The Association of Olfactory Dysfunction, Frailty, and Mortality Is Mediated by Inflammation: Results from the InCHIANTI Study

Alice Laudisio, Luca Navarini, Domenico Paolo Emanuele Margiotta, Davide Onofrio Fontana, Irene Chiarella, Daniele Spitaleri, Stefania Bandinelli, Antonella Gemma, Luigi Ferrucci, and Raffaele Antonelli Incalzi

1Unit of Geriatrics, Department of Medicine, Università Campus Bio-Medico, Rome, Italy
2Unit of Allergology, Immunology, Rheumatology, Department of Medicine, Università Campus Bio-Medico, Rome, Italy
3Geriatric Rehabilitation Unit, Azienda Sanitaria di Firenze, Florence, Italy
4Department of Homecare Service, Azienda Sanitaria Locale Roma E, Rome, Italy
5Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA

Correspondence should be addressed to Alice Laudisio; lavoralice@gmail.com

Received 25 May 2018; Accepted 29 November 2018; Published 20 February 2019

Background. Olfactory dysfunction might unveil the association between age and frailty, as it is associated with declining cognitive function, depression, reduced physical performance, reduced dietary intake, and mortality; all these conditions are characterized by increased levels of inflammatory parameters. The present study is aimed at evaluating the association between olfactory dysfunction, frailty, and mortality and whether such association might be mediated by inflammation.

Methods. We analysed data of 1035 participants aged 65+ enrolled in the “InCHIANTI” study. Olfactory function was tested by the recognition of the smells of coffee, mint, and air. Olfactory dysfunction was defined as lack of recognition of at least two smells. Considering the items “shrinking,” “exhaustion,” “sedentariness,” “slowness,” and “weakness” included in the Fried definition, frailty was defined as the presence of at least three criteria, prefrailty of one or two, and robustness of none. Serum interleukin-6 (IL-6) was measured in duplicate by high-sensitivity enzyme-linked immunosorbent assays. Logistic regression was adopted to assess the association of frailty with olfactory function, as well as with the increasing number of olfactory deficits. Cox regression was used to test the association between olfactory dysfunction and 9-year survival. This association varied according to the presence of frailty or prefrailty status (P for interaction = .011). Impairment of olfactory function might represent a marker of frailty, prefrailty, and consequently reduced survival in an advanced age.

1. Introduction

Due to its prevalence rates exceeding 50% among individuals aged 65-80 years and reaching 80% above the age of 80, olfaction dysfunction is considered a very common problem in older populations [1]. This sensory deficit has important implications for safety, nutrition, quality of life, and social relationships [2]. Olfactory impairment is partially age-related and reflects either central neurodegenerative mechanisms or peripheral cumulative damage of olfactory receptors [1]. In fact, the olfactory system is the only sense which depends upon stem cell turnover, and the olfactory nerve is the only cranial nerve directly exposed to the environment [1].

Frailty is an age-related condition of increased vulnerability, associated with higher risk of several adverse outcomes,
including mortality [3]. Among different criteria proposed to define frailty, the frailty phenotype proposed by Fried and colleagues is among the most commonly adopted [4]; also, prefrailty status has been associated with reduced survival, as compared with robustness [3]. Indeed, frailty can be attenuated and even reversed, so that this syndrome has to be considered a dynamic process, mainly for subjects in their intermediate stage [5]. In an Italian cohort of elderly people, although most participants tended to retain their baseline frailty status, more than one-third of the sample experienced a transition (with either improvement or worsening) in their frailty status over a four-year follow-up [6].

It has been documented that sensory perception, including smell perception, is associated with several components of frailty [7]. On the other hand, it has been acknowledged that both frailty and olfactory loss are associated with reduced survival [3, 8]. Furthermore, both olfactory impairment and frailty are characterized by subclinical inflammation, which could partially explain the adverse outcomes associated with these two conditions.

Olfactory impairment, but not hearing or visual impairment, has been associated with decreased survival in older subjects [9]. However, to our knowledge, neither the association of olfactory impairment with prefrailty nor the impact of frailty phenotypes on the association between olfactory dysfunction and mortality has been so far investigated.

The aim of this study was to assess in an older population the association, if any, of olfactory dysfunction with frailty and mortality and whether such an association might be mediated by frailty status.

2. Methods

2.1. Study Design and Participants. The present study is based upon the data from the “Invecchiare in Chianti” study, a prospective population-based study of older persons in Tuscany, Italy, that is aimed at identifying risk factors for late-life disability [10]. The Italian National Research Council on Aging Ethical Committee ratified the study protocol, and participants provided written consent to participate.

Analyses for this study included all 1035 subjects aged 65+.  

2.2. Frailty. Frailty was defined according to the Fried criteria [4]: unintentional weight loss, self-reported exhaustion, muscle weakness, slowness, and sedentariness. Weight loss was defined as self-reported unintentional weight loss > 4.5 kg within the past year. Exhaustion was defined as a response of “occasionally,” “often,” or “always” to the statement “I felt that everything was an effort.” Muscle weakness was defined as grip strength in the lowest quintile, stratified by sex and BMI quartiles. Grip strength was measured by a handheld dynamometer (Nicholas Muscle Tester, Sammons Preston Inc.). Slowness was defined as the time to walk 4.57 meters or 15 ft. Sedentariness was defined as either complete inactivity or spending <1 h/wk performing low-intensity activities. “Frailty” was defined as the presence of at least three criteria, “prefrailty” of one or two criteria, and “robustness” of none.

This syndrome is thought to emerge from multisystem dysregulation that is common in older adults and characterized by increased vulnerability to stressors and increased risk of disease, disability, and death. Also, frailty is linked to multimorbidity and inflammation.

2.3. Mortality. Data on 9-year mortality were collected using the data from the Mortality General Registry maintained by the Tuscany Region, as well as death certificates delivered immediately after death to the registry office of the municipality of residence.

2.4. Olfactory Function. Olfactory function was self-reported and explored during the medical visit according to the questions: “Does he/she recognize mint?”, “does he/she recognize coffee?”, and “does he/she recognize air?”. Olfactory dysfunction was defined when at least two smells were not recognized. Increasing levels of olfactory impairment (0 to 3 smell losses) were also considered.

2.5. Inflammation. Blood samples were drawn in the morning after a 12-hour overnight fast and resting period. Aliquots of serum were stored at −80°C. Serum interleukin-6 (IL-6) was measured in duplicate by high-sensitivity enzyme-linked immunosorbent assays (ELISAs; kits from BioSource, Camarillo, CA) with a sensitivity of 0.1 pg/mL and an intra-assay coefficient of variations less than 6%.

2.6. Covariates. Data on dietary intake were collected by the questionnaire created for the European Prospective Investigation into Cancer and Nutrition (EPIC) study [11]. Adjudicated disease diagnoses were based on self-reported history, clinical documentation, and medication use, as well as standardized criteria derived from the Women’s Health and Aging Study protocol [12]. Comorbidity was quantified using the Charlson Comorbidity Index score [13]. All drugs assumed by participants were coded according to the Anatomical Therapeutic Chemical codes [14]. Functional ability was estimated using Katz’s activities of daily living [15], depressive symptoms by the original 20-item version of the Center for Epidemiological Studies Depression Scale (CES-D) [16], and cognitive performance by the Mini Mental State Examination [17]. Blood samples were obtained from participants after 12-hour fasting and after resting for at least 15 minutes. Aliquots of serum were stored at −80°C and were not thawed until analysis. Interleukin-6 concentrations were determined by high-sensitivity ELISA using commercial kits (Human Ultrasensitive, BioSource International Inc., Camarillo, CA, USA). Glomerular filtration rate was estimated using the Cockcroft-Gault equation.

2.7. Statistical Analyses. Data were recorded using dedicated software. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS for Mac version 20.0, 2011, SPSS Inc., Chicago, IL); differences were considered significant at the $P < .050$ level.
Table 1: Characteristics of 1035 participants according to olfactory dysfunction.

| Demographics & lifestyle habits, n (%), mean (SD), or median (IQR) | Presence of olfactory dysfunction (n = 590) | Absence of olfactory dysfunction (n = 445) | P    |
|---------------------------------------------------------------|---------------------------------------------|-------------------------------------------|------|
| Age (years)                                                   | 76 (8)                                      | 73 (7)                                    | <.001|
| Sex (female)                                                  | 315 (53)                                    | 262 (59)                                  | .088 |
| Education (years)                                             | 5 (3)                                       | 6 (3)                                     | .003 |
| Living alone                                                  | 241 (41)                                    | 164 (37)                                  | .199 |
| Smoking (former and current)                                  | 253 (43)                                    | 170 (38)                                  | .142 |
| **Dietary intake**                                            |                                             |                                           |      |
| Alcohol (g/day/kg)                                            | 0.11 (0–0.29)                               | 0.10 (0–0.31)                             | .594 |
| Total protein intake (g/day/kg)                               | 1.12 (0.33)                                 | 1.13 (0.31)                               | .657 |
| Total lipid intake (g/day/kg)                                 | 0.96 (0.31)                                 | 0.98 (0.31)                               | .310 |
| Available carbohydrate intake (g/day/kg)                     | 3.73 (1.17)                                 | 3.72 (1.29)                               | .913 |
| Fibre (g/day/kg)                                              | 0.29 (0.08)                                 | 0.29 (0.08)                               | .551 |
| Energy intake (kcal/day/kg)                                  | 28.60 (8.25)                                | 28.71 (8.50)                              | .829 |
| **Comorbid conditions, n (%) or median (IQR)**                |                                             |                                           |      |
| Diabetes                                                      | 67 (11)                                     | 47 (11)                                   | .764 |
| Heart failure                                                 | 39 (7)                                      | 20 (4)                                    | .176 |
| Chronic pulmonary disease                                     | 52 (9)                                      | 37 (8)                                    | .823 |
| Parkinson’s disease                                           | 15 (2)                                      | 12 (3)                                    | .999 |
| Stroke                                                        | 37 (6)                                      | 23 (5)                                    | .503 |
| Hip fracture                                                  | 19 (3)                                      | 19 (4)                                    | .406 |
| Peripheral arterial disease                                   | 80 (14)                                     | 41 (9)                                    | .032 |
| Malignancy                                                    | 28 (5)                                      | 36 (8)                                    | .036 |
| Frailty phenotype                                              | 85 (14)                                     | 26 (6)                                    | <.001|
| Charlson Comorbidity Index                                    | 1 (0–2)                                     | 1 (0–1)                                   | .489 |
| **Medications, n (%), mean (SD), or median (IQR)**            |                                             |                                           |      |
| Neuroleptics                                                  | 18 (3)                                      | 15 (3)                                    | .859 |
| Selective serotonin reuptake inhibitors                       | 13 (2)                                      | 3 (1)                                     | .072 |
| ACE inhibitors                                                | 92 (16)                                     | 49 (11)                                   | .035 |
| Antiplatelets                                                 | 73 (12)                                     | 40 (9)                                    | .088 |
| Anticoagulants                                                | 8 (1)                                       | 5 (1)                                     | .787 |
| Benzodiazepines                                               | 112 (19)                                    | 61 (14)                                   | .029 |
| Loop diuretics                                                | 53 (9)                                      | 32 (7)                                    | .306 |
| Corticosteroids                                               | 8 (1)                                       | 10 (2)                                    | .339 |
| **Biohumoral, physical, and cognitive parameters, n (%) or mean ± SD** |                                             |                                           |      |
| Glomerular filtration rate (mL/min)                           | 62.6 (19.3)                                 | 68.1 (19.2)                               | <.001|
| Total serum proteins (g/dL)                                   | 7.2 (0.4)                                   | 7.1 (0.5)                                 | .308 |
| Interleukin 6 (pg/mL)                                         | 1.49 (0.84-2.32)                            | 1.44 (0.88-2.27)                          | .582 |
| Hemoglobin (g/dL)                                             | 13.6 (1.4)                                  | 13.8 (1.4)                                | .112 |
| CES-D                                                         | 13 (9)                                      | 12 (8)                                    | .035 |
| Mini Mental State Examination                                 | 24.3 (4.3)                                  | 24.7 (5.5)                                | .160 |
| Katz’s activities of daily living                             | 5 (1)                                       | 4 (2)                                     | .107 |
| Body mass index (kg/m²)                                       | 27.3 (4.0)                                  | 27.6 (4.2)                                | .183 |

Data of continuous variables are presented as mean values ± standard deviation or medians and interquartile ranges. Normally distributed variables according to olfactory dysfunction, as well as to mortality, were assessed by the analysis of variance (ANOVA) or the nonparametric Mann–Whitney U test if appropriate. The two-tailed Fisher exact test was used for dichotomous variables.

Multivariable logistic regression was used to evaluate the association of the frailty phenotype with age, sex, and all those variables which differed significantly in univariate analysis, including olfactory dysfunction.

The fully adjusted model was also adopted to evaluate the association of increasing levels of olfactory dysfunction with frailty. Also, the analysis of the interaction terms
“olfactory dysfunction”*interleukin-6” was performed to assess whether the association of frailty with olfactory dysfunction varied according to inflammation. In addition, to evaluate the whole spectrum of the frailty phenotype, the same summary model was analysed in multinomial logistic regression having robustness, prefrailty, and frailty as the dependent variables.

Also, Cox proportional hazard regression analysis was used to estimate the association of mortality with age, sex, and all those variables which differed significantly in univariate analysis, including olfactory dysfunction. Eventually, in Cox regression, the analysis of the interaction terms “olfactory dysfunction*frailty,” “olfactory dysfunction*prefrailty,” and “olfactory dysfunction*
interleukin-6,” was performed to assess whether the association between reduced survival and olfactory dysfunction varied according to the presence of frailty, prefrailty, and inflammatory status.

3. Results

The main characteristics of 1035 participants according to olfactory dysfunction are depicted in Table 1. Frailty was

| Table 3: Characteristics of 1035 participants according to survival status. |
|---------------------------------|-------|-------|-------|
|                                  | Dead  (n = 393) | Alive (n = 642) | P     |
| Demographics & lifestyle habits, n (%), mean (SD), or median (IQR) |       |       |       |
| Age (years)                      | 80 (7) | 72 (5) | <.001 |
| Sex (female)                     | 200 (51) | 377 (59) | .014 |
| Education (years)                | 5 (3) | 6 (3) | <.001 |
| Living alone                     | 206 (52) | 199 (31) | <.001 |
| Smoking (former and current)     | 172 (44) | 251 (39) | .152 |
| Dietary intake                   |       |       |       |
| Alcohol (g/day/kg)               | 0.10 (0–0.26) | 0.10 (0–0.32) | .021 |
| Total protein intake (g/day/kg)  | 1.14 (0.32) | 1.11 (0.32) | .262 |
| Total lipid intake (g/day/kg)    | 0.97 (0.30) | 0.96 (0.32) | .582 |
| Available carbohydrate intake (g/day/kg) | 3.82 (1.26) | 3.67 (1.20) | .066 |
| Fibre (g/day/kg)                 | 0.29 (0.09) | 0.29 (0.08) | .654 |
| Energy intake (kcal/day/kg)      | 29.08 (8.33) | 28.40 (8.37) | .227 |
| Comorbid conditions, n (%) or median (IQR) |       |       |       |
| Diabetes                         | 52 (13) | 62 (10) | .082 |
| Heart failure                    | 46 (12) | 13 (2) | <.001 |
| Chronic pulmonary disease        | 63 (16) | 26 (4) | <.001 |
| Parkinson’s disease              | 21 (5) | 6 (1) | <.001 |
| Stroke                           | 44 (11) | 16 (2) | <.001 |
| Hip fracture                      | 24 (6) | 14 (2) | .002 |
| Peripheral arterial disease      | 86 (22) | 35 (5) | <.001 |
| Malignancy                       | 28 (7) | 36 (6) | .353 |
| Olfactory dysfunction            | 249 (63) | 341 (53) | .001 |
| Frailty                          | 90 (23) | 21 (3) | <.001 |
| Charlson Comorbidity index       | 1 (0–2) | 0 (0–1) | <.001 |
| Medications, n (%), mean (SD), or median (IQR) |       |       |       |
| Neuroleptics                     | 17 (4) | 16 (2) | .143 |
| Selective serotonin reuptake inhibitors | 11 (3) | 5 (1) | .017 |
| ACE inhibitors                   | 72 (18) | 69 (11) | .001 |
| Antiplatelets                    | 65 (16) | 48 (7) | <.001 |
| Anticoagulants                   | 11 (3) | 2 (1) | .001 |
| Benzodiazepines                  | 81 (21) | 92 (14) | .010 |
| Loop diuretics                   | 55 (14) | 30 (5) | <.001 |
| Corticosteroids                  | 11 (3) | 7 (1) | .050 |
| Biohumoral, physical, and cognitive parameters, n (%) or mean ± SD |       |       |       |
| Glomerular filtration rate (mL/min) | 56.4 (19.5) | 69.5 (17.8) | <.001 |
| Total serum proteins (g/dL)      | 7.1 (0.5) | 7.1 (0.4) | .680 |
| Interleukin 6 (pg/mL)            | 1.89 (1.14–3.31) | 1.22 (0.78–1.84) | <.001 |
| Hemoglobin (g/dL)                | 13.4 (1.6) | 13.9 (1.2) | <.001 |
| CES-D                            | 14 (9) | 12 (9) | <.001 |
| Mini Mental State Examination    | 22 (6) | 26 (3) | <.001 |
| Katz’s activities of daily living | 5 (1) | 6 (0) | <.001 |
| Body mass index (kg/m²)          | 27.0 (4.3) | 27.7 (4.0) | .016 |
diagnosed in 111 (11%) subjects, prefrailty in 420 (41%) participants, and robustness in 504 (48%). The main characteristics of subjects according to frailty are shown in Table 2.

Over the 9-year follow-up, 393 (38%) subjects died. The main characteristics of participants according to survival are depicted in Table 3.

Olfactory dysfunction was reported by 590/1035 (57%) participants; specifically, lack of recognition of one smell was recorded in 190 (18%) subjects, two smells in 243 (23%), and three smells in 347 (33%). In particular, failure to recognize air was found in 505 (49%).

In multivariable logistic regression, olfactory dysfunction was associated with increased probability of being frail (OR 1.94, 95% CI = 1.07-3.51; \( P = .028 \)), after adjusting (Table 4). Analysis of the interaction term indicated that the association of frailty with olfactory dysfunction varied according to interleukin-6 levels (\( P \) for interaction = .005).

Also, increasing levels of olfactory dysfunction were associated with increasing probability of frailty (\( P \) for trend = .021).

Both frailty (OR 2.60, 95% CI = 1.39-4.85) and prefrailty (OR 1.59, 95% CI = 1.17-2.16) were associated with olfactory dysfunction in multinomial logistic having robustness as the reference.

According to Cox regression analysis, olfactory dysfunction was associated with reduced survival (HR 1.52, 95% CI = 1.16-1.98; \( P = .002 \)), after adjusting (Figure 1); analysis of the interaction term indicated that this association varied according to the presence of frailty (\( P = .017 \)), prefrailty (\( P = .046 \)), and increased interleukin-6 levels (\( P \) for interaction = .011).

### 4. Discussion

Results of the present study indicate that in older subjects, olfactory dysfunction is associated not only with frailty, but even with prefrailty. This association seems to be mediated by subclinical inflammation.
delirium [2, 26]. Also, impairment in olfactory function has been related to the intake of macro- and micronutrients and directly affects food intake behaviour [27]. Eventually, olfactory dysfunction represents a risk factor for reduced survival [8]. Even better, olfactory dysfunction is the only sense which has been associated with mortality, when compared with hearing or visual impairment [9]. With special regard to the frailty components, olfactory function is associated with mobility, balance, fine motor function, and manual dexterity and independent of cognitive function, with challenging upper- and lower-extremity motor function tasks [28]. Also, olfactory loss represents a risk factor for weight loss, while aerobic exercise might preserve olfactory function in selected populations, such as patients with Parkinson’s disease [2, 29].

Furthermore, our finding of a potential role of IL-6 serum levels in the association between olfactory loss and frailty is of interest. Increased IL-6 levels have been found in serum and nasal mucus of hyposmic patients [30]. On the other hand, increased IL-6 serum levels have also been associated with frailty, as well as mortality, in older populations [31, 32]. Thus, inflammation represents a common pathophysiological pathway that links hypoaemia, frailty, and mortality in the elderly.

In this study, olfactory dysfunction was self-assessed. Self-assessed tools for evaluating olfactory function might underestimate the dysfunction, as compared with objective evaluation. Nevertheless, this would represent a conservative bias, which further supports our findings. Also, regarding the association of olfactory dysfunction with frailty, due to its cross-sectional design, this study does not allow establishing any cause-effect relationship. Nonetheless, this study enrolled a representative community-dwelling population, with high participation rate and with extensive information on risk factors, comorbid conditions, and objective parameters.

In conclusion, olfactory loss represents a correlate of frailty and even of prefrailty; this association seems to affect the role of olfactory dysfunction as a predictor of mortality in older populations. Thus, olfaction seems worth testing in geriatric practice for both clinical and epidemiological purposes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The Italian National Research Council on Aging Ethical Committee ratified the study protocol, and informed consent was obtained from all individual participants included in the study. The present study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Disclosure

None of the sponsoring institutions interfered with the design, methods, subject recruitment, data collections, analysis, and preparation of the paper.

Conflicts of Interest

The authors declare that they have no conflict of interest in this study.

Acknowledgments

The InCHIANTI study baseline (1998–2000) was supported as a targeted project (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts 263 MD 9164 and 263 MD 821336); the InCHIANTI Follow-Up 1 (2001–2003) was funded by the U.S. National Institute on Aging (Contracts N.1-AG-1-1 and N.1-AG-1-2111), Baltimore, Maryland.

References

[1] R. Voegels, F. Pinna, R. Imamura, J. Farfel, and M. Godoy, "Odor discrimination in neurologic and neurodegenerative diseases: a literature review," International Archives of Otorhinolaryngology, vol. 19, no. 2, pp. 176–179, 2015.

[2] A. B. Rosenfeldt, T. Dey, and J. L. Alberts, "Aerobic exercise preserves olfaction in individuals with Parkinson’s disease," Parkinson’s Disease, vol. 2016, pp. 1–6, 2016.

[3] S. F. Chang and P. L. Lin, "Frail phenotype and mortality prediction: a systematic review and meta-analysis of prospective cohort studies," International Journal of Nursing Studies, vol. 52, no. 8, pp. 1362–1374, 2015.

[4] L. P. Fried, C. M. Tangen, J. Walston et al., "Frailty in older adults: evidence for a phenotype," The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, vol. 56, no. 3, pp. M146–M157, 2001.

[5] E. Matsushita, K. Okada, Y. Ito et al., "Characteristics of physical frailty among Japanese healthy older adults," Geriatrics & Gerontology International, vol. 17, no. 10, pp. 1568–1574, 2016.

[6] C. Trevisan, N. Veronese, S. Maggi et al., "Factors influencing transitions between frailty states in elderly adults: the Progetto Veneto Anziani longitudinal study," Journal of the American Geriatrics Society, vol. 65, no. 1, pp. 179–184, 2017.

[7] S. Somekawa, T. Mine, K. Ono et al., "Relationship between sensory perception and frailty in a community-dwelling elderly population," The Journal of Nutrition, Health & Aging, vol. 21, no. 6, pp. 710–714, 2017.

[8] I. Ekström, S. Sjölund, S. Nordin et al., "Smell loss predicts mortality risk regardless of dementia conversion," Journal of the American Geriatrics Society, vol. 65, no. 6, pp. 1238–1243, 2017.

[9] C. R. Schubert, M. E. Fischer, A. A. Pinto et al., "Sensory impairments and risk of mortality in older adults," The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, vol. 72, no. 5, pp. 710–715, 2016.

[10] L. Ferrucci, S. Bandinelli, E. Benvenuti et al., “Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the
M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mental State," *Journal of the American Geriatrics Society*, vol. 48, no. 12, pp. 1618–1625, 2000.

P. Pisani, F. Faggiano, V. Krogh, D. Palli, P. Vineis, and F. Berrino, "Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centres," *International Journal of Epidemiology*, vol. 26, no. 90001, pp. 1525–1560, 1997.

J. M. Guralnik, L. P. Fried, E. M. Simonsick, M. E. Lafferty, and J. D. Kasper, *The Women’s Health and Aging Study: Health and Social Characteristics of Older Women with Disability*. Bethesda, MD: National Institute on Aging, 1995.

M. E. Charlson, P. Pompei, K. L. Ales, and C. R. MacKenzie, "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation," *Journal of Chronic Diseases*, vol. 40, no. 5, pp. 373–383, 1987.

WHO Collaborating Centre for Drug Statistics Methodology, "ATC/DDD methodology: history," 1982.

S. Katz, A. B. Ford, R. W. Moskowitz, B. A. Jackson, M. W. Jaffe, and K. L. White, "Studies of illness in the aged—the index of ADL: a standardized measure of biological and psychosocial function," *Journal of the American Medical Association*, vol. 185, no. 12, pp. 914–921, 1963.

L. S. Radloff, "The CES-D Scale: a self-report depression scale for research in the general population," *Applied Psychological Measurement*, vol. 1, pp. 385–401, 1977.

M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician." *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

X. Liang, the Shanghai Aging Study (SAS), D. Ding et al., "Association between olfactory identification and cognitive function in community-dwelling elderly: the Shanghai aging study," *BMC Neurology*, vol. 16, no. 1, p. 199, 2016.

P. Mahlknecht, A. Gasperi, P. Willeit et al., "Prodromal Parkinson’s disease as defined per MDS research criteria in the general elderly community," *Movement Disorders*, vol. 31, no. 9, pp. 1405–1408, 2016.

K. Y. Peng, P. M. Mathews, E. Levy, and D. A. Wilson, "Apolipoprotein E4 causes early olfactory network abnormalities and short-term olfactory memory impairments," *Neuroscience*, vol. 343, pp. 364–371, 2017.

C. De la Rosa-Prieto, D. Saiz-Sanchez, I. Ubeda-Banon, A. Flores-Cuadrado, and A. Martinez-Marcos, "Neurogenesis, neurodegeneration, interneuron vulnerability, and amyloid-β in the olfactory bulb of APP/PS1 mouse model of Alzheimer’s disease," *Frontiers in Neuroscience*, vol. 10, 2016.

J. C. Sharma and M. Vassallo, "Prognostic significance of weight changes in Parkinson’s disease: the Park-weight phenotype," *Neurodegenerative Disease Management*, vol. 4, no. 4, pp. 309–316, 2014.

R. I. Henkin, L. Schmidt, and I. Velicu, "Interleukin 6 in hyposmia," *JAMA Otolaryngology–Head & Neck Surgery*, vol. 139, no. 7, p. 728, 2013.

P. Soysal, B. Stubbs, P. Lučato et al., "Inflammation and frailty in the elderly: a systematic review and meta-analysis," *Ageing Research Reviews*, vol. 31, pp. 1–8, 2016.

H. Li, W. Liu, and J. Xie, "Circulating interleukin-6 levels and cardiovascular and all-cause mortality in the elderly population: a meta-analysis," *Archives of Gerontology and Geriatrics*, vol. 73, pp. 257–262, 2017.