

# Baseline HbA1c, subsequent frailty, and mortality among middle-aged and older adults with diabetes: a longitudinal cohort study

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## Article

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# Abstract

Frailty may link glycemic status with later mortality among adults with diabetes, but longitudinal evidence accounting for pre-existing frailty is limited. We analyzed data from the 2011, 2015, 2018, and 2020 waves of the China Health and Retirement Longitudinal Study. The primary cohort included 578 adults aged 45 years or older with diabetes. HbA1c and baseline frailty were assessed in 2011, subsequent frailty in 2015, and mortality by 2020. Each 1-percentage-point increase in baseline HbA1c was associated with a 0.053-unit increase in the scaled 2015 Frailty Index (95% CI 0.004–0.102,  $P = 0.034$ ), and each 0.1-unit increase in the 2015 Frailty Index was associated with higher mortality odds (adjusted OR 1.40, 95% CI 1.08–1.81,  $P = 0.011$ ). HbA1c  $\geq 7.0\%$  was associated with higher mortality odds than HbA1c  $< 7.0\%$  (adjusted OR 2.28, 95% CI 1.15–4.59,  $P = 0.018$ ). The indirect association through the 2015 Frailty Index was 0.461 (bootstrap 95% CI -0.001 to 0.831), with similar findings using 2018 frailty. These findings support subsequent frailty as a potential intermediate state linking glycemic status with later mortality.

## Introduction

Diabetes mellitus represents a major global health challenge, with its prevalence projected to increase further through the mid-century<sup>[1]</sup>. Diabetes management in middle-aged and older adults is complicated by heterogeneity in disease duration, multimorbidity, functional limitations, and frailty-related vulnerability<sup>[2]</sup>. These clinical complexities make it difficult to interpret changes in a single biomarker without considering the broader holistic health status of the patient.

Hemoglobin A1c (HbA1c) summarizes average glycemia over the preceding months and is widely used to guide treatment and assess diabetes-related risk<sup>[3]</sup>. Trial evidence supports the importance of glycemic control for reducing microvascular outcomes and, in some settings, macrovascular outcomes<sup>[4]</sup>. Nevertheless, an HbA1c reduction cannot always be assumed to represent therapeutic benefit, particularly when accompanied by illness, weight loss, treatment burden, or functional decline.

Longitudinal studies suggest that the association between HbA1c and mortality in later life may be non-linear and influenced by underlying health status. HbA1c levels may decline before death in some individuals, raising the possibility of reverse causation<sup>[5]</sup>. Conversely, higher glycemic exposure may contribute to vascular and functional consequences over time. Baseline HbA1c provides a clinically relevant measure of glycemic status that can be temporally related to later changes in health, while repeated measurements are needed to characterize variability and longer-term trajectories.

Studies of older populations have reported that time spent outside individualized HbA1c target ranges, greater HbA1c variability, and less stable glycemic profiles are associated with adverse outcomes<sup>[6–8]</sup>. The clinical implications of a given HbA1c level depend on health complexity and individualized goals<sup>[9]</sup>. Pattern-based studies have also linked non-stable HbA1c profiles with subsequent outcomes<sup>[10]</sup>; however, these observational findings do not clarify whether baseline glycemic status is associated with

the later accumulation of frailty-related deficits or whether frailty may partly account for its relationship with mortality <sup>[11]</sup>.

Frailty, commonly operationalized as an accumulation of health deficits, is prevalent among individuals with diabetes and is associated with mortality, hospitalization, cardiovascular events, and diabetes-related complications<sup>[12, 13]</sup>. Frailty may therefore represent an intermediate state of diminished physiological reserve between earlier glycemic status and later mortality. Nevertheless, much of the available evidence is cross-sectional, evaluates frailty and glycemia concurrently, or does not account for pre-existing frailty. Longitudinal evidence that temporally orders baseline HbA1c, subsequent frailty, and later mortality while adjusting for baseline frailty remains limited.

The conceptual framework for the present study proposed that higher baseline HbA1c may be associated with greater subsequent accumulation of health deficits and that subsequent frailty may, in turn, be associated with later mortality. Baseline frailty was included to distinguish pre-existing vulnerability from frailty measured at follow-up. Path analysis was used to estimate direct and indirect associations within this temporal framework <sup>[14]</sup>, building on mediation approaches previously applied to frailty and mortality in other cohorts <sup>[15]</sup>.

This study used longitudinal data from the China Health and Retirement Longitudinal Study (CHARLS) (<http://charls.pku.edu.cn>) to examine baseline HbA1c and frailty assessed in 2011, subsequent frailty assessed in 2015, and mortality reported by the 2020 wave among Chinese adults aged 45 years or older with diabetes. The primary objectives were to estimate the adjusted association between baseline HbA1c and subsequent frailty and to examine the association of subsequent frailty with mortality. A secondary objective was to explore whether frailty represented a potential intermediate pathway between baseline HbA1c and later mortality. Frailty assessed in 2018 was evaluated as a prespecified sensitivity analysis.

## Results

### Participant characteristics and mortality outcomes

Of the 25,586 participants in the harmonized CHARLS dataset, 578 met the eligibility and complete-case requirements for the primary analysis, while 565 were included in the sensitivity analysis using the 2018 Frailty Index (Fig. 1). The primary analytic cohort included 578 middle-aged and older adults with diabetes, of whom 349 had baseline HbA1c < 7.0% and 229 had HbA1c ≥ 7.0% (Table 1). The mean baseline HbA1c was 6.85% ± 1.72%, and 42 participants (7.3%) were reported to have died by the 2020 wave. Mortality occurred in 20 of 349 participants (5.7%) with HbA1c < 7.0% and 22 of 229 participants (9.6%) with HbA1c ≥ 7.0%. The sensitivity cohort using the 2018 FI included 565 participants and 37 deaths.

[Figure 1 near here]

Table 1

Participant characteristics and follow-up outcomes by baseline HbA1c category in the primary analytic cohort

| Characteristic                                                                                                                                                                                                                                                                          | HbA1c < 7.0% (n = 349) | HbA1c ≥ 7.0% (n = 229) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|
| <b>Baseline characteristics</b>                                                                                                                                                                                                                                                         |                        |                        |
| Age, years                                                                                                                                                                                                                                                                              | 59.7 ± 8.5             | 58.4 ± 7.9             |
| Sex, male, n (%)                                                                                                                                                                                                                                                                        | 142 (40.7)             | 94 (41.0)              |
| BMI, kg/m <sup>2</sup>                                                                                                                                                                                                                                                                  | 25.47 ± 4.18           | 25.26 ± 3.57           |
| Diabetes medication use, n (%)                                                                                                                                                                                                                                                          | 153 (43.8)             | 109 (47.6)             |
| HbA1c, %                                                                                                                                                                                                                                                                                | 5.74 ± 0.72            | 8.54 ± 1.40            |
| Frailty Index, 2011                                                                                                                                                                                                                                                                     | 0.176 ± 0.124          | 0.143 ± 0.118          |
| <b>Follow-up measures</b>                                                                                                                                                                                                                                                               |                        |                        |
| Frailty Index, 2015                                                                                                                                                                                                                                                                     | 0.205 ± 0.137          | 0.194 ± 0.144          |
| All-cause mortality by 2020, n (%)                                                                                                                                                                                                                                                      | 20 (5.7)               | 22 (9.6)               |
| <b>Notes:</b> Values are unweighted and presented as mean ± standard deviation or n (%). HbA1c and baseline FI were measured in 2011; subsequent FI was measured in 2015. Higher FI scores indicate greater frailty. <b>Abbreviations:</b> BMI, body mass index; HbA1c, hemoglobin A1c. |                        |                        |

## Adjusted longitudinal associations

After adjustment for baseline frailty, age, sex, BMI, and diabetes medication use, each 1-percentage-point increase in baseline HbA1c was associated with a 0.053-unit increase in the scaled 2015 FI (95% CI 0.004–0.102,  $P = 0.034$ ), equivalent to approximately 0.005 on the original 0–1 FI scale. Baseline FI ( $P = 3.84 \times 10^{-42}$ ) and age ( $P = 0.006$ ) were also positively associated with the 2015 FI.

In the Firth logistic regression model that included the 2015 FI, each 0.1-unit increase in subsequent FI was associated with higher odds of mortality (adjusted OR = 1.40, 95% CI 1.08–1.81,  $P = 0.011$ ) (Table 2). The adjusted OR for the direct association of continuous baseline HbA1c with mortality was 1.15 per 1-percentage-point increase (95% CI 0.95–1.37,  $P = 0.159$ ), and the corresponding total-association OR before inclusion of the 2015 FI was 1.18 (95% CI 0.98–1.40,  $P = 0.081$ ). In the secondary categorical analysis, baseline HbA1c ≥ 7.0% was associated with higher mortality odds than HbA1c < 7.0% (adjusted OR = 2.28, 95% CI 1.15–4.59,  $P = 0.018$ ).

The sensitivity analysis using the 2018 FI produced similar estimates. Each 1-percentage-point increase in baseline HbA1c was associated with a 0.081-unit increase in the scaled 2018 FI (95% CI 0.013–0.148,  $P = 0.019$ ), and each 0.1-unit increase in the 2018 FI was associated with higher mortality odds (adjusted OR = 1.43, 95% CI 1.14–1.78,  $P = 0.002$ ). HbA1c ≥ 7.0% was also associated with mortality in the

categorical sensitivity analysis (adjusted OR = 2.23, 95% CI 1.07–4.73, P = 0.031). The 95% CIs for the quadratic HbA1c terms included 1.0 in both the primary (P = 0.954) and sensitivity (P = 0.891) cohorts.

## Secondary path analysis

In the primary path analysis, baseline HbA1c was positively associated with the scaled 2015 FI ( $\beta = 0.053$ , bootstrap 95% CI 0.005–0.103), although the magnitude of the association was modest. The path from the 2015 FI to mortality was positive ( $\beta = 8.682$ , 95% CI 0.006–9.663) (Fig. 2, Table 3). Paths involving the binary mortality outcome are expressed on the latent-response scale. The direct association between baseline HbA1c and mortality was  $\beta = 0.367$  (95% CI -0.461 to 1.188). The indirect association through the 2015 FI was  $\beta = 0.461$  (95% CI -0.001 to 0.831), and the total association was  $\beta = 0.829$  (95% CI -0.044 to 1.591).

The sensitivity model using the 2018 FI yielded a similar positive indirect estimate ( $\beta = 0.533$ , bootstrap 95% CI 0.003–0.983), while the total association was  $\beta = 0.721$  (95% CI - 0.059 to 1.542). Usable estimates were obtained from 4,797 of 5,000 bootstrap replications in the primary analysis and 4,918 of 5,000 replications in the sensitivity analysis. The consistency in direction across the primary and sensitivity models supports frailty as a potential intermediate pathway between baseline HbA1c and later mortality.

Table 2  
Adjusted associations of baseline HbA1c with subsequent frailty and mortality

| Predictor                                              | 2015 FI<br>model, $\beta$<br><br>(95% CI); p<br>value         | 2018 FI<br>sensitivity<br>model, $\beta$<br><br>(95% CI) ; p<br>value | Mortality<br>model with<br>2015 FI, OR<br><br>(95% CI) ; p<br>value | Mortality<br>model with<br>2018 FI, OR<br><br>(95% CI) ; p<br>value |
|--------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| <b>Primary continuous HbA1c analysis</b>               |                                                               |                                                                       |                                                                     |                                                                     |
| Baseline HbA1c, per 1-<br>percentage-point<br>increase | 0.053<br><br>(0.004–<br>0.102); P =<br>0.034                  | 0.081<br><br>(0.013–0.148);<br>P = 0.019                              | 1.15<br><br>(0.95–1.37); P<br>= 0.159                               | 1.15<br><br>(0.94–1.38); P<br>= 0.171                               |
| Subsequent FI, per 0.1-<br>unit increase               | -                                                             | -                                                                     | 1.40<br><br>(1.08–1.81); P<br>= 0.011                               | 1.43<br><br>(1.14–1.78); P<br>= 0.002                               |
| Baseline FI, per 0.1-unit<br>increase                  | 0.693<br><br>(0.593–<br>0.793); P =<br>$3.84 \times 10^{-42}$ | 0.748<br><br>(0.650–0.846);<br>P = $9.00 \times 10^{-51}$             | 0.93<br><br>(0.66–1.28); P<br>= 0.678                               | 0.93<br><br>(0.68–1.25); P<br>= 0.656                               |
| Age, per year                                          | 0.017<br><br>(0.005–<br>0.030); P =<br>0.006                  | 0.031<br><br>(0.018–0.044);<br>P = $3.84 \times 10^{-6}$              | 1.10<br><br>(1.05–1.14); P<br>= $6.90 \times 10^{-6}$               | 1.09<br><br>(1.04–1.14); P<br>= $8.24 \times 10^{-5}$               |
| Male versus female                                     | -0.009<br><br>(- 0.189 –<br>0.171); P =<br>0.922              | 0.021<br><br>(- 0.199–<br>0.242); P =<br>0.849                        | 2.46<br><br>(1.24–4.98); P<br>= 0.009                               | 2.16<br><br>(1.05–4.57); P<br>= 0.037                               |
| BMI, per kg/m <sup>2</sup>                             | 0.017<br><br>(- 0.006–<br>0.040); P =<br>0.145                | 0.025<br><br>(- 0.007–<br>0.056); P =<br>0.128                        | 0.92<br><br>(0.84–1.01); P<br>= 0.074                               | 0.89<br><br>(0.80–0.98); P<br>= 0.019                               |
| Diabetes medication use                                | -0.035<br><br>(- 0.219 –<br>0.150); P =<br>0.711              | 0.055<br><br>(- 0.168–<br>0.278); P =<br>0.631                        | 1.97<br><br>(0.99–4.03); P<br>= 0.054                               | 1.79<br><br>(0.86–3.81); P<br>= 0.119                               |

Notes: The 2015 FI model was primary and the 2018 FI model was the sensitivity analysis. Values are  $\beta$  or OR (95% CI), followed by two-sided P values. Linear models used HC3 robust Wald tests; mortality models used Firth penalized likelihood-ratio tests. FI estimates correspond to a 0.1-unit increase on the original 0–1 scale. Dashes indicate not applicable. Abbreviations: BMI, body mass index; CI, confidence interval; FI, Frailty Index; HbA1c, hemoglobin A1c; OR, odds ratio.

| Predictor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2015 FI<br>model, $\beta$<br><br>(95% CI); p<br>value | 2018 FI<br>sensitivity<br>model, $\beta$<br><br>(95% CI) ; p<br>value | Mortality<br>model with<br>2015 FI, OR<br><br>(95% CI) ; p<br>value | Mortality<br>model with<br>2018 FI, OR<br><br>(95% CI) ; p<br>value |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| <b>Primary continuous HbA1c analysis</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                       |                                                                       |                                                                     |                                                                     |
| <b>Additional HbA1c analyses</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                       |                                                                       |                                                                     |                                                                     |
| Baseline HbA1c, total<br>association, per 1-<br>percentage-point<br>increase                                                                                                                                                                                                                                                                                                                                                                                                                          | -                                                     | -                                                                     | 1.18<br><br>(0.98–1.40); P<br>= 0.081                               | 1.18<br><br>(0.97–1.42); P<br>= 0.098                               |
| HbA1c $\geq 7.0\%$ versus $< 7.0\%$                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -                                                     | -                                                                     | 2.28<br><br>(1.15–4.59); P<br>= 0.018                               | 2.23<br><br>(1.07–4.73); P<br>= 0.031                               |
| Quadratic HbA1c term                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -                                                     | -                                                                     | 1.00<br><br>(0.93–1.07); P<br>= 0.954                               | 1.00<br><br>(0.92–1.06); P<br>= 0.891                               |
| Notes: The 2015 FI model was primary and the 2018 FI model was the sensitivity analysis. Values are $\beta$ or OR (95% CI), followed by two-sided P values. Linear models used HC3 robust Wald tests; mortality models used Firth penalized likelihood-ratio tests. FI estimates correspond to a 0.1-unit increase on the original 0–1 scale. Dashes indicate not applicable. Abbreviations: BMI, body mass index; CI, confidence interval; FI, Frailty Index; HbA1c, hemoglobin A1c; OR, odds ratio. |                                                       |                                                                       |                                                                     |                                                                     |

[Figure 2 near here]

Table 3

Exploratory direct, indirect, and total associations of baseline HbA1c with mortality through subsequent frailty

| Path or association                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Primary analysis: FI 2015, estimate (95% bootstrap CI) | Sensitivity analysis: FI 2018, estimate (95% bootstrap CI) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------|
| <b>Path A:</b><br>Baseline HbA1c → subsequent FI                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.053 (0.005–0.103)                                    | 0.081 (0.014–0.148)                                        |
| <b>Path B:</b><br>Subsequent FI → mortality by 2020                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 8.682 (0.006–9.663)                                    | 6.607 (0.090–7.975)                                        |
| <b>Path C':</b><br>Baseline HbA1c → mortality (direct)                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.367 (– 0.461–1.188)                                  | 0.188 (– 0.693–1.079)                                      |
| <b>Indirect association through subsequent FI</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.461 (– 0.001–0.831)                                  | 0.533 (0.003–0.983)                                        |
| <b>Total association</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.829 (– 0.044–1.591)                                  | 0.721 (– 0.059–1.542)                                      |
| Notes: Values are unstandardized DWLS path estimates adjusted for baseline FI, age, sex, BMI, and diabetes medication use. 95% CIs were derived from 5,000 participant-level bootstrap replications; mortality paths are on the latent-response probit scale. Abbreviations: BMI, body mass index; CI, confidence interval; FI, Frailty Index; HbA1c, hemoglobin A1c. Path-analysis inference was based on the percentile bootstrap 95% CIs; P values are not reported for these exploratory path estimates. |                                                        |                                                            |

## Discussion

In this longitudinal cohort study, higher baseline HbA1c was associated with modestly greater subsequent frailty after adjustment for baseline frailty and other covariates. Subsequent frailty was consistently associated with mortality reported by the 2020 CHARLS wave. The secondary categorical analysis also showed higher mortality odds among participants with HbA1c  $\geq 7.0\%$  than among those with HbA1c  $< 7.0\%$ . The indirect estimates through the 2015 and 2018 FIs were positive and consistent in direction. The primary indirect estimate had a confidence interval that narrowly included zero, whereas the sensitivity analysis yielded a confidence interval excluding zero. Collectively, these findings support frailty as a potential intermediate pathway linking earlier glycemic status with later mortality.

The present findings are consistent with evidence showing that frailty is clinically relevant among individuals with diabetes and is associated with mortality and other adverse outcomes<sup>[13]</sup>. They extend this evidence by temporally ordering baseline HbA1c, subsequent frailty, and later mortality while accounting for frailty already present at baseline. The positive association between baseline HbA1c and later FI was modest but consistent in the 2015 and 2018 analyses. This pattern supports interpreting

glycemic status in conjunction with health complexity rather than relying on HbA1c as a stand-alone biomarker [6, 9].

Participants with baseline HbA1c  $\geq 7.0\%$  had approximately twice the adjusted odds of mortality compared with those with HbA1c  $< 7.0\%$  in the secondary categorical analyses. This finding was consistent across the 2015 and 2018 FI models and complements the continuous analyses. The 7.0% cut-point provides a clinically interpretable comparison, while individualized glycemic goals remain essential because the clinical implications of HbA1c depend on comorbidity, frailty, treatment burden, and hypoglycemia risk [4, 9].

The proposed intermediate pathway is clinically plausible because frailty reflects the cumulative effects of chronic disease, functional limitation, depressive symptoms, and reduced physiological reserve. Sarcopenia, malnutrition, and related vulnerability are common in diabetes and may contribute to frailty progression and adverse outcomes [13, 16]. Sarcopenia has also been associated with frailty among older Chinese adults and with mortality when accompanied by nutritional risk in older adults with type 2 diabetes [17, 18]. The present findings align with this broader evidence and identify subsequent frailty as a clinically meaningful link between glycemic status and mortality.

Older age and male sex were associated with higher mortality odds in the primary adjusted model, whereas the BMI estimate was below 1.0 with a 95% CI that included 1.0. Previous studies have reported non-linear associations between BMI and mortality among older adults with diabetes [19] and have emphasized the limitations of BMI as a measure of body composition [20]. BMI cannot distinguish fat mass from muscle mass or identify sarcopenic obesity, and its association may also reflect illness-related weight loss.

This study has important strengths. It preserved a clear temporal ordering from baseline HbA1c and frailty in 2011 to subsequent frailty in 2015 and mortality reported by 2020. Adjustment for baseline FI reduced the likelihood that the association with later frailty merely reflected pre-existing vulnerability. The same 22 deficit components were applied across waves, and the consistency of the findings using the 2018 FI strengthened the longitudinal interpretation. Firth penalized logistic regression addressed sparse mortality data, and participant-level bootstrap CIs provided interval estimates for the direct and indirect associations.

Despite these strengths, several notable limitations must be acknowledged. First, HbA1c was measured only at a single baseline wave and thus did not capture long-term stability, trajectories, or glycemic variability; furthermore, the  $< 7.0\%$  versus  $\geq 7.0\%$  threshold was selected for clinical interpretability rather than representing an individualized treatment target. Second, although a consistent 22-deficit index was used across waves, deficit-accumulation indices do not capture every biological mechanism of frailty, and key variables, including sarcopenia, nutritional intake, anemia, and unintentional weight loss, were not directly measured. Third, the observational design and path analysis cannot establish causal mediation, and residual or time-varying confounding remains possible from unmeasured factors such as

diabetes duration, medication changes, hypoglycemia, renal function, cognition, and socioeconomic circumstances.

Fourth, mortality was recorded primarily as a binary status by 2020 without exact dates of death, precluding time-to-event and right-censoring modeling. Consequently, Firth models estimated odds rather than hazards or risks, and SEM paths to mortality were expressed on a latent-response scale. Fifth, the small number of deaths (42 in the primary cohort and 37 in the sensitivity cohort) resulted in wide confidence intervals for certain estimates. Sixth, complete-case requirements and survival to subsequent assessments may have introduced selection and healthy-survivor biases, and the unweighted analysis means findings are not nationally representative. Finally, because CHARLS enrolls adults aged  $\geq 45$  years, findings apply broadly to middle-aged and older Chinese adults with diabetes rather than strictly to adults aged  $\geq 65$  years, highlighting the need for future studies to examine age-stratified differences.

The results support integrating frailty assessment into diabetes care for middle-aged and older adults. Higher baseline HbA1c was associated with modestly greater subsequent frailty, and subsequent frailty was consistently associated with mortality. Clinical assessment may therefore benefit from considering HbA1c alongside functional status, comorbidity burden, depressive symptoms, nutritional risk, fall risk, hypoglycemia, and treatment burden. The categorical finding for HbA1c  $\geq 7.0\%$  reinforces the importance of individualized glycemic goals and repeated evaluation of physiological reserve. Clinicians and multidisciplinary teams can incorporate frailty screening, medication review, nutritional assessment, and functional monitoring into ongoing diabetes care. Treatment decisions should integrate HbA1c with the patient's broader clinical and functional context.

## Conclusions

Higher baseline HbA1c was associated with modestly greater subsequent frailty among middle-aged and older Chinese adults with diabetes, and subsequent frailty was consistently associated with mortality reported by the 2020 CHARLS wave. HbA1c  $\geq 7.0\%$  was associated with higher mortality odds in secondary categorical analyses, while continuous models showed positive estimates with wider confidence intervals. The concordant longitudinal and indirect-association findings support frailty as a potential intermediate pathway linking glycemic status with later mortality. These findings highlight the value of incorporating frailty assessment into individualized diabetes care and provide a basis for larger longitudinal studies with repeated glycemic and frailty measurements.

## Methods

### Study design and data source

This longitudinal cohort study analyzed data from the 2011, 2015, 2018, and 2020 waves of CHARLS, a nationwide survey of Chinese adults aged 45 years and older. The primary temporal sequence comprised

baseline HbA1c, frailty, and covariates measured in 2011; subsequent frailty measured in 2015; and mortality status obtained from the 2020 wave. Frailty measured in 2018 was used in a sensitivity analysis.

## Study population

The target population comprised middle-aged and older adults aged 45 years or older with baseline diabetes, defined by a self-reported physician diagnosis, an HbA1c level of  $\geq 6.5\%$ , or current use of glucose-lowering medication. Participants were required to have a plausible baseline HbA1c value of 3.0%-20.0%, mortality information from the 2020 wave, a valid baseline Frailty Index (FI), and complete data for age, sex, body mass index (BMI), and diabetes medication use. The primary analytic cohort additionally required a valid 2015 FI and included 578 participants. The sensitivity cohort required a valid 2018 FI and included 565 participants.

## Variables

### Baseline HbA1c (2011)

Baseline HbA1c measured in 2011 was the primary exposure and was analyzed continuously, with estimates interpreted per 1-percentage-point increase. HbA1c was centered at 7.0% for model estimation; this centering did not change the exposure coefficient. For a secondary clinically interpretable analysis, HbA1c was classified as  $< 7.0\%$  or  $\geq 7.0\%$ , with  $< 7.0\%$  as the reference category. A quadratic HbA1c term was evaluated in an additional sensitivity analysis to assess possible non-linearity.

### Frailty Index

Frailty was operationalized using the same 22-item deficit-accumulation FI in 2011, 2015, and 2018. The index included six limitations in activities of daily living, five limitations in instrumental activities of daily living, nine chronic conditions other than diabetes, depressive symptoms defined by a 10-item Center for Epidemiologic Studies Depression Scale score of  $\geq 10$ , and poor self-rated health. The FI was calculated as the number of deficits present divided by the number assessed and ranged from 0 to 1, with higher scores indicating greater frailty. At least 18 of 22 items (80%) were required. The 2011 FI was included as baseline frailty, the 2015 FI was the primary subsequent frailty measure, and the 2018 FI was used in sensitivity analyses. For regression and path analyses, FI values were multiplied by 10 so that estimates corresponded to a 0.1-unit increase on the original scale.

**Outcome: All-cause mortality.** Mortality status was obtained from the 2020 CHARLS wave and analyzed as a binary endpoint (alive or died).

**Covariates.** Prespecified baseline covariates measured in 2011 were age, sex, BMI, diabetes medication use, and the baseline FI. Chronic conditions were incorporated within the baseline FI and were not

entered again as a separate count. These covariates were selected a priori to represent demographic characteristics, adiposity, treatment status, and pre-existing health vulnerability.

## Statistical analysis

**Descriptive analysis.** Continuous variables were summarized using means and standard deviations, and categorical variables were summarized using counts and percentages. Characteristics were described for the primary and sensitivity cohorts and by the secondary HbA1c categories.

**Subsequent frailty analysis.** Multivariable linear regression was used to estimate the association between continuous baseline HbA1c and the scaled 2015 FI, adjusting for the scaled 2011 FI, age, sex, BMI, and diabetes medication use. Heteroskedasticity-consistent HC3 standard errors, 95% confidence intervals (CIs), and two-sided robust Wald P values were reported. The analysis was repeated using the 2018 FI as the outcome.

**Mortality analysis.** Firth penalized logistic regression was used to estimate odds ratios (ORs), profile-likelihood 95% CIs, and coefficient-specific two-sided P values from penalized likelihood-ratio inference for mortality. A total-association model included continuous baseline HbA1c, baseline FI, age, sex, BMI, and diabetes medication use. A direct-association model additionally included subsequent FI. Secondary analyses replaced continuous HbA1c with the < 7.0% versus  $\geq 7.0\%$  classification and evaluated a quadratic HbA1c term. All mortality models were repeated using the 2018 FI sensitivity cohort. Given 42 deaths and six covariates, Firth penalized likelihood estimation was selected to reduce small-sample bias.

**Secondary path analysis.** A structural equation model with a diagonally weighted least squares estimator was used to estimate direct and indirect associations among continuous baseline HbA1c, subsequent FI, and binary mortality status. The model adjusted for baseline FI, age, sex, BMI, and diabetes medication use. Participant-level percentile bootstrap 95% CIs were derived from 5,000 resamples. Paths leading to mortality were reported on the latent-response scale. Analyses were performed in R version 4.5.2<sup>[21]</sup> using the lavaan, logistf, sandwich, and lmtest packages. Where inferential tests were performed, tests were two-sided with  $\alpha = 0.05$ ; effect estimates and 95% CIs were emphasized. Path-analysis inference was based primarily on the participant-level percentile bootstrap 95% CIs.

## Declarations

### Ethics approval

The original China Health and Retirement Longitudinal Study (CHARLS) was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and informed consent was obtained from all participants<sup>[22]</sup>. The present study was a secondary analysis of publicly available, de-identified CHARLS data. The study protocol was reviewed and granted an exemption by the Institutional

Review Board of the Chulabhorn Royal Academy (IRB No. 157/2569). No additional informed consent was required for the present secondary analysis.

### **Use of generative artificial intelligence**

ChatGPT (OpenAI) was used to assist with English-language editing. The authors reviewed and approved all AI-assisted revisions.

### **Data availability**

The dataset analyzed during the current study is available from the China Health and Retirement Longitudinal Study (CHARLS) repository. Researchers can obtain access to the data by registering and applying through the official CHARLS website (<http://charls.pku.edu.cn>).

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### **Author contributions**

KN conceptualized the study, conducted the data analysis, and drafted the manuscript. PK, OT, and AS contributed to the interpretation of the data and critically revised the manuscript for important intellectual content. PL provided methodological guidance and refined the statistical analysis. All authors read and approved the final manuscript.

### **Competing interests**

The authors declare that they have no competing interests.

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## Figures

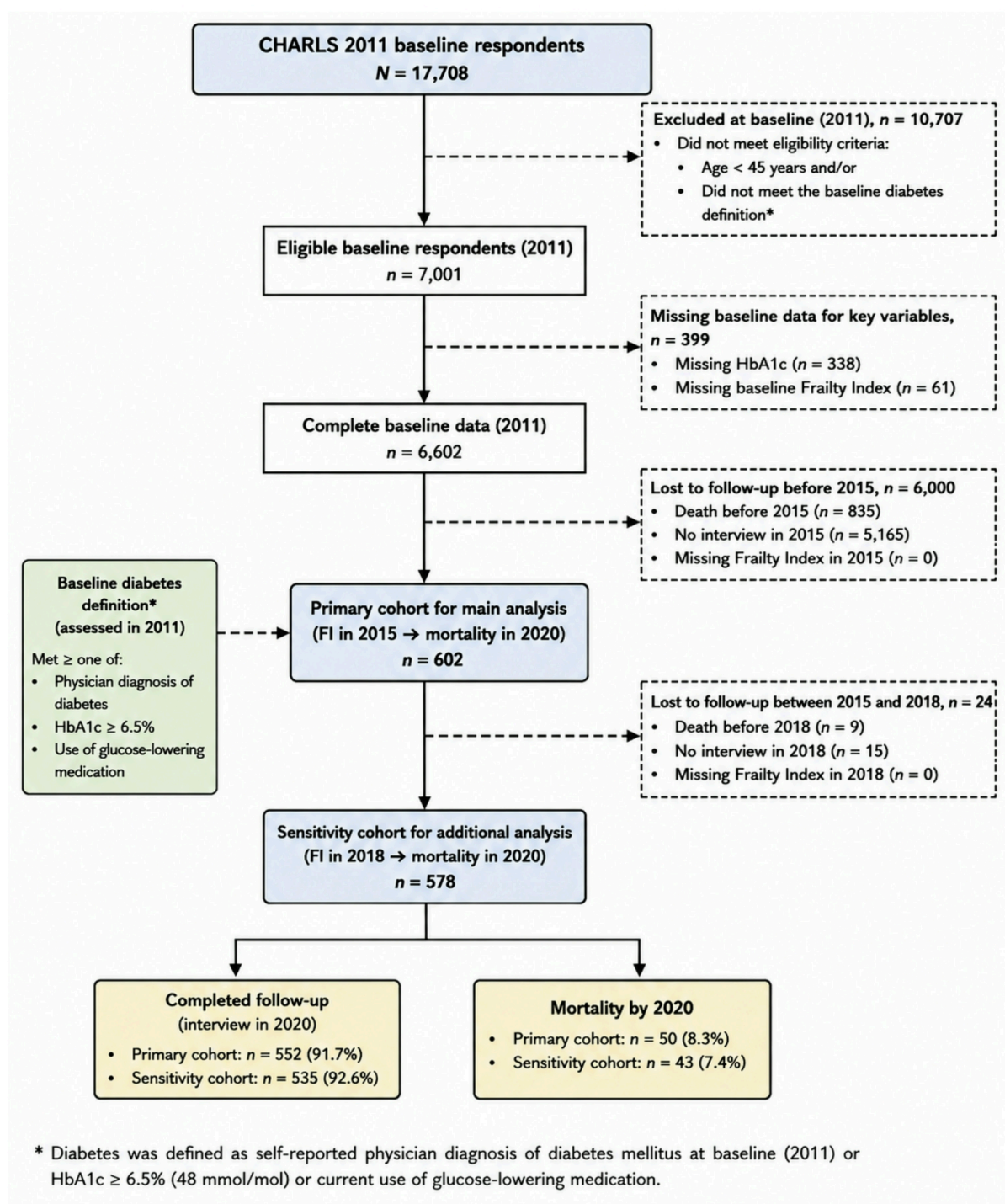
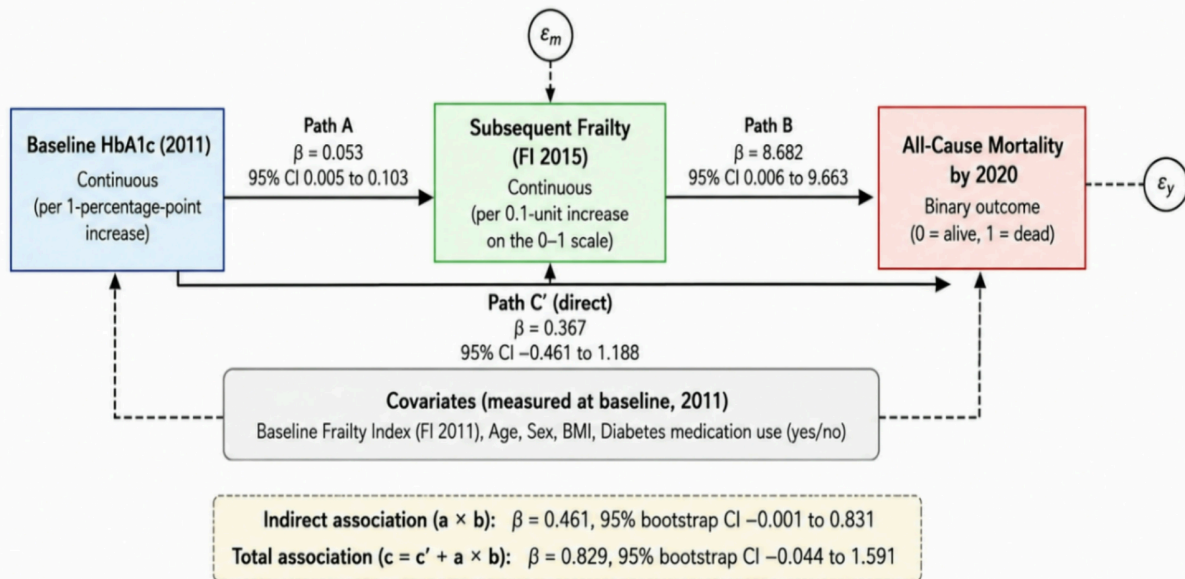


**Figure 1**

Participant flow diagram. Flow of CHARLS participants from the harmonized sample to the primary analytic cohort (baseline 2011 → Frailty Index 2015 → mortality by 2020) and the sensitivity cohort using the 2018 Frailty Index. HbA1c, baseline FI, and covariates were measured in 2011; analyses used unweighted complete-case samples.

## Path Analysis Model: Baseline HbA1c, Subsequent Frailty, and Mortality

(Primary model uses 2015 Frailty Index ( $n = 578$ ; deaths = 42))



### Notes:

- Path coefficients ( $\beta$ ) are unstandardized estimates from diagonally weighted least squares path analysis.
- FI values were multiplied by 10; thus, coefficients for FI correspond to a 0.1-unit increase on the original 0–1 scale.
- Coefficients for paths involving the binary mortality outcome are on the latent-response (probit) scale.
- Models adjusted for baseline FI (2011), age, sex, BMI, and diabetes medication use.
- Bootstrap 95% confidence intervals were derived from 5,000 participant-level replications.
- $\epsilon_m$  and  $\epsilon_y$  represent unexplained variances (residuals) for the mediator and outcome, respectively.

Abbreviations: HbA1c, hemoglobin A1c; FI, Frailty Index; BMI, body mass index; CI, confidence interval.

Figure 2

Path analysis of baseline HbA1c, subsequent frailty, and mortality by 2020. The primary model included 578 participants and 42 deaths and used the 2015 Frailty Index. Values are unstandardized estimates with 95% bootstrap confidence intervals from 5,000 participant-level replications. The model adjusted for baseline FI, age, sex, BMI, and diabetes medication use; paths involving mortality are reported on the latent-response probit scale.