Prospective association between diabetes diagnosis, HbA_{1c}, glycaemia and frailty trajectories in an elderly population

Short running title

Diabetes, HbA_{1c}, glycaemia and frailty trajectories

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ABSTRACT

OBJECTIVE

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

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 two years during a 10-year follow-up among participants from the English Longitudinal Study of Ageing. Mixed-effects models 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 (IQR), 70 (65; 77) years; 45% men), 35% were frail at baseline. In a model time-scale and adjusted for sex, participants with baseline diabetes had increased frailty index compared to 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 increased frailty index. Among non-frail 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. Non-frail participants with diabetes or higher HbA_{1c} also experienced more rapid deterioration of frailty level with ageing. This observation could reflect a role of diabetes complications in frailty trajectories or earlier shared determinants that contribute to both diabetes and frailty risk in later life.

Life expectancy is increasing worldwide. However, the ageing process is heterogeneous with a large inter-individual variability in health status and disability (1). This heterogeneity in ageing 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).

Another consequence of population ageing 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) and the 'multidimensional model' definitions, which assesses different dimensions of functioning, but with less than 30 variables (3) and the 'phenotype of frailty' definitions centered on physical frailty (6). However, despite these differences, most experts agree that frailty is a dynamic process that increases with ageing (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 socio-

79 economic gradient, with deprived populations experiencing a higher risk of the two conditions.
80 However, the long-term effect of diabetes on the evolution of frailty as people get older remains
81 unexplored.
82
83 The purpose of this study was to evaluate the association of diabetes, HbA_{1c} and fasting plasma
84 glucose (FG), with the development of frailty as people age (frailty trajectory). We
85 hypothesized that diabetes, as well as higher HbA_{1c} and FG levels would be associated with
86 higher a level of frailty and with a more marked increase in frailty over time.

RESEARCH DESIGN AND METHODS

Study design, participants and inclusion criteria

This was a longitudinal trajectory analysis. We used data collected between 2004 and 2015 in the English Longitudinal Study of Aging (ELSA). ELSA is an ongoing cohort study based on a representative sample of the elderly English population established in 2002, with data collected at two-year intervals. Data on mental/physical health, determinants of health, social and economic data were assessed over the follow-up period. In ELSA, even waves also included a clinical examination with blood sampling (9). Wave 2 (2004-2005) served as baseline. Participants aged 60 and older who attended the interview and clinical examination of this wave were included because some variables needed to calculate frailty scores were not measured for participants younger than 60 years.

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 primary outcome, the Edmonton Frail Scale (11) and the Phenotype of Frailty score (6) as secondary outcomes.

The 36-FI was calculated based on the frailty index of Searle (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 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 cut-off for defining frailty is 0.2 (10).

The Edmonton Frail Scale (11) is a "multidimensional" frailty score which 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 (14). The scale ranges from 0 to 17. The cut-off for defining frailty is >5.

The Phenotype of frailty score (6), is a frailty score based on a physiological model and centers on physical frailty. The Phenotype of frailty score includes 5 variables: unintentional weight loss, weakness, exhaustion, slow gait and low physical activity. This score was chosen because it is the most cited frailty score (15).The scale ranges from 0 to 5. The cut-off for defining frailty is ≥ 3 and an intermediate pre-frail state is defined when the score is ≥1 and <3.

To facilitate comparisons between the three scales, frailty scores were rescaled on a scale 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. The results were then multiplied by 100.

Diabetes was defined as having a self-reported medical diabetes diagnosis or $HbA_{1c} \geq 6.5\%$ (≥ 48 mmol/mol) or FG > 7mmol/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 they 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 3 levels: high, intermediate and low. Smoking status was categorized as never, former or current smoker. Maximum alcohol consumption per day over the last week was categorized as not at all, 1, 2 and more than 2 units of alcohol per day. Hemoglobin was also included as a covariate because it may influence the HbA_{1c} levels (16), and was analyzed as continuous variable.

The Edmonton Frail Scale and the Phenotype of Frailty score were only calculated in clinical examination waves 2, 4 and 6, due to the need for variables measured only at clinical examinations. The 36-FI was calculated in each wave, as it is mostly calculated with variables from questionnaires and only needs a few objective variables measured in clinical examinations. In order to calculate the 36-FI in all waves, if a necessary variable was only measured at a clinical examination (even waves), the last observation carried forward method was applied.

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 nature of the outcome variable (binary, categorical or continuous). The imputed values of participants who died or were loss 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 (17). Sixty imputed datasets were generated. The number of imputations was decided based on the maximum percentage of missing data (18). All models were run separately in each of the sixty datasets.

The final estimates and the corresponding standard errors were calculated according to Rubin's rules (19). In order to enhance readability, the methods and results from this point onward are described in the language applicable to a single dataset 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-effect 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 exposure (diabetes, HbA1c or FG) adjusted for sex and birth cohort.

In order to isolate the effect of the diabetes diagnosis itself, including its treatments, over and above its function as a dichotomous classification of hyperglycemia, model 1 was further adjusted for HbA1c, family income, social class, smoking status, alcohol consumption, hemoglobin, and diabetes medications (model 2).

Model 3 was model 1 further adjusted for diabetes, family income, social class, smoking status, alcohol consumption, hemoglobin, diabetes medication.

Quadratic terms of continuous variables were included in the models. Interactions with age and each exposure were included in the models.

The same analysis sequence was repeated after exclusion of frail participants at baseline, in order to reduce the potential influence of reverse causation.

186 To analyses the effect of CVD (defined as self-reported myocardial infarction, heart failure, or
187 stroke) on the associations, an analysis stratified by baseline cardiovascular disease status was
188 performed. The same analysis was applied for obesity.
189
190 Mice, mitml, and lme4 (mixed models), packages in R version 3.3.0 were used.

RESULTS

From 9,432 participants who participated in wave two, 5,377 participants fulfilled the inclusion criteria and were included in this study (Supplemental Figure S1). Ten years later in wave seven, 2,692 were still followed-up (50% of the baseline participants).

At baseline, 35% of participants were frail (36-FI). Table 1 shows baseline characteristics stratified by baseline diabetes. The median age of participants was 70 (IQR=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 and throughout the whole age-trajectory, the 36-FI was significantly higher in individuals with baseline diabetes. The diabetes-age interaction was not statistically significant, which suggests that the differences in frailty between participants with and without diabetes remain constant during the follow-up period (Supplemental Table S2).

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 (beta=7 (95% CI 2; 12), (Figure 1, panels B and D).

Panels A and B show frailty trajectories for the birth cohort 1930-1934, while panels 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 2, the estimated level of frailty for a 60-year old man with baseline diabetes was 0.17 (0.15; 0.19). 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 baseline diabetes and frailty status was attenuated in: 9% when adding income and social class, 17 % when adding smoking status, alcohol consumption, and 43% adding hemoglobin and HbA_{1c} to the model. Finally, the strength of the association increased after adding HbA_{1c}-diabetes interaction to the model.

HbA_{1c} as exposure

In model 1, with baseline levels of HbA_{1c} as exposure (Supplemental Table S2), a positive and significant association between HbA_{1c} level and frailty was observed (beta= 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 (beta= 0.10: 95% CI (0.05; 0.15)), which indicates that the differences increased over time (Figure 2). In model 3, the over-all HbA_{1c}-frailty association was not statistically significant. However, the HbA_{1c}-diabetes interaction was negative (beta= -5 (95% CI -8, -3) for 36-FI). This suggests increased frailty with lower baseline HbA_{1c} values (Figure 2, panels 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

240 HbA_{1c} was associated with higher frailty levels throughout the follow-up (Figure 2, panels A
241 and B).
242 In the non-frail population, lower levels of HbA_{1c} were associated with higher levels of frailty.
243 (Supplemental Table S3).
244
245 When adding possible confounders to the HbA_{1c} less adjusted model, the strength of the
246 association baseline HbA_{1c} and frailty status was attenuated in: 10% adding income and social
247 class, 36 % adding smoking status, alcohol consumption and hemoglobin and 114% adding the
248 interaction HbA_{1c}-diabetes.
249
250 **Fasting plasma glucose as exposure**
251 In models 1 and 3 with FG, no statistically significant associations with frailty were observed.
252 However, quadratic FG was significant in model 3, suggesting that there could be a non-linear
253 association (Supplemental Table S2).
254
255 **Stratification by CVD and obesity**
256 At baseline, participants with CVD (n=738) were more frail than those without CVD
257 (n=4,639). Diabetes was only significantly associated with frailty at baseline in participants
258 without CVD (Supplemental Table S4, figures S5 and S6). These differences did not amplify
259 over time.
260 Similarly, with model 1 and baseline HbA_{1c} as exposure, there were significant differences in
261 frailty trajectories throughout the follow-up period at different levels of baseline HbA_{1c}, only
262 in participants without CVD. With model 2, HbA1c levels were not associated with frailty in
263 any case. When the analysis was stratified by baseline obesity, diabetes was significantly
264 associated in both non-obesity and obesity groups in model 1. In contrast, with model 2,

baseline diabetes was associated to increased frailty trajectories only in the non-obesity group. In HbA1c models (1 and 3), different levels of HbA1c were associated with frailty trajectories only with model 1 and in non-obesity participants (Supplemental Table S5, figures S7 and S8).

When comparing among the 3 frailty scores, the results were similar for associations between exposures and frailty trajectories (Supplemental Table S2 and Supplemental Figures S2, S3 and S4)

CONCLUSIONS

This study showed that baseline diabetes and higher HbA_{1c} levels were significantly associated with higher frailty trajectories measured from age 60 and older.

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 the last decades of life with higher levels of frailty. This frailty levels broadly corresponding to levels only reached more than a decade later by their peers without diabetes.

Among non-frail individuals at baseline, diabetes and higher levels of HbA_{1c} were associated with an accelerated increase in frailty compared to 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 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 (20). Garcia-Esquinas et al (21) 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 cardio-metabolic biomarkers, suggesting that 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 glycaemia for the development of frailty, but to show to which degree

298 patients with diabetes and even people with non-diabetic intermediate glycemic levels
299 experience frailty in later life.
300
301 To explore the effect of relevant risk factors, we performed additional analyses, which showed
302 attenuation of the strength of the association with income/ social class (9%). This suggests that
303 these risk factors could be confounding variables, although the results are still significant in
304 the more adjusted model.
305
306 The results of this study also show that participants with diabetes have a similar frailty level to
307 participants without diabetes who were 12 years older (table 2), which is consistent with a
308 study by Hubbard et al (22).
309
310 A possible explanation for the observed higher frailty levels seen as individuals with diabetes
311 is that diabetes and frailty have some root causes in common, such as low socio-economic
312 status(23), low physical fitness / functioning / activity(24), and presence of multi-morbidity
313 (25). Diabetes and ageing process share pathophysiological mechanisms such as a chronic state
314 of low-grade inflammation (26). Advanced age is accompanied by an increase in the prevalence
315 of sarcopenia, insulin resistance and obesity. Sarcopenia is accentuated at higher levels of
316 HbA_{1c} and attenuated with the use of insulin (27). In addition to this evidence, metabolic
317 syndrome variables and insulin resistance have been prospectively associated with the
318 phenotype of frailty score in a general elderly population (28).
319
320 The inverse phenomenon, frailty influencing diabetes progression, is also possible. Veronese
321 et al. studied a cohort of elderly individuals and found that frailty was associated with higher
322 incidence of diabetes. They attribute these results to the fact that at baseline, frail individuals

have a higher prevalence of diabetes risk factors such as obesity (29). The underlying mechanisms that could be involved are mediated by adipose tissue dysfunction, where accelerated aging is driven by an increase in pro-inflammatory cytokines, macrophage dysfunction, and increased oxidative stress (30). 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 glycaemia 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 be 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 as 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 or depends partly by 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 diabetes-HbA_{1c}, smoking

348 status and alcohol had the maximum attenuation effects. This suggests that the effects are
349 explained by the preceding confounding factors.
350
351 In contrast, among people with diabetes and at earlier ages, lower levels of HbA_{1c} showed a
352 tendency of association with higher levels of frailty (Figure 2). Zaslavsky et al. found a U-
353 shape relationship in the relation FG/HbA_{1c}-frailty, with both extreme high and low levels
354 associated with frailty (31). The cause of this is U-shape relationship is probably confounding
355 by indication or reverse causation. For example, people with frailty may be monitored more
356 closely, leading to stricter glycemic control while individuals, who are non-frail may be treated
357 less intensively. Another possibility is that individuals who are frail may be more compliant
358 with medication. Indeed, there is evidence that compliance to cardiovascular medication
359 increases when people with diabetes have more than one prescription (32).
360
361 We did not find that FG was associated with frailty trajectories. One explanation of the stronger
362 association seen with HbA_{1c} compared to FG is that $HbA_{1c,}$ is more strongly associated with
363 diabetes comorbidities than FG (33). Also, in this study FG has more missing data than $HbA_{1c,}$
364 which could have diluted the results with FG. Finally, HbA_{1c} may capture the relevant exposure
365 with more precision than FG. HbA_{1c} reflects the long-term average glycemic level and thus
366 reflects the total glycemic exposure more closely than fasting glucose values, which represents
367 a state most people experience only for a few hours of the day. Our results differ from the
368 results reported by Zaslavsky et al. who showed a prospective association between FG and
369 frailty 4-5 years later. (31). These different results could be explained by the fact that
370 Zaslavsky et al. combined the results of HbA_{1c} and glycaemia with Bayesian methods, while
371 we analyzed FG and HbA_{1c} separately.
372

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 (34) 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 due to 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 with participants without CVD, in participants with CVD, diabetes was not associated with an additional change of accelerated progression of frailty. Bouillon et al found that CVD risk scores measured in participants free of CVD were associated with future frailty (35).The mechanisms of these associations are related to the fact that CVD risk factors and frailty have in common inflammatory processes that can lead to atherosclerosis and also to accelerated catabolism associated to frailty (36).

This study has several strengths. It has a prospective design with repeated measurement of frailty. 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 the confidence that our 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 dataset which integrates many dimensions such physical and mental health, determinants/risk factors, and social an economical aspects. ELSA is a representative large sample of the English elderly population with repeated measures of subjective/objective variables and biomarkers relevant to frailty and the ageing process. It is one of the best available longitudinal data sources to address our research questions.

The study has also 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 (37). 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. Another limitation was the missing data that could be a source of bias. However, we tried to deal with this issue by applying multiple imputation and fitting mixed-effect models. (38).
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 (39). Future research should examine the causality and mechanisms of this association.

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551 **Table 1- Baseline characteristics of 5,377 participants by diabetes diagnosis**

Characteristics	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
Glycaemia, mm/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
Cardiovascular disease, %‖	12	25
36-item frailty index, units	14 (8, 24)	22 (13, 25)
Phenotype of frailty, units	27 (7, 47)	33 (20, 53)
Edmonton frail scale, units	12 (6, 20)	18 (10, 27)
Frailty index, % frail	32	53
Phenotype of frailty, % prefrail/% frail	78/13	73/23
Edmonton frail scale, % frail	10	19

552 Data are mean ± SD, median (IQR) or %. *Diabetes was defined as self-reported medical diagnosis or fasting
553 glucose >=7 mml/L or HbA_{1c} ≥6.5% (48mmol/mol). † Number of participants: no diabetes=3689; diabetes=303.
554 ‡Number of participants: no diabetes=2217; diabetes=65; §under/normal weight BMI (kg/m2) ≤ 20 kg,
555 overweight BMI >20 & BMI<30; obesity= BMI ≥ 30; ‖Medical diagnosis of infarction or heart failure or stroke.
556

Table 2-Predicted values of 36-item frailty index by sex, baseline diabetes diagnosis and age

	Men		Women	
	No diabetes	Diabetes	No diabetes	Diabetes
Age	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% confidence intervals 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 born 1930-1934 with HbA1c=5.5% (37 mmol/mol), intermediate family income, middle social class former smokers, alcohol abstinent, no diabetes medications, with hemoglobin 15mg/dl in men and 14 mg/dl in women.

Figure legends

Figure 1. Frailty trajectories (36-item frailty index) by baseline diabetes
Panels A and C in all 5,377 participants (frail and not frail at baseline).
Panels B and D in 3,457 participants that were not frail at baseline.
Model 2 adjusted by sex (men), birth cohort*, family income (intermediate), social class (middle), smoking status (former smoker), alcohol consumption (no alcohol), hemoglobin (15mg/dl in men and 14 mg/dl in women), HbA_{1c} (5.5%, 37 mmol/mol) and diabetes medications (no). Continuous lines are estimates and dotted lines are 95% confidence intervals. Green lines: frailty trajectory for participants without baseline diabetes; red lines: frailty trajectory for participants with baseline diabetes.
In panels A and B, trajectories are plotted in the 1930-1934-birth cohort interval.
In panels C and D, trajectories are plotted in 6 birth cohort intervals (1940-1945, 1935-1939, 1930-1934, 1925-1929, 1920-1924, and 1911-1919).

Figure 2. Frailty trajectories (36-item frailty index) at two different values of HbA1c (5% (31 mmol/mol) and 6% (42 mmol/mol)) in 5,377 participants.
Model 3 adjusted by baseline diabetes (without baseline diabetes in panels A and B, with baseline diabetes in panels C and D), sex (men in panels A and C; women in panels B and D), birth cohort (1930-1934), family income (intermediate), social class (middle), smoking status (former smoker), alcohol consumption (no alcohol), hemoglobin (15mg/dl in men and 14 mg/dl in women), and diabetes medications (no). Continuous lines are estimates and dotted lines are 95% confidence intervals.
Green lines: frailty trajectory for participants with baseline HbA1c=5% (31 mmol/mol); blue lines= frailty trajectory for participants with baseline HbA1c=6% (42 mmol/mol).