*Adjusted for the following: age, race, sex, walking and exercise category, performance score, use of anti-inflammatory drugs, smoking status, PVD, heart failure, CAD, BMI, statin use, estrogen use, A1C, fasting glucose, diabetes, and impaired glucose tolerance. †Adjusted for the following: age, race, sex, walking and exercise category, performance score, use of anti-inflammatory drugs, smoking status, PVD, heart failure, CAD, BMI, statin use, estrogen use, education, A1C, and fasting glucose. ‡Adjusted for all the above covariates plus impaired glucose tolerance. §There was a significant interaction between tertile and diabetes, $P = 0.05$.

functional limitation by tertiles of IL-6 and CRP in the entire cohort and separated by diabetes status are presented in Table 2. Those in the highest tertiles of CRP and IL-6 had the highest risks of functional limitation. The unadjusted HRs (95% CI) for becoming functionally limited over the first 3.5 years of the study for the highest tertile of CRP and IL-6 were 2.1 (1.8–2.4) and 2.2 (1.9–2.5), respectively, with the referent group of participants in the lowest tertile. After adjusting for several demographic and clinical factors (age, race, sex, performance score at baseline, use of anti-inflammatory drugs, current smoking status, PVD, heart failure, CAD, BMI, current estrogen use, and statin use), those in the highest tertiles of CRP and IL-6 had the highest risks of functional limitation: HR 1.5 (1.2–1.6) and 1.7 (1.4–2.0), respectively.

Comparing the highest to the lowest levels of CRP, unadjusted analysis showed that the HRs (95% CI) for functional limitation were 2.3 (1.7–3.0) and 1.9 (1.6–2.3) for participants with and without diabetes, respectively. Adjusted analysis also showed that the HRs for functional limitation were 1.7 (1.2–2.3) and 1.4 (1.1–1.6) for participants with and without diabetes, respectively. Similarly, comparing the highest with the lowest levels of IL-6, unadjusted analysis showed that the rates of functional limitation were 2.1 (1.6–2.7) and 2.1 (1.7–2.5) greater for participants with and without diabetes, respectively. Adjusted analysis showed HRs for functional limitation of 1.8 (1.3–2.5) and 1.6 (1.4–2.0), respectively, for participants with and without diabetes. A statistically significant linear trend with time was observed for both CRP and IL-6 among participants with or without diabetes ($P < 0.05$). For both CRP and IL-6, the interaction between diabetes and inflammation was not significant in a comparison of the lowest with the highest tertiles.

Obesity, inflammation, and functional limitation

Participants in the highest BMI category were most likely to have incident functional limitation. The incidence of functional limitation was 21.2 per 100 person-years among those who were obese (BMI $\geq$30 kg/m^2) and 10.3 per 100 person-years among those who were nonobese. In addition to CRP and IL-6 levels, this analysis controlled for age, race, sex, performance score at baseline, use of anti-inflammatory drugs, current smoking status, PVD, heart failure, CAD, and current estrogen and statin use. In the adjusted analysis for both CRP and IL-6 levels, the HRs (95% CI) for functional limitation for those without diabetes were 1.3 (1.1–1.5) for overweight versus normal and 1.6 (1.3–1.9) for obese versus normal. In those with diabetes, these same functional limitation rates were 1.6 (1.1–2.2) for overweight versus normal and 1.9 (1.3–2.7) for obese versus normal.

CONCLUSIONS — This study demonstrates that among well-functioning community-dwelling older adults, higher levels of inflammatory markers are associated with an increased incidence of significant and persistent decline in mobility; in unadjusted analysis, this association is more pronounced in individuals

with diabetes. In both adjusted and unadjusted analyses, those in the highest tertile of CRP or IL-6 compared with the lowest had a greater incidence of persistent functional limitation. Other factors associated with higher rates of functional limitation in the entire cohort included sex, walking exercising, health performance score, nonsteroidal anti-inflammatory drug use, smoking, education, PVD, heart failure, CAD, and BMI. These associations are consistent with previous studies (6,41).

Diabetes, in the presence of inflammation at baseline, predicted functional limitation in a large cohort of older adults. The association between inflammation and functional decline was present even at intermediate levels of inflammation in diabetic participants. Inflammation appears to present an independent risk of disability among those with diabetes. Finally, the interaction of diabetes and CRP or IL-6 was not significant, which suggests that CRP and IL-6 levels are associated with functional limitation similarly for those with and without diabetes.

After adjustment for vascular predictors and global factors such as BMI or baseline performance score, there was no statistically significant effect of diabetes alone on functional limitation, even though we observed a higher incidence rate of functional limitation among those with diabetes compared with those without. Several plausible mechanisms exist for these results. Diabetes was associated with functional limitation in previous analyses (6,42). Because diabetes is associated with a higher risk of vascular and neurological compromise (12,14), small increases in already existing vascular disease might increase the rate at which the participants reached the point of mobility limitation. The risk of functional decline seen in this study may also be moderated by factors such as obesity, hypertension, or atherosclerotic disease (29,43). By controlling for the factors that differed between those with and without diabetes (see Table 1), we also controlled for the excess risk seen among those with diabetes. This excess risk included obesity. However, obesity alone did not account for the differences between those with and without diabetes, because in our analysis at all levels of BMI, those with diabetes had a higher risk of persistent functional limitation.

Although, at a population level, physical disability appears to be linked to an increase in cardiovascular outcomes; inflammation has also been shown to predict disability independently of cardiovascular events (16). Because the risk of developing functional limitation in the adjusted model was not explained by diabetes or baseline glucose control, as measured by A1C, there is probably an independent effect of inflammation on disability in those with diabetes. We unfortunately cannot assess the specific measures of cardiovascular complications that would allow us to test this hypothesis.

Increased rates of functional decline were seen in our sample with CRP values as low as 1.18 mg/l, the lower end of our middle tertile. In predicting cardiovascular disease, CRP levels of 3.0 mg/l and the diagnosis of diabetes add to the Framingham risk score (34). This finding suggests that we cannot assume that levels of CPR predicting CAD risk are similar to those predicting risk of functional limitation. Researchers may need to develop new risk definitions for functional limitations to predict outcomes and enhance interventions.

It currently remains unclear whether we can reduce the risks of disability in those at high risk by lowering the levels of inflammatory markers. Several strategies that decrease inflammation are used in diabetes including statin medications and thiazolidinediones, which have been shown to decrease plasminogen-activator inhibitor type 1 and CRP (44). Insulin resistance is also linked with measures of inflammation (45). In our sample, people with diabetes in the middle tertile were at similar risk of functional limitation as those in the highest tertile but without diabetes. Earlier use of these medications to lower or prevent incident functional limitation in those with diabetes remains a possibility. Further studies are needed to address this theory. Because CRP level was predictive of functional limitation independent of diabetes, measuring inflammation among those with diabetes can help predict different and potentially important factors influencing physical limitation that are separate from glycemic control.

The use of self-reported difficulty with mobility-related tasks as the primary end point is a potential limitation of this study. However, studies have shown the validity and clinical significance of self-reported physical limitation assessments (46). Also, use of two consecutive reports reduces the influence of transient limitation. Because subjects in the population used for this study were high functioning and generally healthy, markers of inflammation were unlikely to be the result of overt disease or malnutrition. Thus, they may be regarded as indicators of subclinical inflammation and early markers of vascular complications. The study also measured two markers of inflammation in a sample of community-dwelling adults, making the results more generalizable. Because there was only limited information on severity of baseline disease status and inflammation was only assessed at baseline, changes in inflammation before or after functional limitation could not be addressed.

In summary, CRP and IL-6 were predictive of functional limitation in a group of older adults with and without diabetes. Whereas in the unadjusted analysis, individuals with both previously diagnosed and newly diagnosed diabetes were at increased risk of functional limitation, the effect of diabetes disappeared in an adjusted analysis. Other clinical and demographic variables predicted functional limitation in those with and without diabetes. Our study suggests that trials to evaluate the causal role of inflammation in development of disability are needed. Ultimately, understanding the link between inflammation and disability would allow clinicians to identify patients who are at greatest risk of disability. Subsequently, strict glucose control and medication with aspirin and statins could be adopted to prevent disability.

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