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## Nutrition and Aging

# Low Nutrient Intake Is an Essential Component of Frailty in Older Persons

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***Background.*** Poor nutrient intake is conceptualized to be a component of frailty, but this hypothesis has been little investigated. We examined the association between low energy and nutrient intake and frailty.

***Methods.*** We used data from 802 persons aged 65 years or older participating to the InCHIANTI (Invecchiare in Chianti, aging in the Chianti area) study. Frailty was defined by having at least two of the following criteria: low muscle strength, feeling of exhaustion, low walking speed, and reduced physical activity. The European Prospective Investigation into Cancer and nutrition (EPIC) questionnaire was used to estimate the daily intake of energy and nutrients. Low intake was defined using the value corresponding to the lowest sex-specific intake quintile of energy and specific nutrients. Adjusted logistic regression analyses were used to study the association of frailty and frailty criteria with low intakes of energy and nutrients.

***Results.*** Daily energy intake $\leq$21 kcal/kg was significantly associated with frailty (odds ratio [OR]: 1.24; 95% CI: 1.02–1.5). After adjusting for energy intake, a low intake of protein (OR: 1.98; 95% CI: 1.18–3.31); vitamins D (OR: 2.35; 95% CI: 1.48–3.73), E (OR: 2.06; 95% CI: 1.28–3.33), C (OR: 2.15; 95% CI: 1.34–3.45), and folate (OR: 1.84; 95% CI: 1.14–2.98); and having a low intake of more than three nutrients (OR: 2.12; 95% CI: 1.29–3.50) were significantly and independently related to frailty.

***Conclusions.*** This study provides evidence that low intakes of energy and selected nutrients are independently associated with frailty.

FRAILTY is a syndrome associated with reduced functional reserve, impairment in multiple physiological systems, and reduced ability to regain physiological homeostasis after a stressful, destabilizing event. Frail older persons are at high risk of accelerated physical and cognitive functional decline, disability, and death (1–4). Identification of frailty in its early stage is important because interventions may, potentially, prevent or delay its clinical consequences.

Recently, Fried and colleagues (2) defined frailty as a vicious cycle connecting specific signs and symptoms. Using data from the Cardiovascular Health Study, these authors developed and validated an operational definition of frailty as a clinical syndrome characterized by three or more of the following criteria: low muscle strength, unintentional weight loss, feeling of exhaustion, poor physical performance, and reduced physical activity. This definition of frailty was proposed and adopted at a recent American Geriatrics Society- and National Institute on Aging-sponsored national conference on the research agenda on frailty.

In conceptualizing frailty, Fried and colleagues postulated that inadequate dietary intake is a component of the syndrome, which may trigger and/or sustain the cascade of the other processes that lead to frailty. Because nutritional data were not available in the Cardiovascular Health Study, weight loss was used as a proxy measure for inadequate dietary intake. However, because weight loss may be caused by diseases that increase catabolism (5), this measure may not be specific enough or sensitive to reduced energy and nutrient intakes. Additionally, when energy intake is adequate but the diet is deficient in certain nutrients, weight loss may not result.

Muscle strength and exercise tolerance are at the core of the Fried and colleagues definition of frailty. Nutritional intake may affect muscle strength and exercise tolerance through a number of different mechanisms such as the proficiency of energy production in the aerobic metabolism, the regulation of muscle protein synthesis and/or breakdown, and scavenging of free radicals that may produce muscle damage and atrophy (6).

The purpose of this study was to establish whether frailty as a syndrome and its components are associated with inadequate diet independent of major confounders. The InCHIANTI (Invecchiare in Chianti, aging in the Chianti area) study is particularly suited to address this gap in knowledge because it includes complete information on the Fried and colleagues frailty criteria as well as a detailed assessment of dietary intake. This study will help to refine the definition of frailty and, as a consequence, to improve the chances of its prevention and treatment.

## Methods

InCHIANTI is a community-based study of risk factors for disability performed in Greve in Chianti and Bagno a Ripoli, two municipalities adjacent to the city of Florence (Italy). InCHIANTI has been described in detail elsewhere (7).

In brief, 1299 participants aged 65 years or older were randomly selected from the population registry, using a multistage stratified sampling method. Data collection was conducted between September 1998 and March 2000. In total, 1260 participants were eligible, because 39 had died or moved away from the area. The participation rate was 91.6% (1154/1260).

Overall, 1017 participants aged ≥65 years had complete data on both dietary intake and frailty criteria. Participants needing help in one or more Basic Activities of Daily Living ($n = 89$) (8) had severe cognitive impairment defined as a Mini Mental State Examination Score (MMSE) <18 ($n = 27$) (9), and those with gastrointestinal diseases ($n = 43$) and cancer ($n = 56$) were excluded from the analysis. The final analytical sample included 802 participants with an age range of 65–93 years.

The National Institute of Research and Care of Aging ethical committee approved the InCHIANTI study protocol, and all participants received an extensive description of the purposes of the study procedures and signed an informed participation consent form.

### *Data Collection*

Trained interviewers administered two standardized questionnaires at the participants' home: 1) a food frequency questionnaire aimed at collecting data on dietary intake over the last year and 2) a multipurpose, structured questionnaire including questions on sociodemographic characteristics and general information on health, physical activity, functional and cognitive status, and depression. Depressive symptoms were identified by using the Center for Epidemiological Studies-Depression (CES-D) scale (10). Each participant was asked to specify the level of physical activity in the last year, and was classified as ''sedentary'' if reported to be ''mostly sitting'' or to walk outside the home for less than 1 hour per week. Physical function and performance was objectively assessed by trained physical therapists. Grip strength (in kilograms) was measured in both hands using a hydraulic dynamometer (Smith & Nephew, Agrate Brianza, Milan, Italy), and the average of the left and right measures was used for the present analysis. The time to walk was defined using the mean (time in seconds) of two walks on a 15-foot course at usual pace. Time was measured by an optoelectronic system connected to a digital chronometer and a printer (Chronoprinter Tag-Heuer CR501; Zingerle Sports Timing, Bolzano, Italy).

### *Assessment of Dietary Intake*

Data on dietary intake were collected by the food-frequency questionnaire created for the European Prospective Investigation into Cancer and nutrition (EPIC) study (11). Although the EPIC questionnaire was originally developed for and validated in middle-aged persons, our previous study suggested that this tool provides good estimates of dietary intake when administered to older persons (12). Participants were asked to specify how frequently (weekly, monthly, yearly) each specific food and beverage was consumed in the last year. To estimate quantities, colored photographs were shown with different sizes of portions for the main dishes. Specific software created for the EPIC study transformed data on food consumption into daily intake of energy, macronutrients, and micronutrients.

Low intake was defined using the value corresponding to the lowest sex-specific quintile of intake of energy and specific nutrients: protein (men, <66 g; women, <55 g), vitamin D (men, <1.4 μg; women, <1.1 μg), vitamin E (men, <5.1 mg; women, <4.5 mg), vitamin A (men, <468 μg; women, <413 μg), vitamin C (men, <75.2 mg; women, <73.6 mg), folate (men, <214 μg; women, <184 μg), iron (men, <11.7 mg; women, <8.8 mg), calcium (men, <639 mg; women, <561 mg), and zinc (men, <62.8 mg; women, <62.8 mg). By summing the number of nutrients with low intake, we obtained a ''nutritional score'' ranging from 0 to 9. The main purpose of this study was to evaluate the effect of nutrients on frailty and its components independent of energy intake. We did not include carbohydrates and lipids in the nutritional score because their global effect in the causal pathway to frailty is probably due to the fact that they are the major source of daily energy intake (approximately 55% for carbohydrates and 25%–30% for lipids). We had a strong rationale for including in the score protein (which provides about 15% of total energy intake) because of its important effect on muscle protein anabolism.

In preliminary analyses, we found that having a low intake of more than three nutrients was associated with an increased mean number of frailty criteria. Accordingly, we categorized the nutritional score into: 0, 1–3, or >3 nutrients with low intake, and named the last category (>3) ''poor nutritional score.''

### *Definition of Frailty*

We used the operational definition of frailty developed by Fried and colleagues (2). Because our purpose was to establish a link between dietary intake and the frailty syndrome, we did not include ''weight loss'' in our operational definition. Therefore, frailty was defined as having two or more of the following four criteria: 1) exhaustion [self-reported feeling that ''everything I did was an effort,'' at least three times a week in the last month. This information was obtained from the CES-D scale (10)]; 2) low physical activity (sedentary state or performing light intensity physical activity [i.e., walking less than 1 hour/week]); 3) poor muscle strength (grip strength in the lowest quintile, stratified by gender and body mass index [BMI] quartiles); and 4) low walking speed (time to walk 15 feet in the highest quintile, stratified by gender and standing height).

### *Other Variables*

Trained geriatricians conducted a comprehensive evaluation of health status and anthropometrical measures using standardized methods (13,14). BMI was calculated as weight (kg)/height (m)$^2$ and used as a continuous variable. Presence of major chronic diseases was ascertained by trained geriatricians according to standard algorithms based on information on medical history, drug treatments, signs and symptoms, medical documents, and hospital discharge records (15). We used as an indicator of comorbidity the number of diseases (from 0 to 14), computed as a continuous variable. Smoking habits were classified as never smoker, former smoker, or current smoker. Because information on one of the components of frailty (feeling of exhaustion) was derived from the CES-D scale, we used the question ''How much do you feel happy, on a scale from 0 (very much unhappy) to 10 (very much happy)?'' to adjust the analysis for depressive mood, defining ''unhappy'' those referring a value ≤5. In preliminary analyses, we found that 92% of those defined as ''unhappy'' had a CES-D score >20.

### *Statistical Analyses*

Multiple logistic regression was used to evaluate the association of low intake of energy and nutrients with frailty and each of the frailty criteria. A graphical exploratory analysis was used to verify whether there was a threshold of energy intake that best discriminated frail from not frail participants. The identified threshold of 21 kcal/kg/day, corresponding to the lowest quintile of energy intake, was tested by using a general linear model. Then, the variable of energy intake was dichotomized as ≤21 versus >21 kcal/kg. For energy and each nutrient intake deficiency, dummy variables were entered in separate models to test their association with frailty independent of age, gender, education, socioeconomic status, household composition, smoking status, number of diseases, MMSE, BMI, and ''happiness.'' In additional models, low intake of nutrients was also adjusted for energy intake. All analyses were performed using the SAS statistical software, version 8.1 (16).

## Results

Main characteristics of the participants are reported in Table 1. Twenty-one percent of the sample had a low intake for more than three nutrients and 20% were frail. Among frail participants, 53% had a deficient intake of at least one of the selected nutrients (Table 2). The percentage of participants with frailty, and with each one of the frailty criteria, increased with the number of nutrient deficiencies. Independent of age, gender, education, socioeconomic status, household composition, smoking status, number of diseases, MMSE score, BMI, and ''happiness,'' a daily intake of energy ≤21 kcal/kg versus >21 kcal/kg was significantly associated with frailty (odds ratio [OR]: 1.24; 95% confidence interval [CI]: 1.02–1.50). After adjusting for potential confounders, participants with poor nutritional score were significantly more likely to be frail (OR: 2.12; 95% CI: 1.29–3.50) compared to those participants with no low intakes, and the strength of this association was substantially unchanged after adjustment for energy intake considered as both a dichotomous (≤21 vs >21 kg/day) and as a continuous variable. A poor nutritional score was significantly associated with feeling of exhaustion and poor muscle strength. After adjusting for energy intake, this association remained significant for poor muscle strength, but not for feeling of exhaustion. In addition, a low intake of protein, vitamins D, E, C, and folate was independently associated with frailty after adjustment for energy intake (Table 3). The weight lost in the last year was not associated with energy intake ($p = .64$).

Table 1. Main Characteristics of the Population Sample ($N = 802$)

| Characteristics | Participants (Mean ± *SD*, or %) |
|---|---|
| Age (y) | 74.1 ± 6.5 |
| Male gender (%) | 44.0 |
| Education (y) | 5.6 ± 3.3 |
| Marital status (%) | |
| Single | 6.6 |
| Married | 64.0 |
| Widowed | 28.6 |
| Separated | 0.8 |
| Household composition (%) | |
| 1 (alone) | 17.7 |
| 2 persons | 45.9 |
| 3 persons | 16.6 |
| ≥4 persons | 19.8 |
| Economic status (%) | |
| Good | 32.6 |
| Sufficient | 56.0 |
| Bad | 8.5 |
| No answer | 3.0 |
| Smoking status (%) | |
| Never smoker | 59.0 |
| Former smoker | 29.2 |
| Current smoker | 11.8 |
| Body mass index (kg/m$^2$) | |
| <25 | 28.4 |
| 25–29.9 | 47.0 |
| ≥30 | 26.6 |
| Weight loss (at least 4.5 kg in the last y, %) | 7.9 |
| Mini-Mental State Examination (MMSE) score | 25.6 ± 2.8 |
| Chronic diseases (%) | |
| Diabetes mellitus | 9.8 |
| Hypertension | 35.5 |
| Congestive heart failure | 3.5 |
| Peripheral arterial disease | 5.1 |
| Myocardial infarction | 4.9 |
| Stroke | 3.4 |
| Chronic bronchitis/emphysema | 6.7 |
| Frailty syndrome criteria (%) | |
| Exhaustion | 16.5 |
| Low physical activity | 14.2 |
| Poor muscle strength | 24.6 |
| Slow walking speed | 20.3 |
| Frailty score (No. of criteria, %) | |
| 0 | 52.6 |
| 1 | 27.4 |
| ≥2 | 20.0 |
| No. of nutrients with low intake (%) | |
| 0 | 43.5 |
| 1–3 | 35.2 |
| >3 | 21.3 |
| Energy intake (kcal) | 1954 ± 571 |

*Note*: *SD* = standard deviation.

Table 2. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Frailty Syndrome and Frailty Components as Predicted by Number of Nutrients With Low Intake

| | No. of Nutrients With Low Intake | | | Not Adjusted for Energy* | | Adjusted for Energy*,† |
|---|---|---|---|---|---|---|
| | 0 | 1–3 | >3 | 1–3 vs 0 | >3 vs 0 | >3 vs 0 |
| Frailty and Its Components | % | % | % | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Frailty syndrome | | | | | | |
| 2 or more criteria | 13.4 | 20.5 | 32.8 | 1.39 (0.86–2.11) | 2.12 (1.29–3.50) | 2.53 (1.44–4.46) |
| Frailty components | | | | | | |
| Feeling of exhaustion‡ | 12.6 | 18.4 | 21.2 | 1.43 (0.90–2.25) | 1.72 (1.05–2.86) | 1.72 (0.97–3.06) |
| Low physical activity | 9.7 | 15.9 | 20.5 | 1.29 (0.76–2.19) | 1.47 (0.83–2.60) | 1.60 (0.85–3.04) |
| Poor muscle strength | 20.0 | 23.0 | 36.8 | 1.10 (0.73–1.65) | 1.74 (1.12–2.69) | 1.90 (1.16–3.11) |
| Low walking speed | 17.0 | 18.1 | 30.4 | 0.87 (0.55–1.39) | 1.35 (0.83–2.20) | 1.64 (0.95–2.84) |

*Notes*: *Also adjusted for age, sex, education, economic status, household composition, smoking status, number of diseases, cognitive function, body mass index, and ''happiness.''

†Energy intake was entered in the model as dichotomous variable, using as the cutoff point the identified threshold of 21 kcal/kg/day.

‡Analyses related to exhaustion are not adjusted for ''happiness.''

## Discussion

The purpose of this study was to evaluate whether a low intake of energy and nutrients is associated with frailty in older persons. We found that having an intake of energy ≤21 kcal/kg/day was associated with frailty, and a low intake of more than three nutrients (poor nutritional score) was significantly associated with frailty, independent of energy intake and other potential confounders. Poor nutritional score was associated with feeling of exhaustion and poor muscle strength, which are frailty criteria. After adjusting for energy intake, however, the association with feeling of exhaustion was no longer statistically significant, indicating that low energy intake may lead to exhaustion. Instead, the association with poor muscle strength remained significant, suggesting that the quality of diet plays an important role in muscle efficiency.

The link between nutrition and frailty likely involves multiple pathophysiologic pathways. For example, energy and nutrient deficiency may affect mitochondrial function leading to muscle-related symptoms, including fatigue and weakness (7); protein intake is the major factor responsible for muscle protein anabolism in older persons (17); unopposed oxidative stress may be detrimental for skeletal muscle (18,19); and antioxidant vitamins may play a preventive role in reducing oxidative injury (20,21). Our previous study (22) suggested that a deficiency of antioxidants is associated with reduced muscle strength. Accordingly, we found here that low intakes of vitamins E and C were associated with frailty, independent of protein and energy intake. Our finding of an association between low intake of vitamin D and frailty is also interesting given that a considerable number of vitamin D receptors are located on the surface of muscle cells (23).

Table 3. Odds Ratio (OR) (95% Confidence Interval [CI] for Frailty Associated With Low Intake of Specific Nutrients

| | Frailty Syndrome | | | |
|---|---|---|---|---|
| | Not Adjusted for Energy† | | Adjusted for Energy† | |
| Nutrient Intake* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Protein (g/day) | 1.75 (1.12–2.73) | .014 | 1.98 (1.18–3.31) | .009 |
| Iron (mg/day) | 1.37 (0.87–2.14) | .174 | 1.45 (0.85–2.47) | .171 |
| Calcium (mg/day) | 1.31 (0.83–2.07) | .242 | 1.32 (0.81–2.14) | .266 |
| Vitamin D (μg/day) | 2.27 (1.45–3.53) | .002 | 2.35 (1.48–3.73) | .001 |
| Vitamin E (mg/day) | 1.96 (1.25–3.07) | .004 | 2.06 (1.28–3.33) | .003 |
| Vitamin A (μg/day) | 1.57 (0.99–2.47) | .053 | 1.56 (0.99–2.48) | .057 |
| Vitamin C (mg/day) | 2.12 (1.34–3.36) | .001 | 2.15 (1.34–3.45) | .001 |
| Folate (μg/day) | 1.76 (1.12–2.75) | .014 | 1.84 (1.14–2.98) | .013 |
| Zinc (mg/day) | 1.04 (0.64–1.68) | .887 | 1.01 (0.61–1.67) | .969 |

*Notes*: *The first quintile of each selected nutrient was used as the cutoff point to define low intake.

†Adjusted for age, sex, education, economic status, household composition, smoking status, number of diseases, Mini-Mental State Examination score, body mass index, and ''happiness.'' Energy intake was introduced as a dichotomous variable.

Overall, our findings suggest that poor nutritional intake is an important factor associated with the frailty syndrome. A low intake of nutrients is associated with frailty even independent of energy intake. There are important implications with this finding. First, the quality of diet expressed by the intake of specific nutrients is an important factor affecting the health of older persons, and a low intake of specific nutrients may contribute to the development of the frailty syndrome. Second, this study suggests that weight loss may not be a sensitive proxy measure of inadequate diet, and the assessment of nutritional intake may be useful as part of the screening, diagnosis, and treatment of the syndrome.

An important strength of this study is the low number of persons in our sample (4%) who used nutritional supplements; this validates our findings. When we repeated the analysis excluding those participants who used supplements, the results were not substantially changed.

To our knowledge, this is the first study to evaluate the relationship between dietary intake deficiency and frailty, considering as the reference an operational definition of frailty (2), and using a population-based sample including a large number of older persons. Previous studies considered nutrition as an important domain in the pathogenesis of frailty, but most of them used weight loss as proxy measure of undernutrition, included disabled persons, and included hospitalized or institutionalized participants (24,25). Consequently, those findings cannot be extended to the general older population.

The most important limitation of this study is its cross-sectional nature; this makes impossible to establish a causal role of low intake of nutrients in frailty. In a previous study, we found that having physical and cognitive limitations were associated with increased risk of having inadequate dietary intake (26). We tried to minimize the effect of reverse causality in this study by excluding disabled participants and those participants with severe cognitive impairment (MMSE < 18).

## Conclusion

This study provides evidence that low intakes of energy and specific nutrients are associated with frailty. By using nutritional intake, it may be possible to target older persons at an early stage of frailty, before changes in body composition, biochemical markers, and their consequences become clinically evident and likely irreversible. Moreover, weight loss and altered biochemical markers may be caused by different factors (diseases, reduced absorption, metabolism, or inadequate diet); therefore, the best strategy for their treatment remains uncertain. Our results bridge this gap and open a potential avenue for the prevention of frailty: Nutritional intake is certainly an important factor.

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