Prospective Association Among Diabetes Diagnosis, HbA_{1c}, Glycemia and Frailty Trajectories in an Elderly Population

Gloria A. Aguayo,[1] Adam Hulman,[2,3,4] Michel T. Vaillant,[5] Anne-Françoise Donneau,[6] Anna Schritz,[5] Saverio Stranges,[1,7] Laurent Malisoux,[1] Laetitia Huiart,[1] Michèle Guillaume,[6] Séverine Sabia,[8,9] and Daniel R. Witte[2,3]

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OBJECTIVE

Frailty is a dynamic state of vulnerability in the elderly. We examined whether individuals with overt diabetes or higher levels of HbA_{1c} or fasting plasma glucose (FG) experience different frailty trajectories with aging.

RESEARCH DESIGN AND METHODS

Diabetes, HbA_{1c}, and FG were assessed at baseline, and frailty status was evaluated with a 36-item frailty index every 2 years during a 10-year follow-up among participants from the English Longitudinal Study of Ageing. Mixed-effects models with age as time scale were used to assess whether age trajectories of frailty differed as a function of diabetes, HbA_{1c}, and FG.

RESULTS

Among 5,377 participants (median age [interquartile range] 70 [65, 77] years, 45% men), 35% were frail at baseline. In a model adjusted for sex, participants with baseline diabetes had an increased frailty index over aging compared with those without diabetes. Similar findings were observed with higher levels of HbA_{1c}, while FG was not associated with frailty. In a model additionally adjusted for income, social class, smoking, alcohol, and hemoglobin, only diabetes was associated with an increased frailty index. Among nonfrail participants at baseline, both diabetes and HbA_{1c} level were associated with a higher increased frailty index over time.

CONCLUSIONS

People with diabetes or higher HbA_{1c} levels at baseline had a higher frailty level throughout later life. Nonfrail participants with diabetes or higher HbA_{1c} also experienced more rapid deterioration of frailty level with aging. This observation could reflect a role of diabetes complications in frailty trajectories or earlier shared determinants that contribute to diabetes and frailty risk in later life.

Life expectancy is increasing worldwide. However, the aging process is heterogeneous with a large interindividual variability in health status and disability (1). This heterogeneity in aging can also affect people with diabetes, who are also living longer than before. Although the age-specific prevalence of diabetic complications is lower now than in the past, the cumulative lifetime prevalence of complications in older adults with diabetes and the co-occurrence of having multiple medical conditions are higher (2).

[1]Population Health Department, Luxembourg Institute of Health, Strassen, Luxembourg
[2]Department of Public Health, Aarhus University, Aarhus, Denmark
[3]Danish Diabetes Academy, Odense, Denmark
[4]Steno Diabetes Center Aarhus, Aarhus, Denmark
[5]Competence Center for Methodology and Statistics, Luxembourg Institute of Health, Strassen, Luxembourg
[6]Department of Public Health, University of Liège, Liège, Belgium
[7]Departments of Epidemiology and Biostatistics and Family Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada
[8]INSERM U1153, Epidemiology of Ageing and Neurodegenerative Diseases, Paris, France
[9]Department of Epidemiology and Public Health, University College London, London, U.K.

Corresponding author: Gloria A. Aguayo, gloria.aguayo@lih.lu

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Another consequence of population aging is an increase in the number of frail elderly people, who are easily affected by stressors. Frailty is a state of vulnerability in the elderly, which increases the risk of poor health outcomes such as falls, fractures, hospitalization, institutionalization, disability, and mortality (3). Frailty is highly prevalent in elderly populations, with an estimated prevalence between 4 and 59%, depending on which instrument is used to assess frailty (4). There are many different operational definitions of frailty. These are based on different underlying concepts, such as the accumulation of deficit definitions, which emphasize the number of deficits out of at least 30 variables (5); the multidimensional model definitions, which assess different dimensions of functioning but with less than 30 variables (3); and the phenotype of frailty definitions, which are centered on physical frailty (6). However, despite these differences, most experts agree that frailty is a dynamic process that increases with aging (3). There is evidence that frailty progression can be slowed or reverted by treatment, highlighting the need to detect it at early stages to minimize potential health consequences (7).

Diabetes and frailty share some pathophysiological mechanisms, such as low-grade inflammation, insulin resistance, and sarcopenia (2). There is also epidemiological evidence supporting the association between diabetes and frailty (8), and both have a strong socioeconomic gradient, with deprived populations experiencing a higher risk of the two conditions. However, the long-term effect of diabetes on the evolution of frailty as people get older remains unexplored.

The purpose of this study was to evaluate the association of diabetes, HbA_{1c}, and fasting plasma glucose (FG) with the development of frailty as people age (frailty trajectory). We hypothesized that diabetes, as well as higher HbA_{1c} and FG levels, would be associated with a higher level of frailty and with a more marked increase in frailty over time.

RESEARCH DESIGN AND METHODS

Study Design, Participants, and Inclusion Criteria

The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study that is based on a representative sample of the elderly English population established in 2002, with data collected at 2-year intervals. Mental/physical health data, determinants of health, and social and economic data were assessed over the follow-up period. In ELSA, even-numbered waves also included a clinical examination with blood sampling (9). Wave 2 (2004–2005) served as the baseline of the current study. Participants aged $\geq$60 years who attended the interview and clinical examination of this wave were retained in the analysis because some variables needed to calculate frailty scores were not measured for participants aged $<$60 years. The current study used data collected between 2004 (wave 2) and 2015 (wave 7).

Outcome, Exposures, and Potential Confounders

The outcome was defined as frailty trajectories measured from wave 2 to wave 7. Frailty was measured by three different frailty scores. A 36-item Frailty Index (36-FI) (10) was studied as the primary outcome; the Edmonton Frail Scale (EFS) (11) and the phenotype of frailty score (6) were secondary outcomes (Supplementary Table 1).

The 36-FI was calculated on the basis of the frailty index of Searle et al. (10), which is from the accumulation of deficit approach, including variables describing disability, comorbidity (excluding diabetes), physical functioning, and mental health. The 36-FI was chosen as the primary outcome because of its high reliability as well as its predictive and discriminative ability for mortality (12,13). It was possible to calculate the 36-FI in all waves. The score dichotomizes most variables as 0 (deficit not present) or 1 (deficit present). The 36-FI is calculated by adding the current deficits and is subsequently rescaled to range from 0 (robust) to 1 (maximum frailty) and considered as a continuous variable in our analyses. The cutoff for defining frailty is 0.2 (10).

The EFS (11) is a multidimensional frailty score that includes 11 variables of different dimensions, such as cognition, social support, self-reported health, continence, nutrition, disability, and mood. The EFS was chosen because it has high discriminative ability for mortality (13). The scale ranges from 0 to 17. The cutoff for defining frailty is $>$5.

The phenotype of frailty score (6) is based on a physiological model and centers on physical frailty. This score includes five variables: unintentional weight loss, weakness, exhaustion, slow gait, and low physical activity. The score was chosen because it is the most cited frailty score (14). The scale ranges from 0 to 5. The cutoff for defining frailty is $\geq$3, and a prefrail state is defined when the score is $\geq$1 and $<$3.

The EFS and the phenotype of frailty score were calculated only in waves 2, 4, and 6 because of the need for variables measured only at clinical examinations. The 36-FI was calculated in each wave because it is mostly calculated with variables from questionnaires and only needs a few objective variables measured in clinical examinations. To calculate the 36-FI in all waves, if a necessary variable was only measured at a clinical examination (even-numbered waves), the last observation carried forward method was applied.

To facilitate comparisons among the three scales, frailty scores were rescaled from 0 (robust) to 100 (maximum frailty). The frailty scores were rescaled by dividing the obtained output by the maximum value possible for this score and multiplying the result by 100.

Diabetes was defined as having a self-reported medical diabetes diagnosis or HbA_{1c} $\geq$6.5% ($\geq$48 mmol/mol) or FG $>$7 mmol/L. HbA_{1c} and FG were analyzed as continuous variables. Exposures were measured at baseline and handled as time-invariant variables.

Potential confounders were demographic and lifestyle variables at baseline and included sex, year of birth, family income, social class, smoking status, maximum self-reported alcohol intake per day, and hemoglobin. Year of birth was categorized in 5-year intervals. Family income and social class were categorized into three levels: high, intermediate, and low. Smoking status was categorized as never, former, or current smoker. Maximum alcohol consumption per day over the past week was categorized as not at all, 1, 2, and $>$2 units of alcohol per day. Hemoglobin was also included as a covariate because it may influence HbA_{1c} levels (15) and was analyzed as a continuous variable.

Statistical Analysis

Multiple imputation was applied to deal with missing outcome data. To obtain the most plausible values, the imputation

was performed on the underlying variables necessary to calculate the frailty scores. The method of imputation was adapted to the original nature of the outcome variable (binary, categorical, or continuous); imputed variables were thus categorized if needed to build the frailty scores. The imputed values of participants who died or were lost to follow-up were deleted. Missing data in the exposure variables (HbA_{1c} and FG) were not imputed. The percentage of missing data ranged from 0 to 59%. A missing-at-random mechanism was assumed, and the chained equations approach was applied (16). Sixty imputed data sets were generated. The number of imputations was decided on the basis of the maximum percentage of missing data (17). All models were run separately in each of the 60 data sets. The final estimates and the corresponding SEs were calculated according to Rubin's rules (18). To enhance readability, the methods and results from this point onward are described in the language applicable to a single data set analysis. However, all results presented in the tables were calculated according to the 60-fold multiple imputation procedure.

Frailty trajectories over age were fitted using linear mixed-effects models. Individual-specific random intercepts and slopes were included in the model. Age, HbA_{1c}, and FG were centered for better interpretability of the coefficient estimates. Separate models were fitted with diabetes, HbA_{1c}, and FG as exposures (fixed effects) at different levels of adjustment. Model 1 was outcome adjusted for sex and birth cohort. Model 2 was model 1 further adjusted for HbA_{1c}, family income, social class, smoking status, alcohol consumption, hemoglobin, and diabetes medications. Model 3 was model 1 further adjusted for diabetes, family income, social class, smoking status, alcohol consumption, hemoglobin, and diabetes medication. Quadratic terms of continuous variables were included in the models. Interactions between age and each exposure were included in the models to account for the effect of the exposure variable on change in frailty index over aging.

The same analysis sequence was repeated after exclusion of frail participants at baseline to reduce the potential influence of reverse causation. To assess the effect of cardiovascular disease (CVD) (defined as self-reported myocardial infarction, heart failure, or stroke) on the associations, an analysis stratified by baseline CVD was performed. Mice, mitml, and lme4 (mixed models) packages in R 3.3.0 were used.

RESULTS

From 9,432 participants in wave 2, 5,377 fulfilled the inclusion criteria and were included in this study (Supplementary Fig. 1). Ten years later in wave 7, 2,692 were still followed (50% of the baseline participants).

At baseline, 35% of participants were frail on the basis of the 36-FI. Table 1 shows baseline characteristics stratified by baseline diabetes. The median age of participants was 70 years (interquartile range 65, 77 years), 45% were men, and 12% had diabetes. From those who had diabetes, 82% were self-reported diagnoses.

Diabetes as Exposure

Figure 1 shows estimated frailty trajectories by baseline diagnosis of diabetes in the most adjusted model 2. At age 60 years and throughout the whole age range, the 36-FI was significantly higher in individuals with baseline diabetes. The diabetes-age interaction was not

Table 1—Baseline characteristics of 5,377 participants by diabetes diagnosis

Characteristic	No diabetes (n = 4,742)	Diabetes* (n = 635)
Age (years)	70 (65, 77)	72 (66, 77)
HBA_{1c} (%)†	5.5 ± 0.5	7.0 ± 0.4
Glycemia (mmol/L)‡	4.9 ± 0.8	7.0 ± 0.5
BMI (kg/m^2)	27.5 ± 4.8	30.1 ± 4.8
Male	43	54
Antidiabetic drugs	0	57
Income		
Low	33	35
Middle	32	38
High	35	27
Social class		
Low	21	26
Middle	45	46
High	34	29
Smoking status		
Current	12	12
Former	51	57
Never	37	31
Maximum alcohol consumption		
>2 units/day	19	12
2 units/day	17	11
1 unit/day	13	9
Not at all	51	68
Physical activity		
Low–sedentary	33	49
Moderate–high	67	51
Nutritional status§		
Obesity	26	45
Overweight	44	39
Under/normal weight	29	16
CVD‖	12	25
36-FI (units)	14 (8, 24)	22 (13, 25)
Phenotype of frailty (units)	27 (7, 47)	33 (20, 53)
EFS (units)	12 (6, 20)	18 (10, 27)
Frailty index (% frail)	32	53
Phenotype of frailty (% prefrail/% frail)	78/13	73/23
EFS (% frail)	10	19

Data are mean ± SD, median (interquartile range), or %. *Diabetes was defined as self-reported medical diagnosis, FG ≥7 mmol/L, or HbA_{1c} ≥6.5% (48 mmol/mol). †No diabetes, n = 3,689; diabetes, n = 303. ‡No diabetes, n = 2,217; diabetes, n = 65. §Under/normal-weight BMI ≤20 kg/m^2, overweight BMI >20 to <30 kg/m^2; obese BMI ≥30 kg/m^2. ‖Medical diagnosis of infarction, heart failure, or stroke.

significant, which suggests that the differences in frailty between participants with and without diabetes remained constant during the follow-up period (Supplementary Table 2). Figure 1 also shows that although exclusion of participants with baseline frailty leads the frailty trajectories to start at a lower level, their progression with climbing age is somewhat steeper, and the difference between participants with and without baseline diabetes remains present (Fig. 1*B* and *D*).

Figure 1*A* and *B* show estimated frailty trajectories for the birth cohort 1930–1934, while Fig. 1*C* and *D* show trajectories plotted for six different birth cohorts. At the same age, more-recent cohorts showed higher frailty levels, but the difference between those with and without diabetes was of similar magnitude.

Table 2 shows estimated values of the 36-FI by baseline diabetes. In model 1, the estimated level of frailty for a 60-year-old man with baseline diabetes was 17 (95% CI 15, 19). This value was similar to the estimated level of frailty for a 74-year-old man without baseline diabetes. Similar results were observed in women.

When adding possible confounders to the less-adjusted model with diabetes as exposure, the strength of the association between baseline diabetes and frailty status was attenuated by 9% when adding income and social class, 17% when adding smoking status and alcohol consumption, and 43% when adding hemoglobin and HbA_{1c} to the model. Finally, the strength of the association increased after adding the HbA_{1c}-diabetes interaction to the model. When comparing among the three frailty scores, the results were similar for associations between exposures and frailty trajectories (Supplementary Table 2 and Supplementary Figs. 2–4).

HbA_{1c} as Exposure

In model 1, with baseline levels of HbA_{1c} as exposure (Supplementary Table 2), a positive and significant association between HbA_{1c} level and frailty was observed (β = 4.2 [95% CI 2.5, 5.9]). This means that higher levels of HbA_{1c} at baseline were associated with higher values of frailty. The HbA_{1c}-age interaction was positive and significant (β = 0.10 [95% CI 0.05, 0.15]), which indicates that the differences increased over time (Fig. 2). In model 3, the overall HbA_{1c}-frailty association was not statistically significant. However, the HbA_{1c}-diabetes interaction was negative for 36-FI. This suggests increased frailty with lower baseline HbA_{1c} values (Fig. 2*C* and *D*) in those with diabetes at baseline. Also in this model, the HbA_{1c}-age interaction was significant and positive, which means that the differences tended to increase over time. In participants without baseline diabetes, higher HbA_{1c} was associated with higher frailty levels throughout the follow-up (Fig. 2*A* and *B*). In the nonfrail population, lower levels of HbA_{1c} were associated with higher levels of frailty (Supplementary Table 3). When adding possible confounders to the HbA_{1c} less-adjusted model, the strength of the association baseline HbA_{1c} and frailty status was attenuated by 10% when adding income and social class; 36% when adding smoking status, alcohol consumption, and hemoglobin; and 114% when adding the HbA_{1c}-diabetes interaction.

FG as Exposure

In models 1 and 3 with FG, no statistically significant associations with frailty were observed. However, the quadratic FG and FG-diabetes interaction were significant with model 3, suggesting that there could be a nonlinear association in participants without baseline diabetes (Supplementary Table 2).

Stratification by CVD

At baseline, participants with CVD (n = 738) were more frail than those without CVD (n = 4,639). Baseline diabetes was only significantly associated with frailty in participants without CVD (Supplementary Table 4 and Supplementary Fig. 5). These differences did not amplify over time. Similarly, with model 1 and baseline HbA_{1c} as exposure, there were significant differences in frailty trajectories at different levels of baseline HbA_{1c} only in participants without CVD (Supplementary Table 4 and Supplementary Fig. 6). With model 3, HbA_{1c} levels were not associated with frailty in any case.

CONCLUSIONS

This study showed that baseline diabetes and higher HbA_{1c} levels were significantly associated with higher frailty trajectories measured from age $\geq$60 years. Our finding of an association between diabetes and frailty in a longitudinal setting, even after adjustment for potential confounders, indicates that people with diabetes experience higher levels of frailty during aging. These frailty levels broadly correspond to levels only reached more than a decade later by their peers without diabetes. Among nonfrail individuals at baseline, diabetes and higher levels of HbA_{1c} were associated with an accelerated increase in frailty compared with participants without diabetes.

Although we did not find studies evaluating frailty trajectories as outcome, there are longitudinal studies associating diabetes and frailty with results consistent with ours. Ottenbacher et al. (19) studied elderly Mexican Americans, evaluating a series of exposures of frailty, and found that diabetes at baseline was associated with higher frailty status 10 years later. García-Esquinas et al. (20) found a prospective association of baseline diabetes with incident frailty up to 3 years later. They also observed that the strength of the diabetes-frailty association was lower after adjustment for health behavior, abdominal obesity, comorbidity, and cardiometabolic biomarkers, suggesting that it is at least in part confounded by exposures or metabolic pathways shared between diabetes and frailty.

Indeed, the possibility exists that the association between diabetes and frailty in our study is still residually confounded, despite adjustment for multiple potential confounders. However, our primary aim was not to isolate the etiological role of glycemia for the development of frailty but to show to what degree patients with diabetes and even people with nondiabetic, intermediate glycemic levels experience frailty in later life.

To explore the effect of relevant risk factors, we performed additional analyses, which showed attenuation of the strength of the association with income/social class (9%). This suggests that these risk factors could be confounding variables, although the results are still significant in the more-adjusted model. The results of this study also show that participants with diabetes have a similar frailty level to participants without diabetes who were 12 years older (Table 2), which is consistent with a study by Hubbard et al. (21).

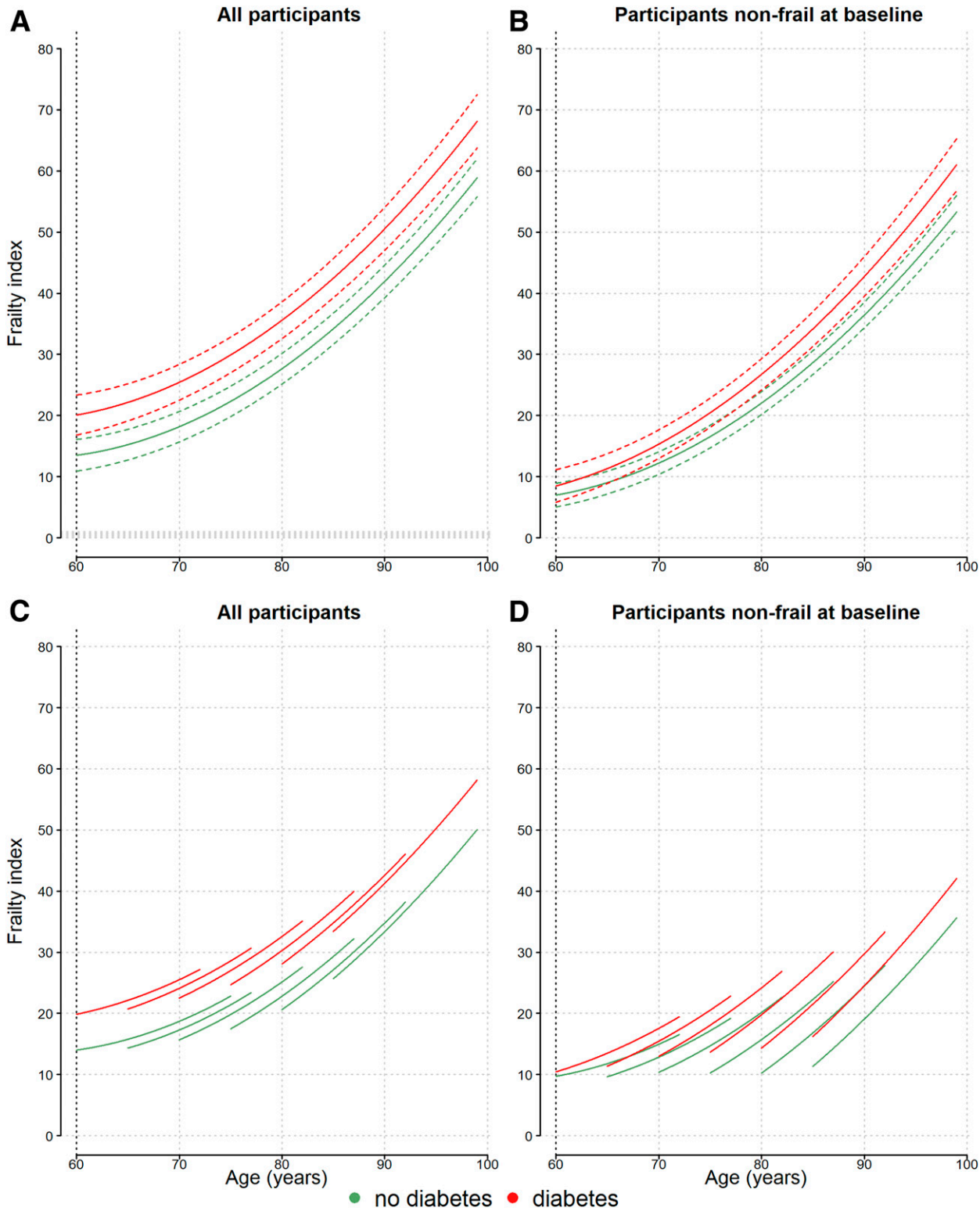

Figure 1—Frailty trajectories (36-FI) by baseline diabetes in all 5,377 participants (frail and not frail at baseline) (*A* and *C*) and in 3,457 participants who were not frail at baseline (*B* and *D*). Model 2 was adjusted by HbA_{1c} (5.5% [37 mmol/mol]), sex (men), birth cohort, family income (intermediate), social class (middle), smoking status (former smoker), alcohol consumption (no alcohol), hemoglobin (15 mg/dL in men, 14 mg/dL in women), and diabetes medications (no). Continuous lines are estimates, and dotted lines are 95% CIs. Green lines indicate frailty trajectory for participants without baseline diabetes, and red lines indicate frailty trajectory for participants with baseline diabetes. Trajectories in *A* and *B* are plotted in the 1930–1934 birth cohort interval. Trajectories in *C* and *D* are plotted in six birth cohort intervals (1940–1945, 1935–1939, 1930–1934, 1925–1929, 1920–1924, and 1911–1919).

Table 2—Predicted values of 36-FI by sex, baseline diabetes diagnosis, and age

Age (years)	Men		Women	
	No diabetes	Diabetes	No diabetes	Diabetes
	Estimate (95% CI)*	Estimate (95% CI)*	Estimate (95% CI)*	Estimate (95% CI)*
Model 1†				
60	10 (9, 11)	17 (15, 19)	12 (11, 13)	19 (18, 21)
62	10 (10, 11)	18 (16, 19)	13 (12, 14)	20 (18, 22)
64	11 (10, 12)	19 (17, 20)	14 (13, 15)	21 (19, 23)
66	12 (11, 13)	20 (18, 21)	15 (14, 16)	22 (21, 24)
68	13 (12, 14)	21 (20, 22)	16 (15, 17)	23 (22, 25)
70	15 (14, 16)	22 (21, 24)	17 (16, 18)	25 (24, 26)
72	16 (15, 17)	24 (23, 25)	19 (18, 19)	26 (25, 28)
74	18 (17, 19)	26 (25, 27)	20 (20, 21)	28 (27, 30)
76	20 (19, 21)	28 (27, 29)	22 (21, 23)	30 (29, 32)
78	22 (21, 23)	30 (29, 31)	24 (23, 25)	33 (31, 34)
80	24 (23, 25)	32 (31, 34)	27 (26, 27)	35 (33, 36)
82	26 (26, 27)	35 (33, 36)	29 (28, 30)	37 (36, 39)
84	29 (28, 30)	38 (36, 39)	32 (31, 33)	40 (39, 42)
86	32 (31, 33)	41 (39, 42)	34 (33, 35)	43 (41, 45)
88	35 (34, 36)	44 (42, 46)	37 (36, 38)	46 (44, 48)
90	38 (37, 39)	47 (45, 49)	41 (39, 42)	50 (47, 52)
Model 2‡				
60	9 (8, 11)	16 (13, 19)	21 (17, 24)	42 (30, 53)
62	10 (8, 11)	17 (14, 20)	21 (18, 24)	42 (31, 54)
64	11 (9, 12)	18 (15, 20)	22 (19, 25)	43 (32, 55)
66	12 (10, 13)	19 (16, 21)	23 (20, 26)	44 (33, 56)
68	13 (11, 14)	20 (17, 23)	24 (21, 27)	46 (34, 57)
70	14 (13, 15)	21 (19, 24)	25 (22, 29)	47 (35, 59)
72	15 (14, 17)	23 (21, 26)	27 (24, 30)	49 (37, 60)
74	17 (16, 19)	25 (22, 28)	29 (25, 32)	50 (39, 62)
76	19 (18, 21)	27 (24, 30)	31 (27, 34)	53 (41, 64)
78	21 (20, 23)	29 (27, 32)	33 (29, 36)	55 (43, 66)
80	23 (22, 25)	32 (29, 34)	35 (32, 38)	57 (46, 69)
82	26 (24, 27)	34 (31, 37)	37 (34, 41)	60 (48, 71)
84	29 (27, 30)	37 (34, 40)	40 (37, 43)	63 (51, 74)
86	31 (30, 33)	40 (37, 43)	43 (40, 46)	66 (54, 77)
88	35 (33, 36)	43 (40, 46)	46 (43, 49)	69 (57, 80)
90	38 (36, 39)	47 (43, 50)	49 (46, 53)	72 (60, 84)

*95% CI calculated according to Rubin's rules. †Model 1: predictions for men and women of birth cohort 1930–1934. ‡Model 2: predictions for men and women of birth cohort 1930–1934 with an HbA_{1c} of 5.5% (37 mmol/mol), intermediate family income, middle social class, former smokers, alcohol abstinent, no diabetes medications, and a hemoglobin of 15 mg/dL in men and 14 mg/dL in women.

A possible explanation for the observed higher frailty levels seen in individuals with diabetes is that diabetes and frailty have some common root causes, such as low socioeconomic status (22); low physical fitness, functioning, and activity (23); and presence of multimorbidity (24). Diabetes and the aging process share pathophysiological mechanisms, such as a chronic state of low-grade inflammation (25). Advanced age is accompanied by an increase in the prevalence of sarcopenia, insulin resistance, and obesity. Sarcopenia is accentuated at higher levels of HbA_{1c} and attenuated with the use of insulin (26). In addition to this evidence, metabolic syndrome variables and insulin resistance have been prospectively associated with the phenotype of frailty score in a general elderly population (27).

The inverse phenomenon—frailty influencing diabetes progression—is also possible. Veronese et al. (28) studied a cohort of elderly individuals and found that frailty was associated with a higher incidence of diabetes. They attributed these results to the fact that at baseline, frail individuals have a higher prevalence of diabetes risk factors, such as obesity. The underlying mechanisms that could be involved are mediated by adipose tissue dysfunction, where accelerated aging is driven by an increase in proinflammatory cytokines, macrophage dysfunction, and increased oxidative stress (29). Furthermore, frail individuals tend to have lower physical activity levels, which in turn leads to higher insulin resistance. Taken together, the evidence suggests that the association between glycemia and frailty is likely to be bidirectional and may be due to shared determinants and underlying pathophysiological pathways. However, the complex ways in which these determinants and pathways act and affect each other remains difficult to disentangle.

We found that when at baseline frail participants were excluded, diabetes was associated with faster frailty progression over time. This finding should be interpreted with caution. Although it could be regarded as consistent with diabetes or its treatments accelerating the development of frailty, it could also be due to regression to the mean, where our exclusion of those above a given frailty threshold has left a population more likely to have higher subsequent values, all else being equal. Furthermore, it should be noted that because our outcome measure has a ceiling value, those with low frailty values have more room to increase than those already at high levels. On the other hand, the effect of regression to the mean is likely to be limited to the first observation period after the baseline exclusion of frail individuals, and differences in the latter part of the follow-up time are far less likely to be affected. It is possible that the steeper frailty trajectory observed during follow-up is mediated by or depends partly on the development of diabetes complications. We did not have the possibility of studying this in detail.

Higher levels of HbA_{1c} were associated with higher frailty over time. However, these effects were lost when adjusting for potential confounders. The interaction of diabetes-HbA_{1c}, smoking status, and alcohol had the maximum attenuation effects. This suggests that the effects are explained by the preceding confounding factors.

In contrast, among people with diabetes and at earlier ages, lower levels of HbA_{1c} showed a tendency of association with higher levels of frailty (Fig. 2). Zaslavsky et al. (30) found a U-shaped relationship in the FG/HbA_{1c}-frailty interaction, with both extreme high and low levels associated with frailty. The cause of this is U-shaped relationship is

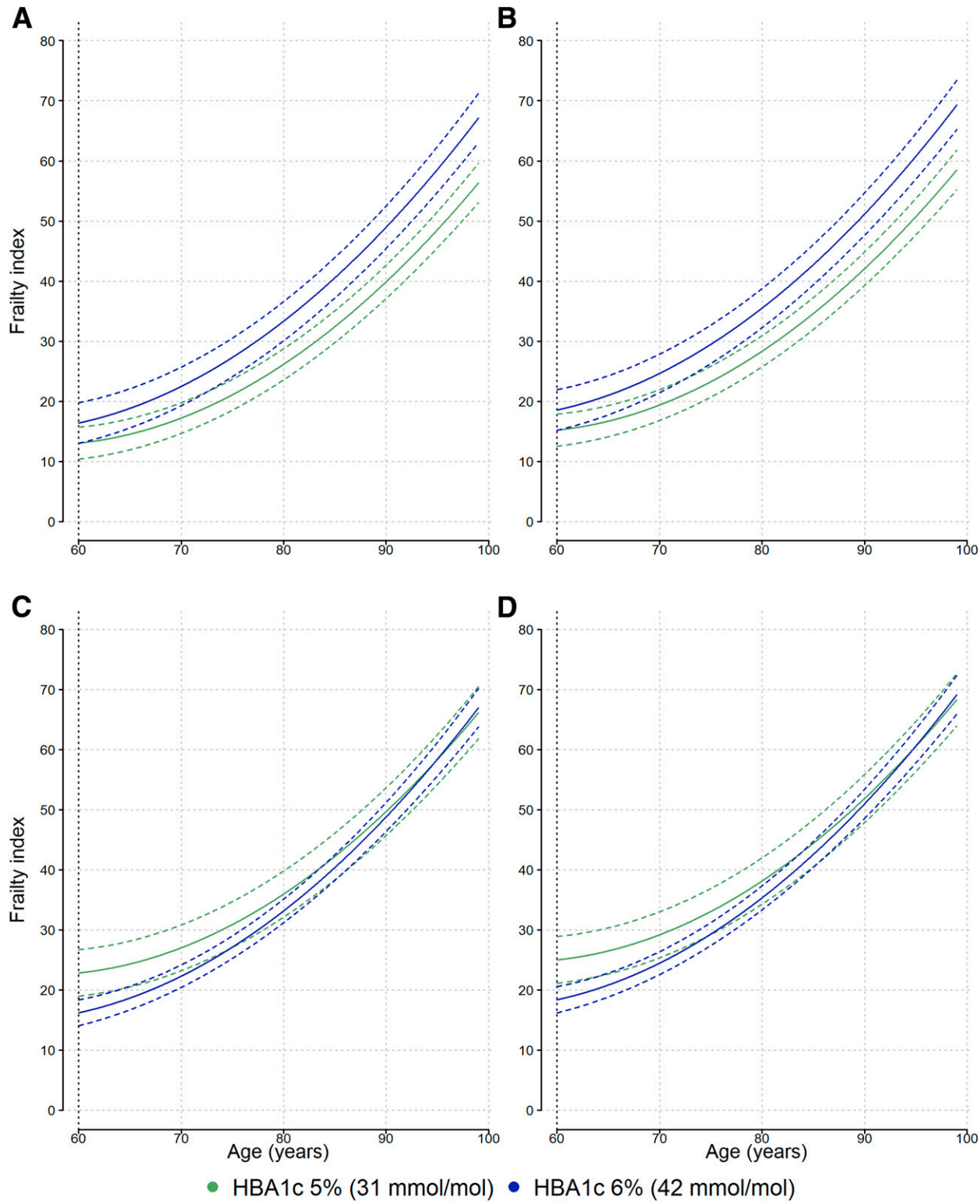

Figure 2—Frailty trajectories (36-FI) at two different values of HbA_{1c} in 5,377 participants. Model 3 was adjusted without baseline diabetes (*A* and *B*) and with baseline diabetes (*C* and *D*), sex (men in *A* and *C*, women in *B* and *D*), birth cohort (1930–1934), family income (intermediate), social class (middle), smoking status (former smoker), alcohol consumption (no alcohol), hemoglobin (15 mg/dL in men, 14 mg/dL in women), and diabetes medications (no). Continuous lines are estimates, and dotted lines are 95% CIs. Green lines indicate frailty trajectory for participants with a baseline HbA_{1c} of 5% (31 mmol/mol), and blue lines indicate frailty trajectory for participants with a baseline HbA_{1c} of 6% (42 mmol/mol).

probably confounding by indication or reverse causation. For example, people with frailty may be monitored more closely, leading to stricter glycemic control, while individuals who are nonfrail may be treated less intensively. Another possibility is that individuals who are frail may be more compliant with medication. Indeed, there is evidence that

compliance with CVD medication increases when people with diabetes have more than one prescription (31).

We did not find that FG was associated with frailty trajectories. One explanation of the stronger association seen with HbA_{1c} compared with FG is that HbA_{1c} is more strongly associated with diabetes comorbidities than FG (32). Also, in this study, FG had more missing data than HbA_{1c}, which could have diluted the results with FG. Finally, HbA_{1c} may capture the relevant exposure with more precision than FG. HbA_{1c} reflects the long-term average glycemic level and thus reflects the total glycemic exposure more closely than FG values, which represents a state most people experience only for a few hours of the day. Our results differ from the results reported by Zaslavsky et al. (30), who showed a prospective association between FG and frailty 4–5 years later. These different results could be explained by the fact that Zaslavsky et al. combined the results of HbA_{1c} and glycemia with Bayesian methods, while we analyzed FG and HbA_{1c} separately.

We observed that more-recent birth cohorts were more frail than older cohorts at the same age. This is consistent with a study by Yu et al. (33) in older individuals, reporting that the more recent cohorts had higher levels of frailty at a similar age. This observation could be at least partially due to selective loss to follow-up. For example, in older birth cohorts, frail individuals may have died much earlier, either before our study's baseline or at the early stages of our follow-up window, while in the younger birth cohorts, frail individuals may be surviving much longer with frailty as a result of better care.

The finding that baseline diabetes was only significantly associated with frailty trajectories in participants without CVD and the fact that the exposure-frailty association only subsists in those without CVD indicates that CVD may be a modifying factor in the association. In contrast to participants without CVD, in participants with CVD, diabetes was not associated with an additional change of accelerated progression of frailty. Bouillon et al. (34) found that CVD risk scores measured in participants free of CVD were associated with future frailty. The mechanisms of these associations are related to the fact that CVD risk factors and frailty have inflammatory processes in common that can lead to atherosclerosis as well as to accelerated catabolism associated with frailty (35). Similar findings were observed for obesity status, with association observed mainly in nonobese participants. Taken together, these results suggest that diabetes influences frailty, particularly in those free of CVD events and who are nonobese.

This study has several strengths. It had a prospective design with frailty as a repeated measurement. Our analytic approach took into account the dynamic nature of frailty by examining longitudinal trajectories. We used three different instruments to define frailty and found consistent results, strengthening our confidence that the findings are not driven by one particular concept of frailty. The main results concerning diabetes, HbA_{1c}, and FG were consistent with the three frailty scores, supporting the notion that the results of this study apply to the general concept of frailty rather than to a specific operationalization. ELSA is a high-quality data set that integrates many dimensions, such as physical and mental health, determinants/risk factors, and social and economic aspects. ELSA is a large representative sample of the English elderly population with repeated measures of subjective/objective variables and biomarkers relevant to frailty and the aging process. It is one of the best available longitudinal data sources to address our research questions.

The study also has some limitations. Some variables were not collected consistently across waves. In these cases, we used the most similar variable in the analysis. We could not differentiate between type 1 and type 2 diabetes, although type 1 diabetes constitutes a minority of cases in elderly populations (36). A further limitation is that we could not include some relevant variables in the adjusted models because they were also part of the 36-FI. In addition, no information on diet was available at baseline, precluding us to account for this covariate in the analysis. A final limitation was the missing data, which could be a source of bias. However, we tried to deal with this issue by applying multiple imputation and fitting mixed-effects models (37). Our results are mostly generalizable to general elderly populations of European origin because ELSA included very few participants of non-European origin.

To conclude, this study suggests that diabetes is associated with increased frailty in an elderly population. These results highlight the relevance of a timely diabetes diagnosis because of the likelihood of a faster increasing frailty trajectory than among individuals without diabetes (38). Future research should examine the causality and mechanisms of this association.

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