Simple carbohydrate intake and higher risk for physical frailty over 15 years in community-dwelling older adults

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Abstract

Insulin resistance is a major mechanism involved in the onset of physical frailty (PF). Although rich carbohydrate diets may promote insulin resistance, few studies have examined their association with PF risk. This study aimed to investigate the spectrum of carbohydrate exposure, including carbohydrate intake (simple, complex, and total), glycemic load (measure of the diet-related insulin-demand), and adherence to a low-carbohydrate diet with the incident risk of PF in community-dwelling older adults. Baseline carbohydrate exposure was assessed in non-frail participants of the Three-City-Bordeaux cohort using a 24H dietary recall. Over 15 years of follow-up, participants were screened for PF, defined by the FRAIL scale (≥3 criteria out of Fatigue, Resistance, Ambulation, Illnesses, and weight Loss). Associations were estimated using mixed-effects logistic models adjusted for sex, age, education, smoking status, alcohol consumption, depressive symptomatology, global cognitive performances, and protein and energy intakes. The sample included 1,210 participants (62% females, mean age 76 years). Over the follow-up, 295 (24%) incident cases of PF were documented (28% in females, 18% in males). Higher intake of simple carbohydrates was significantly associated with greater odds of incident PF (per 1-SD increased: OR = 1.29; 95% CI = 1.02–1.62), specifically among males (OR = 1.52; 95% CI = 1.04–2.22). No association was observed with complex or total carbohydrate intake, glycemic load, or low-carbohydrate diet. Among the whole carbohydrate exposure, only higher consumption of simple carbohydrates in older age was associated with a higher risk of developing PF. Further studies are required to explore underlying mechanisms.

Keywords: FRAIL scale; glycemic load; low-carbohydrate diet; mixed model; prospective cohort study

Introduction

Global population aging has brought recent medical and socio-economic challenges in the field of geriatric care. To promote healthy aging, a focus has been made on conditions that precede disability, such as physical frailty (PF) (1). This period of increased vulnerability, marked by a loss of muscle mass and function, also increases the risk of falls, need for hospitalization, and death (2–5), and affects around 10% of the older population (6).

Many aspects of the diet have drawn interest as major lifestyle factors that can prevent or contribute to the onset of PF (7). While protein-energy malnutrition, fats and deficiency in micronutrients may be risk factors for PF (8–12), diets rich in fruits and vegetables and healthy dietary patterns, such as the Mediterranean diet (13,14), have generally been associated with reduced PF risk. Regarding data-driven dietary patterns, adopting a ”biscuits and snacking” rich diet was associated with an increased risk of PF over time, compared with a “prudent” pattern, in the French Three-City (3C) cohort (15). This last finding suggested a possible relationship between carbohydrates and the risk of PF and supported a biological plausibility: excess glucose exposure and insulin resistance are indeed proposed as possible mechanisms of the PF-related loss of muscle mass and function (16–19).

Recently, consumption of sweetened beverages has been associated with higher risk of PF in the Nurses’ Health Study, a prospective US cohort of more than 70,000 females followed for 22 years (20). To our knowledge, two other cohorts of male and mixed-sex older adults (1,000 to 2,000 participants) have investigated the role of carbohydrates in PF risk (8,21,22). In the mixed-sex sample, a higher intake of added sugars was associated to a higher risk of PF, while no association was reported with higher intake of simple carbohydrates, complex carbohydrates or total carbohydrates, including sugars naturally present in foods (8,21). In the cohort exclusively constituted of males, a data-driven “high sugar dietary pattern” was not associated to the risk of PF (22). To date, the association between carbohydrate exposures

and the risk for PF thus remains controversial. However, among three cohorts, the first two studied only one sex, the last two had only a single assessment of frailty after a short follow-up (3 years), and all three were limited to the evaluation of carbohydrate intake, ignoring their key nutritional properties. Indeed, insulin status is affected by both the quantity and the quality of the consumed carbohydrates. Yet, glycemic load, a measure of the insulin-demand induced by the diet affecting the insulin resistance status (23,24), has not been studied for its association with the risk of PF. Moreover, the low-carbohydrate diet (i.e. ≤45% of total energy intake provided by carbohydrates), recommended to improve the long-term glycemic control of patients with type 2 diabetes (25), has also not been investigated in relation to PF. In contrast to previous works, this study intended not only to consider a broad spectrum of what carbohydrate exposure involves, but also to include both sexes in a large population-based sample and to benefit from the consideration of multiple evaluations of frailty over a long follow-up period.

The aim of the present study was thus to investigate the associations between simple, complex and total carbohydrate intakes, glycemic load, and adherence to a low-carbohydrate diet, with the risk of incident PF over 15 years in the community-dwelling older adults of the 3C-Bordeaux cohort.

Methods

Study design and population

The 3C-study is a population-based cohort study of vascular risk factors of dementia. The complete methodology has been previously described (26). Eligible participants, aged 65 years or older and initially non-institutionalized, were randomly sampled in 1999–2000 from electoral rolls of three French cities (Bordeaux, Dijon and Montpellier). The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital (Paris, France), and all participants provided written informed consent.

Seven follow-up visits with face-to-face interviews with a neuropsychologist were performed at home at year 2, 4, 7, 10, 12, 14 and 17. A comprehensive dietary survey, including a food frequency questionnaire and a 24-hour dietary recall, was completed in the Bordeaux center at the first follow-up (year 2), which served as baseline in the present analyses. Information on carbohydrate intake was available for 1,658 of the 2,104 participants initially included in the 3C-Bordeaux cohort (n = 64 deceased; n = 382 lost to follow-up between the recruitment and dietary survey). We first excluded participants with diabetes (n = 142) as they already had impaired insulin secretion and might have changed their dietary habits to manage their disease. We also excluded, at baseline, participants confined to bed or with disability, dementia, Parkinson's disease, a history of stroke, deafness or blindness, for which incident PF could have been a direct consequence (n = 164) (2,27), as well as those with missing frailty status (n = 21) or prevalent frailty (n = 121). Finally, 1,210 participants (632 non-frails, 578 pre-frails) were included in the statistical analyses. The study participant flow is depicted in **eFigure 1**. Non-included participants (n = 894) were older, more often depressed,

exhibited lower education and global cognitive performances, and reported lower total energy intake, simple, complex, and total carbohydrate intakes, and therefore a lower glycemic load (**eTable 1**).

Carbohydrate Intake, Glycemic Load and Low-Carbohydrate Diet

At baseline, a 24-hour dietary recall was administered at home for each participant during a face-to-face interview with a specifically trained dietitian (28). Participants were asked to report all dietary intakes they had during the 24 hours preceding their awakening on the day of the interview. Serving sizes were estimated using a photograph book depicting 236 foods and beverages.

The dietician then registered the collected data in the BILNUT® software (SCDA Nutrisoft, Cerelles, France), which includes food composition tables for France, to estimate the nutrient content of each food and beverage, including the amount of carbohydrates. The daily simple, complex and total carbohydrate consumptions (g/d) of each participant was then calculated and the adherence to a low-carbohydrate diet was determined if ≤45% of the total daily energy intake were provided by carbohydrates (25).

The glycemic index for each food and beverage item was obtained from the International Tables of Glycemic Index (29–31). The glycemic index is a ratio (range 0–100) of the 2-hour blood glucose response after ingestion of the tested food compared to the response to a standard food (glucose or white bread) with the same quantity of carbohydrates. This ratio represents the food potential to raise blood glucose: a higher glycemic index indicates a higher glycemic response. We then computed the glycemic load (U/d) for each participant by adding glycemic load values of each food or beverage consumed, calculated by the following formula: glycemic load = (glycemic index * amount of carbohydrate intake (g)) / 100. **eTable 2** shows examples of calculations on a speculated daily menu designed from foods and

quantities reported by participants in the 24-hour dietary recall. **eFigure 2** shows contribution of main categories of foods reported in the 24-hour dietary recall for each quantitative carbohydrate exposure.

Physical frailty

PF was assessed at each follow-up visit using the FRAIL scale. The scale is defined with 5 criteria: fatigue, resistance (ability to climb 1 flight of stairs), ambulation (ability to walk 1 block), illnesses (greater than 5) and loss of weight (>5%) (32). In our study, fatigue was scored positive when participants answered "a moderate amount of the time" or "most of the time" to at least one of the following statements from the Center for Epidemiological Studies-Depression scale (CES-D) (33): "I felt that everything I did was an effort" and "I could not get going". Resistance and ambulation were evaluated using the Rosow and Breslau scales (34) and were scored positive if the participant declared to be unable to walk up and down stairs to the second floor or to walk half a kilometer, respectively. The criterion of more than five illnesses was evaluated considering high blood pressure, incident diabetes, hypercholesterolemia, angina pectoris, arrhythmias, arteritis of the lower limbs, cardiac failure, incident stroke, a history of myocardial infarction, asthma, osteoporosis, dyspnea, incident dementia, incident Parkinson's disease, cancer, thyroid disorders, incident blindness or incident deafness. These diseases were self-reported except for dementia, clinically diagnosed and validated by a consensus of expert for the primary aim of the 3C study. In addition, participants with at least six medications (checked by the interviewer with the prescription) were also considered positive for the "Illnesses" component. Finally, participants were identified as having loss of weight if they declared having a recent and unintentional weight loss of more than 3 kg (item of the Mini Nutritional Assessment tool

(35)) and, in the rare cases for whom this information was missing (10 to 30 participants, depending on the visit), body mass index <21 kg/m² was used as a proxy.

Finally, following the definition of the scale, participants were considered frail if they had three or more positive components, pre-frail if they had one or two, and non-frail if none. Besides, at each visit, participants who needed assistance for at least one activity from the Katz Index of Independence in Activities of Daily Living were registered disabled, and not considered as incident frail (36).

PF was also assessed by the Fried's frailty phenotype, defined by ≥3 criteria out of unintentional weight loss, exhaustion, slowness, weakness and low physical activity, as previously described (27). Items were available 2 years before the dietary survey (at baseline of the 3C-study) and at year 10, 12, 14 and 17 (**eFigure 3**); therefore, the FRAIL scale was preferred to the frailty phenotype for main analyses.

Other variables

Covariates were ascertained at the time of nutritional survey. Sex, education (no or primary school / secondary or high school / university), and smoking status (never smokers / current and past smokers) were recorded. Alcohol consumption (g/d), protein intake (g/d), and total energy intake (kcal/d) were estimated using the 24-hour dietary recall. Depressive symptomatology was determined using the 20-item CES-D (according to the French cut-off scores, females ≥23 and males ≥17 were considered having depressive symptoms) and global cognitive performances were evaluated with the Mini-Mental State Examination (MMSE) test (0–30 points, a higher score indicating better cognitive status) (37).

Statistical analyses

To account for the repeated measurements of PF over the follow-up, mixed-effects logistic regressions, with age as time scale and a random effect at the individual level, were used to study the associations between baseline measures of carbohydrates (simple, complex and total carbohydrate intakes (g/d), glycemic load (U/d) and adherence to a low-carbohydrate diet) and incident PF. Covariates were chosen for their potential confounding effect on these relationships based on the literature and visualized through a directed acyclic graph (**eFigure 4**). Models 1 included sex, age, protein intake, total energy intake, and the baseline pre-frail status (non-frail; pre-frail with 1 in 5 criteria; pre-frail with 2 in 5 criteria). Indeed, we consider that people who are pre-frail (with a higher number of diseases at baseline for example) tend to be more likely to develop frailty versus their non-frail counterparts. To adjust for total energy intake, we applied the residuals method (38,39) on macronutrient consumptions (protein and carbohydrate intakes) and macronutrient-dependent measure (glycemic load, but not the low-carbohydrate diet which is already a ratio of the total energy intake). Odds ratio (OR) and 95% confidence intervals (95% CIs) were estimated for one additional SD of residuals for each exposure of interest (simple carbohydrates: 40 g/d; complex carbohydrates: 40 g/d; total carbohydrates: 50 g/d; glycemic load: 25 U/d). Models 2 were additionally adjusted for education, smoking status, alcohol consumption, depressive symptomatology, and MMSE score. Statistical interactions between carbohydrate exposures and age were tested to assess effect modification. Models 2 were undertaken as complete-case analyses, since only 4 participants had missing (not at random) data on covariates (i.e. MMSE score and depressive symptomatology status). Sex hormones having a direct influence on both insulin sensitivity and muscle mass (40–42), we also provided results of sex-stratified analyses. Linearity of relationships between quantitative variables and PF status

was checked by fractional polynomials. We also conducted stratified analyses for participants who were non-frail or pre-frail at baseline, and to identify the main drivers of the observed associations, we investigated the relationships between carbohydrate exposures found associated with the PF risk in the main analyses and the incidence of each frailty criterion. Finally, we conducted analyses with PF assessed by the Fried's frailty phenotype.

All statistical analyses were performed with R software (version 3.5.2) and statistical significance was set at $p < 0.05$.

Results

The 1,210 non-frail study participants (752 females, 458 males) were 76 years-old (range 68–92) on average at baseline (**Table 1**). Participants were mostly university graduates, never smokers, with an alcohol consumption of more than 10 g/d on average, non-depressed, and with good global cognitive performances. Half the sample (n = 578) was pre-frail at baseline, with 12% of participants exhibiting two criteria out of five on the FRAIL scale, and 36% a single criterion. Pre-frail participants mostly positively scored for illnesses, fatigue, and loss of weight. Mean protein and total energy intakes were 83 g/d and 1,829 kcal/d, respectively. The average carbohydrate intake was 209 g/d, with 100 g/d of simple carbohydrates and 109 g/d of complex carbohydrates. The average glycemic load was 107 U/d, and 45% of the studied sample reported a low-carbohydrate diet.

Compared with females, males were better educated, more often smokers, with higher average alcohol consumption and higher protein and total energy intakes at baseline. Males also had significantly higher average consumption of simple (107 g/d), complex (132 g/d) and total carbohydrates (240 g/d) and higher glycemic load (124 U/d), compared to females (95 g/d, 95 g/d, 190 g/d and 97 U/d, respectively) (**Figure 1**). Moreover, 49% of males reported a low-carbohydrate diet compared with 42% females (P = 0.022).

During a mean follow-up of 11.6 ± 3.9 years (mean ± standard deviation), 213 females (28%) and 82 males (18%) were identified as frail at least once (**Table 2**). Of these frail participants, more than one female out of four and one male out of five recovered to a pre-frail or non-frail status over time. Among frail criteria inducing incident frailty, we observed that 91% of participants positively scored for the "illnesses" criterion, 86% for resistance, 84% for ambulation, 50% for fatigue and 19% for loss of weight. Compared with participants who remained free of frailty during the follow-up, those with incident frailty were older at baseline, less likely to be smokers, more often female and depressed, and with lower education (**Table 1**). They also were more often pre-frail at baseline, exhibiting more often the illnesses, fatigue, and resistance criteria. Regarding nutritional exposures, incident frail participants had lower average consumption at baseline of complex and total carbohydrates, lower glycemic load, and lower protein and total energy intakes than those who remained free of frailty. However, on average, simple carbohydrate intake and adherence to a low-carbohydrate diet were similar between groups.

In models adjusted for sex, age, protein intake, total energy intake, and baseline pre-frail status, no association was observed between carbohydrate exposures and PF among the overall studied sample (**Table 3**). In the fully adjusted models (additionally controlled for education, smoking status, alcohol consumption, depressive symptomatology and MMSE score), higher intake of simple carbohydrates was significantly associated with greater odds of incident PF over 15 years (per 1-SD increased: OR = 1.29; 95% CI = 1.02–1.62; p = .034). In sex-stratified analyses, this association was only observed among males (per 1-SD increased: OR = 1.52; 95% CI = 1.04–2.22; p = .029). Conversely, in fully adjusted models, complex carbohydrate, total carbohydrate, and glycemic load exposures were not significantly associated with the odds of PF, neither in the overall sample nor in sex-stratified analyses. Similarly, adherence to a low-carbohydrate diet was not associated with the odds of

developing PF (in the overall sample and analyses stratified by sex). Age was not an effect modifier of the studied associations.

As participants who are pre-frail tend to be more likely to develop frailty versus their non-frail counterparts, we also conducted stratified analysis. In the non-frail subsample at baseline, higher intake of simple carbohydrates was significantly associated with a higher risk for physical frailty over time (n = 630; per 1-SD increased: OR = 1.60; CI 95% = 1.07–2.41; p = .023) while higher intake of complex carbohydrates was significantly associated with a lower risk for physical frailty over time (n = 630; per 1-SD increased: OR = 0.64; CI 95% = 0.41–0.99; p = .045). Other results were non-significant, including those of sex-stratified analyses. In the pre-frail subsample at baseline, a higher glycemic load was significantly associated with a higher risk for physical frailty in males only (n = 194; per 1-SD increased: OR = 1.60; CI 95% = 1.03–2.50; p = .039).

To investigate the main drivers of the association between simple carbohydrates and PF risk, we also examined the associations with the incidence of each frailty criterion. We found no significant results, except in the subsample of baseline non-frail male participants (n = 194) for whom a higher intake of simple carbohydrates was significantly associated with higher odds of illnesses >5 over time (per 1-SD increased: OR = 1.45; CI 95% = 1.03–2.04; p = .032).

In analyses defining PF using the Fried's frailty criteria, 1,045 non-frail participants (637 females, 408 males) were included. Over follow-up, 231 participants (22%) developed a frailty phenotype, including 165 females and 66 males. We did not observe any association between intake of simple carbohydrates (OR = 1.21; 95% CI = 0.95–1.55), complex carbohydrates (OR = 0.90; 95% CI = 0.70–1.17), total carbohydrates (OR = 1.09; 95% CI = 0.84–1.43), the glycemic load (OR = 1.15; 95% CI = 0.92–1.45), or a low-carbohydrate diet (OR = 1.10; 95% CI = 0.70–1.74), and an incident risk of frailty phenotype among the whole

studied sample. Non-significant results were also observed in the sex-stratified samples, although the strength of the association between simple carbohydrates and frailty phenotype in males was similar to that from primary analysis (OR = 1.50; 95% CI = 0.97–2.32) (**eTable 3**).

Discussion

This large prospective cohort of French community-dwelling older adults highlighted a significant association between a higher consumption of simple carbohydrates and a higher risk of developing PF over 15 years in males.

To our knowledge, the relationship between carbohydrate exposures and PF has been investigated in three different cohorts to date. The British Regional Heart Study reported a lack of association between a high sugar dietary pattern in males (*n* = 945; 78-y old on average) and the risk of developing PF (assessed by the Fried's frailty phenotype) after an average follow-up of 3 years (22). Within the Seniors-ENRICA cohort (2,000 Spanish older adults of 69-y old on average) (8,21), no association was observed between intake of simple carbohydrates (including sugars naturally appearing in foods), complex carbohydrates or total carbohydrates and the frailty phenotype risk at 3 years. Higher intake of added sugars were yet associated with a 3-y increased risk of PF in this cohort (21). Finally, in a large sample of 70,000 females enrolled in the Nurses' Health Study (USA) and followed for up to 22 years, a significant association was observed between higher consumption of sweetened beverages and a higher risk of PF, assessed by the FRAIL scale (20). The present results, that not only consider a broad spectrum of carbohydrate exposure but also include both sexes and benefit from a long follow-up period, are thus in accordance with findings from two out of three other cohorts and consolidate a previous result observed in the 3C study (i.e. a "biscuits and snacking" rich diet was associated with an increased risk of PF over time (15)), which overall

strengthened the potential relationship between carbohydrate consumption and incidence of PF. More importantly, these findings emphasize the type of carbohydrate exposure as a key element in this relationship: added sugars are indeed simple carbohydrates commonly used to sweeten foods, including beverages, which could explain the null results reported when examining the overall carbohydrates exposures, in the present study or previous ones, such as total carbohydrate intake. As participants who are pre-frail tend to be more likely to develop frailty versus their non-frail counterparts, we also conducted stratified analysis. The results confirmed the relevance of adopting a diet poor in simple carbohydrates, and in GL, while favoring complex carbohydrates. Mechanisms of an adverse health effect of simple carbohydrate consumption may involve skeletal muscle damage, which is commonly observed in PF (19). Excess exposure to hyperglycemia, which can be obtained by excess exposure to simple carbohydrates, indeed contributes to the development of oxidative stress, inflammation, and insulin resistance (17). These physiopathological processes may in turn enhance muscle protein catabolism, leading to loss of muscle mass and function (i.e. physical frailty) (17). Regarding glycemic load, it combines both the quality (i.e. the glycemic index) and the quantity of ingested carbohydrates: rapidly digested, absorbed, and metabolized foods often contain simple carbohydrates and added sugars, facilitating the raise of blood glucose. Therefore, an association between glycemic load and the risk of PF have been expected in the present analysis. Non-significant result in the main analyses could be in part explained by the role of the fructose, a simple carbohydrate found in fruits, but also commonly used as added sugar in processed foods. Fructose is known to induce a low glycemic load but is likely highly involved in the onset of insulin resistance (43,44). It means that a diet rich in added simple carbohydrates in the form of fructose, might not be a high-glycemic load diet, but could nonetheless be a potential risk-factor of insulin resistance and therefore of PF.

The low-carbohydrate diet is involved in the management of insulin resistance too and could have been expected to be associated with the PF risk, while this hypothesis was not confirmed by the present study. The lack of available literature on this topic to date deserves further research. Finally, the relationship between simple carbohydrate intake and PF was observed in males, but not in females. This difference could be a consequence of sex differences in the management and impairment of the glucose homeostasis (42,45). Males might indeed be more prone to isolated impaired fasting glucose (IFG) than females, and inversely females might be more prone to isolated impaired glucose tolerance (IGT) than males. However, the impact of IFG on the skeletal muscle metabolism tend to be less important than the impact of IGT, which does not support this hypothesis (46). Another explanation might be the type of diet through which simple carbohydrates are provided. Nutrients are indeed rarely ingested alone and interact with others. For examples, catechin (antioxidant), guar gum (additive), soluble fiber, whey protein (dietary supplement) and olive oil (probably with the mono-unsaturated fatty acid) reduce the absorption of dietary carbohydrates in the intestinal tract (47,48). Dietary fats might also be relevant in the onset of PF, while this topic remains inconclusive to date and deserves better attention (10,11). Differences in the overall diet of males and females could therefore impact the carbohydrate–PF relationship. Inconsistent results between studies according to sex further complicates conclusions about the role of sex in the carbohydrate–PF relationship because these inconsistencies could be explained by the heterogeneity in the measurement of carbohydrate exposures, the assessment of PF or the follow-up duration.

The study's limitations included the evaluation of the nutrient intakes through a unique 24-hour dietary recall. A food frequency questionnaire was administered at baseline (49) but was not appropriate (no portion size) for assessing the carbohydrate consumptions, the adherence to a low-carbohydrate diet, and for computing the glycemic load. Although misclassification

is always an issue with use of a single 24-hour recall, we previously found acceptable correlations between various nutrients estimated from that recall and food groups from our food frequency questionnaire (50). Moreover, misclassification is more likely with foods not consumed on a daily basis than macronutrients, such as carbohydrates, consumed every day. Regarding the calculation of the glycemic load, glycemic indexes are measured when foods are consumed alone, whereas they are often consumed as part of an overall diet, with nutrients that interact and may act synergistically or compete, influencing the glycemic response (47,48). Cooking and baking procedures and individual metabolism can also influence the dynamics of glucose availability and insulin response to food intake. Regarding the outcome, the FRAIL scale criteria are mostly subjective, which questioned its reproducibility (32). Accordingly, the Fried's frailty phenotype has been largely used. However, as measures of grip strength, or walking speed, were not available at each visit of the 3C cohort, we chose to consider the FRAIL scale for the main analysis. Prevalence of PF assessed with the FRAIL scale (5% to 10% across follow-ups) were consistent with those reported in previous studies on PF in similar age groups (6). Moreover, the FRAIL scale is useful for spotting PF in everyday clinical practice and predicts disability, falls, hospitalization and death too (51–54). Finally, in analyses using the Fried's frailty phenotype, similar findings were observed regarding the strengths of the associations, while results were non-significant. The lack of statistical significance may be a consequence of an insufficient statistical power as the Fried's frailty phenotype, unlike the FRAIL scale, was missing at three visits of the 3C-study.

This analysis has several strengths as well. The 3C-study is set in a large population-based sample, representative of the older population of Bordeaux (55) and, in contrast with previous works on the topic, simultaneously includes both sexes and benefits from a long prospective follow-up period (12 years on average for this study) with a close monitoring (up to 6

assessments of the frailty status over time). To limit loss to follow-up, mainly due to age-related disability, follow-up visits were conducted at home and questionnaires were standardized, detailed, and filled by trained and specialized interviewers (neuropsychologists and dietitian). The easy implementation of the FRAIL scale criteria limited the number of participants for whom the diagnosis of frailty status was missing (less than 5% for each visit). Our analyses were adjusted for multiple potential cofounders, including protein and total energy intakes, while residual confounding may exist in this observational study. Another strength in this field is our innovative statistical approach: mixed models enabled us to consider the longitudinal and repeated measures of PF and the potential reversibility of this syndrome over time. The PF status indeed appeared in part transitory in this subsample.

Conclusion

Results of the present study suggested that older people with diets rich in simple carbohydrates have an increased risk of developing PF, especially males. While carbohydrate intake is essential for life, lowering carbohydrate intake, especially simple carbohydrates, may contribute to decrease risk of pejorative outcomes during aging. Disability being one of the major global public health problems regarding older adults, and frailty being an early stage of disability with recovery potential, research efforts, especially in the field of nutrition, should address both the prevention of the onset of the frailty process and the promotion of such recovery over time.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

VC performed statistical analyses and drafted the manuscript; CF supervised the research project and contributed to the drafting of the manuscript; MG contributed to the collection of the data; MG, SA, CB, VR, KP, CH, and CS reviewed the manuscript; CH participated in the design and the protocol of the Three-City study.

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Table 1. Baseline characteristics across sex and status for incident physical frailty. Three-City Study, Bordeaux (France), 2001-2002

Characteristics	Overall	Females	Males		Free from physical frailty over time	Incident physical frailty
	n = 1,210	*n* = 752	*n* = 458	*p*-value	*n* = 915	*n* = 295
Age (y)	75.6 ± 4.8	75.7 ± 4.8	75.5 ± 4.8	.387	75.0 ± 4.6	77.5 ± 4.8
Education				<.001		
No or primary school	369 (30.5)	254 (33.8)	115 (25.1)		256 (28.0)	113 (38.3)
Secondary or high school	325 (26.9)	210 (27.9)	115 (25.1)		248 (27.1)	77 (26.1)
University	516 (42.6)	288 (38.3)	228 (49.8)		411 (44.9)	105 (35.6)
Smoking status				<.001		
Never smokers	777 (64.2)	627 (83.4)	150 (32.8)		572 (62.5)	205 (69.5)
Current and past smokers	433 (35.8)	125 (16.6)	308 (67.2)		343 (37.5)	90 (30.5)
Alcohol consumption (g/d)	13.0 ± 16.5	7.3 ± 10.2	22.4 ± 20.3	<.001	13.5 ± 16.7	11.6 ± 15.8
Depressive symptomatology	66 (5.5)	44 (5.9)	22 (4.8)	.438	42 (4.6)	24 (8.2)
MMSE score	27.8 ± 1.9	27.7 ± 1.9	27.9 ± 1.8	.155	27.9 ± 1.9	27.7 ± 1.8
Status on the FRAIL scale				<.001		
Non-frail	632 (52.2)	368 (48.9)	264 (57.6)		540 (59.0)	92 (31.2)

Pre-frail (1/5 criteria)	438 (36.2)	277 (36.8)	161 (35.2)		293 (32.0)	145 (49.2)
Pre-frail (2/5 criteria)	140 (11.6)	107 (14.2)	33 (7.2)		82 (9.0)	58 (19.7)
FRAIL scale criteria						
Fatigue	176 (14.6)	121 (16.2)	55 (12.0)	.047	111 (12.1)	65 (22.4)
Resistance	36 (3.0)	28 (3.7)	8 (1.8)	.050	20 (2.2)	16 (5.4)
Ambulation	31 (2.6)	22 (2.9)	9 (2.0)	.305	20 (2.2)	11 (3.7)
Illnesses >5	369 (30.5)	263 (35.0)	106 (23.1)	<.001	225 (24.6)	144 (48.8)
Loss of weight	106 (8.8)	57 (7.6)	49 (10.7)	.064	81 (8.9)	25 (8.5)
Protein intake (g/d)	83.1 ± 28.8	77.4 ± 28.1	92.3 ± 27.7	<.001	84.5 ± 29.1	78.4 ± 27.7
Simple carbohydrate intake (g/d)	99.9 ± 43.6	95.3 ± 39.2	107.4 ± 49.0	<.001	100.0 ± 44.0	99.4 ± 42.4
Complex carbohydrate intake (g/d)	109.0 ± 50.4	94.9 ± 44.3	132.0 ± 51.3	<.001	112.6 ± 50.9	97.6 ± 47.2
Total carbohydrate intake (g/d)	208.8 ± 74.2	190.2 ± 64.9	239.5 ± 78.1	<.001	212.6 ± 74.8	197.0 ± 71.0
Glycemic load (U/d)	107.4 ± 41.2	97.1 ± 35.8	124.4 ± 43.7	<.001	109.2 ± 41.4	101.7 ± 39.9
Low-carbohydrate diet	541 (44.7)	317 (42.2)	224 (48.9)	.022	411 (44.9)	130 (44.1)
Total energy intake (kcal/d)	1,829.4 ± 561.3	1,645.9 ± 490.0	2,130.6 ± 540.8	<.001	1,869.4 ± 563.6	1,705.1 ± 536.3

Notes: MMSE = Mini-Mental State Examination (0–30 points). Values are *n* (%) or mean ± standard deviation.

Table 2. Evolution observed in participants with incident physical frailty over the follow-up period. Three-City Study, Bordeaux (France), 2001-2016

	Overall	Females	Males
Incident physical frailty	*n* = 295	*n* = 213	*n* = 82
Stability over time	86 (29.2)	62 (29.1)	24 (29.3)
Transition towards disability or death	131 (44.4)	90 (42.3)	41 (50.0)
Recovery	78 (26.4)	61 (28.6)	17 (20.7)

Note: Values are *n* (%).

Table 3. Associations of carbohydrate exposures with incident physical frailty over 15 years. Three-City Study, Bordeaux (France), 2001-2016

Carbohydrate exposure	Model	Overall (*n* = 1,210)		Females (*n* = 752)		Males (*n* = 458)	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Simple carbohydrate intake[a]	1	1.20 (0.96–1.50)	.112	1.11 (0.83–1.50)	.479	1.36 (0.95–1.93)	.089
	2	1.29 (1.02–1.62)	.034	1.15 (0.85–1.55)	.370	1.52 (1.04–2.22)	.029
Complex carbohydrate intake[a]	1	0.86 (0.67–1.09)	.206	0.86 (0.63–1.17)	.330	0.89 (0.60–1.33)	.582
	2	0.87 (0.68–1.11)	.266	0.86 (0.63–1.18)	.356	0.88 (0.59–1.33)	.556
Total carbohydrate intake[a]	1	1.04 (0.82–1.31)	.746	0.97 (0.71–1.33)	.847	1.19 (0.84–1.69)	.326
	2	1.12 (0.88–1.44)	.362	1.00 (0.72–1.39)	.992	1.32 (0.90–1.93)	.158
Glycemic load[a]	1	1.07 (0.88–1.31)	.503	1.02 (0.77–1.34)	.900	1.21 (0.89–1.64)	.219
	2	1.14 (0.92–1.41)	.236	1.04 (0.79–1.39)	.770	1.30 (0.94–1.81)	.115
Low-carbohydrate diet	1	1.02 (0.68–1.53)	.938	1.05 (0.64–1.72)	.862	0.92 (0.44–1.92)	.822
	2	0.97 (0.64–1.49)	.898	1.06 (0.63–1.76)	.833	0.83 (0.38–1.81)	.640

Notes: Model 1 = sex (except for the sex-stratified analyses), age, protein intake, total energy intake (except for the low-carbohydrate diet), and baseline pre-frail status; Model 2 = Model 1 + education, smoking status, alcohol consumption, depressive symptomatology, and global cognitive performances (*n* = 4 participants with missing data for these last two variables).

[a]per 1-SD increase = simple carbohydrate: 40 g/d; complex carbohydrate: 40 g/d; total carbohydrate: 50 g/d; glycemic load: 25 U/d.

Figure 1. Glycemic load distribution among females and males at baseline. Three-City Study, Bordeaux (France), 2001-2002