Number of pregnancies and trajectory of Frailty Index: English Longitudinal Study of Ageing.

Gotaro Kojima, PhD[1,2]; Kohei Ogawa, MD, PhD[3]; Steve Iliffe, FRCGP[2]; Yu Taniguchi, PhD[4]; Kate Walters, PhD[2].

1 Videbimus Clinic Research Center, Tokyo, Japan
2 Department of Primary Care and Population Health, University College London, London, UK
3 Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan.
4 Center for Health and Environmental Risk Research, National Institute for Environmental Studies, Tsukuba, Japan

Address for correspondence:
Gotaro Kojima, PhD
Videbimus Clinic Research Center
Shimbashi Plaza Building 2F
4-9-1 Shimbashi, Minato, Tokyo 105-0004, Japan
Phone: +81-(0)3-6447-5028
Fax: +81-(0)3-6447-5267
Email: gotarokojima@yahoo.co.jp

Keywords: Pregnancy, Parity, Frailty; Frail elderly; Trajectory.

Funding sources: ELSA has been funded by the National Institute of Aging in the United States and a consortium of UK government departments coordinated by the Office for the National Statistics, and the data are available through the UK Data Archive (http://data-archive.ac.uk). No specific funding was obtained for this research project.

ABSTRACT

Objectives: Women are frailer than men across different populations and age groups. However, the mechanisms are still not fully understood. One possible cause is pregnancy and motherhood. The objectives of this study were to examine trajectories of Frailty Index over time according to the number of pregnancies and to make a comparison between women and men.

Design: A prospective study with repeated measures over 14 years.

Setting and participants: Community-dwelling older people (2060 women and 1985 men) aged 60 years or more in England.

Methods: The number of pregnancies was calculated as a sum of the number of live births and the number of miscarriages, still-births or abortions. The Frailty Index (FI) was constructed using 60 deficits and repeatedly calculated every 2 years over 14 years. Baseline mean FI was compared between women and men. Trajectories of FI according to the number of pregnancies were estimated by a mixed-effects model.

Results: At baseline, women (mean FI=0.15) were frailer than men (mean FI= 0.12). A mixed-effects model adjusted for age, smoking, alcohol use, education and wealth showed that FI increased over time for both women and men. Among women, a higher number of pregnancies was significantly associated with a higher FI (Estimate=0.0047, 95% confidence interval (CI)=0.0020-0.0074). Men had the lowest trajectory of FI (fittest), just below the trajectory of women with no pregnancy.

Conclusions and implications: The current study showed that a higher number of pregnancies was significantly associated with a higher degree of frailty at baseline and over time. Pregnancy and child-rearing may explain some of the observed excess risk of frailty in women compared to men. Pregnancy-related factors, such as pregnancy loss, types of delivery, length of pregnancy, childbearing and childrearing, should be examined in relation to frailty in future studies.

INTRODUCTION

Frailty is a geriatric syndrome characterised by an age-related decline in multiple body systems and decreased physiological reserve.[1] This condition also leads to poor resolution of homeostasis.[1] Therefore, frail individuals are highly predisposed to multiple adverse health outcomes, such as falls,[2] disability,[3,4] fractures,[5] dementia[6] and death.[7-9] Frailty is also associated with higher use of healthcare resources[10-13] and higher healthcare costs.[14] Thus, frailty not only significantly impacts elderly people but also challenges societies and healthcare systems.[15] Due to the global population ageing, an unprecedented demographic shift towards an elderly population is ongoing.[16] With the number of frail elderly people expected to increase, the importance of frailty has been highlighted as a major public health priority.[15,17]

Gender differences exist in frailty. Although women live longer than men, women are more likely to have morbidities and disabilities.[18] In terms of frailty, women are frailer than men across different populations,[19,20] and this gender difference persists in all age groups.[21] Despite attempts by previous studies to explain the gender-frailty paradox by focusing on environmental, lifestyle, psychological or evolutionary factors,[22] the mechanisms are still not fully understood. One possible and plausible factor is reproductive history. Pregnancy is an important event in the life of women, involving multiple adaptations.[23] During pregnancy, women tend to eat differently, gain weight and exercise less,[24] and can be affected physically and psychologically in various ways.[25] Some of the consequences may persist in their later life.[26] A recent systematic review and meta-analysis paper involving over 150 thousands participants from 10 studies showed a significant association between the number of parity and cardiovascular risk.[27]

The only published cohort study on this topic examined cross-sectional associations between lifetime parity and frailty status in approximately 1,000 elderly women aged 64-75 years. However, the results were not statistically significant.[28] No longitudinal studies were found.[28] Given the limited evidence, the associations between reproductive history and frailty require further investigation. The objectives of this study were to examine frailty trajectories over time according to the number of pregnancies (live and non-live births together and separately) among community-dwelling elderly women. We also examined how differently live births and non-live births affected frailty risk.

METHOD

Design and Population

The English Longitudinal Study of Ageing (ELSA) is a panel study of a nationally representative cohort of community-dwelling men and women aged ≥50 years in England.[29] ELSA was launched and the first wave (wave 1) took place in 2002-2003. The initial participants were recruited from households participating in the Health Survey for England (HSE), an annual cross-sectional survey designed to monitor the health of the general population in England.[30] Subsequent waves were held at a 2-year interval to collect follow-up data.[29] Ethical approval for the ELSA study was granted by the National Research and Ethics Committee, and informed consent was obtained from all participants.[29]

Among 3,955 women aged 60 or older at the baseline of wave 1, 78 women were excluded due to missing frailty data at wave 1 and 1,817 women were excluded due to missing data on reproductive history, leaving 2,060 women as an analytic sample for this study.

Predictor variable: the number of pregnancies

The related information was obtained during the life history interview at wave 3 in 2006. The number of pregnancies was calculated as a sum of the number of children whom a woman had given birth to (the number of live births) and the number of miscarriages, still-births, or abortions (the number of non-live births). The number of adopted children, foster children, and step children of a partner were not considered.

Outcome variable: trajectory of frailty

The Frailty Index (FI) was used to estimate the frailty status of each participant and was measured repeatedly at waves 1 to 8 over 14 years. The FI was constructed according to a standard procedure used in previous studies[31] at each wave using 60 health deficits, which are summarised in **Supplementary Table 1**. The health deficits considered were disabilities, diseases, symptoms, or signs that covered a range of systems, were biologically sensible, accumulated with age, and that did not peak out at early ages, such as presbyopia occurring mostly by 55 years.[31] Each of the deficits was scored as 1 if the deficit was present and 0 if absent, or graded between 0 and 1 to describe the severity of the deficits. The FI was calculated by adding the scores of the deficits and dividing by the total number of the deficits available for each participant.[31] Missing deficits were excluded from both the numerator and denominator. The FI can range from 0 (no deficit) to 1 (maximum deficits present). For example, if a participant has 14 deficits present, 42 deficits absent, and missing data for 4 deficits, the FI can be calculated as 14/(14+42)=0.25.

Covariates

Covariates considered in this study included age, smoking, alcohol use, education, and wealth, and were obtained through the interview at wave 1. Age was categorised into five groups: 60-64, 65-69, 70-74, 75-79 and 80+ years old. Smoking was categorised into three groups: never smokers, past smokers and current smokers. Alcohol use was categorised into three groups: not at all/special occasions only, once a month to twice a week and almost daily or more. Education was categorised into three groups: higher education (national vocational qualification (NVQ) level 4, level 5, degree or equivalent), intermediate education (NVQ level 1/Certificate of Secondary Education equivalent, level 2/General Certificate of Education (GCE) O level equivalent, level 3/ GCE A level equivalent, higher education below degree, or foreign/other qualification) and no qualification. Wealth was measured as quintiles of total net wealth, including savings, investments, business wealth, and housing wealth, deducting financial debt and mortgage debt.

Statistical Analysis

Mean and standard deviation of FI at Wave 1 was calculated according to socio-demographic variables at Wave 1.

Trajectories of frailty over waves 1 to 8 according to the number of pregnancies were estimated by a mixed-effects model with a person-specific random intercept and slope (Stata "*xtmixed*" command), assuming an unstructured covariance matrix among repeated measurements. Linear and quadratic terms for time were tested to account for non-linear frailty trajectories over time. A better fitting with the quadratic terms for time was confirmed based on the likelihood-ratio tests. The FI scores at waves 1 to 8 were treated as a time-variant continuous variable. The number of pregnancies and covariates were treated as time-invariant variables. Models were adjusted for age, smoking, alcohol use, education, and wealth. An interaction terms between time and variable, such as the number of pregnancies, education and wealth, were tested.

In supplementary analyses, the number of live births and the number of non-live births were entered into the fully adjusted models separately as well as altogether.

All statistical analyses were performed using StataSE 14 (StataCorp LP, College Station, Texas, USA) and were based on 2-tailed tests with the significance level set at 0.05.

RESULTS

Table 1 presents the baseline characteristics of 2,060 older women. The number of women with no, 1, 2, 3, 4 and 5+ pregnancies was 254, 256, 612, 482, 250 and 206, respectively. The number of women who had the FI at each of waves 1 to 8 were 2,060, 2,004, 2,056, 1,788, 1,601, 1,410, 1,188 and 1,188, respectively. The mean FI at each wave was 0.15 [standard deviation (SD)=0.11], 0.17 (SD=0.12), 0.18 (SD=0.12), 0.18 (SD=0.12), 0.20 (SD=0.13), 0.20 (SD=0.13), 0.20 (SD=0.13) and 0.18 (SD=0.13), respectively. The number of women who had 1, 2, 3, 4, 5, 6, 7 and 8 measurements of the FI were 0, 12, 207, 226, 211, 237, 67 and 1,100, respectively.

Table 2 shows that estimated coefficients of mixed-effects models predict changes in FI over time, adjusted for age, smoking, alcohol use, education and wealth. **Figure 1** graphically depicts the trajectories of estimated FI who were between the ages of 60 and 64, never smokers, non-drinkers, with no educational qualification and in the lowest wealth quintile, according to the number of pregnancies. FI was estimated to increase over time. A higher number of pregnancies was significantly associated with a higher degree of frailty (more frail). One increase in the number of pregnancies was associated with an approximately 0.005 increase in FI (Estimate 0.0047, 95%CI=0.0020-0.0074, Standard error=0.0014). The interaction terms were observed for education and wealth. The FI trajectories with higher education and higher wealth were less steep (slower frailty progression). The interaction term between time and the number of pregnancies was non-significant, which suggests that the trajectory of FI did not change by the number of pregnancies.

As a supplementary analysis, instead of the number of pregnancies, the number of live births and the number of non-live births were entered into the fully adjusted model. Both the number of live births and non-live births were positively associated with FI. The effect of the number of non-live births (Estimate 0.0090, 95%CI=0.0029-0.0151, Standard error=0.0031, $p<0.01$) was twice stronger than that of the number of live births (Estimate 0.0041, 95%CI=0.0010-0.0072, Standard error=0.0016, p=0.01). When both variables were entered into the same model, they were still associated with FI independently (live birth: Estimate 0.0036, 95%CI=0.0005-0.0068, Standard error=0.0016, p=0.02, non-live birth: Estimate 0.0082, 95%CI=0.0021-0.0143, Standard error=0.0031, $p<0.01$).

DISCUSSION

The current study of English community-dwelling older women showed that a higher number of pregnancies was significantly associated with a higher degree of frailty over time. One extra pregnancy was associated with 0.0047 increase in FI, which means approximately 3-4 pregnancies correspond to 1 deficit. Both the higher number of pregnancies of live births and non-live births were also associated with frailty separately and independently.

It is not completely understood why women with a higher number of pregnancies were frailer in their old age. A higher number of pregnancies has been shown to be associated with increased adiposity, increased insulin resistance, decreased glucose tolerance, and elevated inflammation,[32,33] and been linked to an increased risk of diabetes[34,35] and some types of

cancer.[36,37] However, the number of pregnancies was inversely associated with developing breast cancer.[38] Some women experience complications during pregnancy, such as gestational diabetes, hypertensive disorder, pre-eclampsia and psychological problems, and those women are at increased risk of developing cardiovascular and metabolic diseases in later life.[39-41] Women with multiple pregnancies may have larger families, which could cause accumulated stress of childrearing, economic costs and role overload.[42] These factors can have complex impacts on women's health and may increase the risk of frailty.

Although there is very little evidence regarding the association between the number of pregnancies and frailty risk, multiple studies have focused on the effects of women's reproductive factors on other health outcomes. In particular, parity has been extensively studied. Dose-response meta-analysis studies showed that higher parity was linearly associated with higher risk of diabetes[34] and cardiovascular disease[27] while a J-shaped association was observed between parity and mortality with the lowest mortality risk reduction for those with 3-4 parity.[43]

This study also shows that effects of non-live birth on frailty was more than twice than that of live birth (Estimates 0.0090 vs 0.0041). It should be noted that non-live birth is different from live birth in many ways. Non-live births would not be followed by child-rearing and, if miscarriage or abortion, the duration would be shorter than pregnancy of live birth. However, women with miscarriage may have had a higher risk of frailty due to underlying poor health status.[44] Women who had a non-live birth may have been exposed to unhealthy lifestyle factors, such as smoking or obesity.[45,46] All of these factors are risk factors for both miscarriage and frailty, and may have increase the association between pregnancy and frailty risk.

Furthermore, loss of baby can be a traumatic event for women and can cause emotional distress. Pregnancy loss is shown to be associated with anxiety, depression or post-traumatic stress disorder.[47] These psychological issues may persist and have long-lasting impacts on mental wellbeing that increase frailty risk.

In this cohort of English older people, pregnancy was significantly associated with frailty in a dose-response manner. Therefore, pregnancy may explain some of the gender differencee. Other potential pathophysiology of the higher frailty risk in women includes women's higher risks of disability and sarcopenia and higher social vulnerability.[48] A combination of many of these factors can be responsible for the gender differences in frailty.

The strengths of the current study are use of data from a nationally representative sample of English older women in the community, the size of the cohort and the prospective study design. FI was constructed using 60 deficits based on standardised procedures.[31] The analyses were controlled for a range of important confounders. Supplementary analysis was conducted to explore how frailty status was affected by the consequences of pregnancies (live births vs non-live births).

However, this study is not without limitations. First, the ELSA cohort used in this study was mainly white older women in England and the findings may not be generalisable to other populations or settings. Second, the reproductive history was self-reported, therefore the data may be subject to recall bias. However, it has been shown that the self-reported reproductive history is accurate.[49] Third, types of delivery for live births and length of pregnancy for non-live births could have affected the frailty risks but these data were not available. Fourth, in

the current study, frailty was defined by the Frailty Index. In contrast to the frailty phenotype, the Frailty Index is an objective measure of accumulating deficits rather than a physiological measure.[50]

Conclusions and Implications

This study using a representative cohort of community-dwelling older women in England showed that a higher number of pregnancies was significantly associated with a higher degree of frailty at baseline and higher frailty trajectories over time. These findings are to be confirmed in other populations to enhance understanding of associations between pregnancy and frailty. Pregnancy-related factors, such as types of pregnancy loss, delivery, length of pregnancy, childbearing and childrearing, should also be examined in relation to frailty, which will lead to further elucidating the underlying gender disparity in frailty.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Acknowledgements:

ELSA has been funded by the National Institute of Aging in the United States and a consortium of UK government departments coordinated by the Office for the National Statistics, and the data are available through the UK Data Archive (http://data-archive.ac.uk).

Sponsor's role:

None.

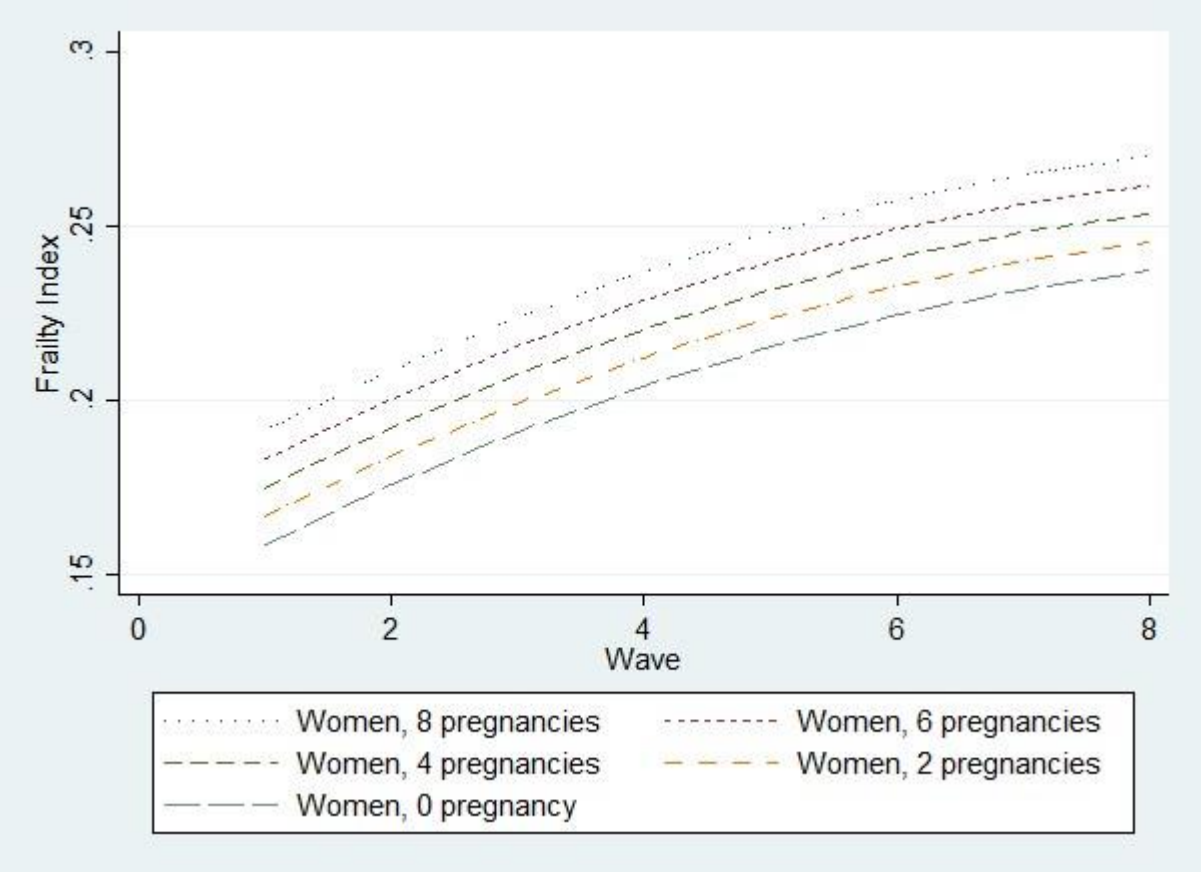
REFERENCES

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-762.
2. Kojima G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association. 2015;16(12):1027-1033.
3. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. Disability and rehabilitation. 2017;39(19):1897-1908.
4. Kojima G. Quick and Simple FRAIL Scale Predicts Incident Activities of Daily Living (ADL) and Instrumental ADL (IADL) Disabilities: A Systematic Review and Meta-analysis. Journal of the American Medical Directors Association. 2018;19(12):1063-1068.
5. Kojima G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. Bone. 2016;90:116-122.
6. Kojima G, Taniguchi Y, Iliffe S, Walters K. Frailty as a Predictor of Alzheimer Disease, Vascular Dementia, and All Dementia Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association. 2016;17(10):881-888.
7. Kojima G. Frailty defined by FRAIL scale as a predictor of mortality: A systematic review and meta-analysis. Journal of the American Medical Directors Association. 2018;19(6):480-483.
8. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age and ageing. 2018;47(2):193-200.
9. Kojima G, Taniguchi Y, Kitamura A, Shinkai S. Are the Kihon Checklist and the Kaigo-Yobo Checklist compatible with the Frailty Index? Journal of the American Medical Directors Association. 2018;19(9):797-800.
10. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association. 2015;16(11):940-945.
11. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. Journal of epidemiology and community health. 2016;70(7):722-729.
12. Kojima G. Frailty as a Predictor of Nursing Home Placement among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. Journal of Geriatric Physical Therapy. 2018;41(1):42-48.
13. Kojima G. Frailty as a Predictor of Emergency Department Utilization among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association. 2019;20(1):103-105.
14. Kojima G. Increased healthcare costs associated with frailty among community-dwelling older people: A systematic review and meta-analysis. Archives of Gerontology and Geriatrics. 2019.
15. Kojima G, Liljas A, Iliffe S. Frailty Syndrome: implications and challenges for healthcare policy. Risk management and healthcare policy. 2019;12:23-30.
16. Ageing and health, World Health Organization. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. Published 2018. Accessed 4 November, 2019.
17. Cesari M, Prince M, Thiyagarajan JA et al. Frailty: An Emerging Public Health Priority. Journal of the American Medical Directors Association. 2016;17(3):188-192.
18. Alberts SC, Archie EA, Gesquiere LR, Altmann J, Vaupel JW, Christensen K. The male-female health-survival paradox: a comparative perspective on sex differences in aging and mortality. In: *Sociality, hierarchy, health: Comparative biodemography: A*

collection of papers. National Academies Press (US); 2014.
19. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60(8):1487-1492.
20. Da Mata FA, Pereira PP, Andrade KR, Figueiredo AC, Silva MT, Pereira MG. Prevalence of Frailty in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. PloS one. 2016;11(8):e0160019.
21. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: A systematic review and meta-analysis. Exp Gerontol. 2017;89:30-40.
22. Hubbard RE. Sex Differences in Frailty. Interdiscip Top Gerontol Geriatr. 2015;41:41-53.
23. Zeng Z, Liu F, Li S. Metabolic adaptations in pregnancy: a review. Annals of Nutrition and Metabolism. 2017;70(1):59-65.
24. Dutton H, Borengasser SJ, Gaudet LM, Barbour LA, Keely EJ. Obesity in Pregnancy: Optimizing Outcomes for Mom and Baby. Med Clin North Am. 2018;102(1):87-106.
25. Walsh K, McCormack CA, Webster R et al. Maternal prenatal stress phenotypes associate with fetal neurodevelopment and birth outcomes. Proc Natl Acad Sci U S A. 2019;116(48):23996-24005.
26. Keenan K, Grundy E. Fertility History and Physical and Mental Health Changes in European Older Adults. Eur J Popul. 2019;35(3):459-485.
27. Li W, Ruan W, Lu Z, Wang D. Parity and risk of maternal cardiovascular disease: A dose-response meta-analysis of cohort studies. Eur J Prev Cardiol. 2019;26(6):592-602.
28. Gomes CS, Pirkle CM, Barbosa JFS, Vafaei A, Camara SMA, Guerra RO. Age at First Birth, Parity and History of Hysterectomy Are Associated to Frailty Status: Cross-Sectional Analysis from the International Mobility in Aging Study -Imias. J Cross Cult Gerontol. 2018;33(4):337-354.
29. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. International journal of epidemiology. 2013;42(6):1640-1648.
30. Mindell J, Biddulph JP, Hirani V et al. Cohort profile: the health survey for England. International journal of epidemiology. 2012;41(6):1585-1593.
31. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC geriatrics. 2008;8:24.
32. Zhang X, Shu XO, Gao YT, Yang G, Li H, Zheng W. Pregnancy, childrearing, and risk of stroke in Chinese women. Stroke. 2009;40(8):2680-2684.
33. Rosenberg N, Daviglus ML, DeVon HA, Park CG, Eldeirawi K. The Association between Parity and Inflammation among Mexican-American Women of Reproductive Age Varies by Acculturation Level: Results of the National Health and Nutrition Examination Survey (1999-2006). Womens Health Issues. 2017;27(4):485-492.
34. Guo P, Zhou Q, Ren L, Chen Y, Hui Y. Higher parity is associated with increased risk of Type 2 diabetes mellitus in women: A linear dose-response meta-analysis of cohort studies. J Diabetes Complications. 2017;31(1):58-66.
35. Li P, Shan Z, Zhou L et al. MECHANISMS IN ENDOCRINOLOGY: Parity and risk of type 2 diabetes: a systematic review and dose-response meta-analysis. Eur J Endocrinol. 2016;175(5):R231-245.
36. Guan HB, Wu QJ, Gong TT. Parity and kidney cancer risk: evidence from epidemiologic studies. Cancer Epidemiol Biomarkers Prev. 2013;22(12):2345-2353.
37. Guo P, Xu C, Zhou Q et al. Number of parity and the risk of gallbladder cancer: a systematic review and dose-response meta-analysis of observational studies. Arch Gynecol Obstet. 2016;293(5):1087-1096.
38. Lambertini M, Santoro L, Del Mastro L et al. Reproductive behaviors and risk of

developing breast cancer according to tumor subtype: A systematic review and meta-analysis of epidemiological studies. Cancer Treat Rev. 2016;49:65-76.
39. Brunton RJ, Dryer R, Saliba A, Kohlhoff J. Pregnancy anxiety: A systematic review of current scales. J Affect Disord. 2015;176:24-34.
40. O'Hara MW, McCabe JE. Postpartum depression: current status and future directions. Annu Rev Clin Psychol. 2013;9:379-407.
41. Neiger R. Long-Term Effects of Pregnancy Complications on Maternal Health: A Review. J Clin Med. 2017;6(8).
42. Grundy E, Read S. Pathways from fertility history to later life health: results from analyses of the English Longitudinal Study of Ageing. Demographic Research. 2015;32:107-146.
43. Zeng Y, Ni ZM, Liu SY et al. Parity and All-cause Mortality in Women and Men: A Dose-Response Meta-Analysis of Cohort Studies. Sci Rep. 2016;6:19351.
44. Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC Med. 2013;11:154.
45. Kojima G, Iliffe S, Walters K. Smoking as a predictor of frailty: a systematic review. BMC Geriatr. 2015;15:131.
46. Stenholm S, Strandberg TE, Pitkälä K, Sainio P, Heliövaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. J Gerontol A Biol Sci Med Sci. 2014;69(1):73-78.
47. Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. Hum Reprod Update. 2018;24(6):731-749.
48. Gordon EH, Hubbard RE. Differences in frailty in older men and women. Med J Aust. 2019.
49. Ellison GT, de Wet T, Matshidze KP, Cooper P. The reliability and validity of self-reported reproductive history and obstetric morbidity amongst Birth to Ten mothers in Soweto. Curationis. 2000;23(4):76-80.
50. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age and ageing. 2014;43(1):10-12.

Figure 1. Estimated trajectories of the FI over 14 years according to the number of pregnancies.



The FI was estimated for women who were aged 60-64, never smokers, non-drinkers, with no qualification and in the lowest wealth quintile.

Table 1. Baseline characteristics of 2,060 older women in England from the English Longitudinal Study of Ageing (ELSA).

Variable*	n=2,060	mean FI at Wave 1
Number of pregnancies	2.5 + 1.7 (range 0-14)	-
None	254 (12.3%)	0.14 + 0.10
1 pregnancy	256 (12.4%)	0.16 + 0.11
2 pregnancies	612 (29.7%)	0.14 + 0.11
3 pregnancies	482 (23.4%)	0.14 + 0.11
4 pregnancies	250 (12.1%)	0.16 + 0.12
5 pregnancies or more	206 (10.1%)	0.19 + 0.14
Age group		
60-64	532 (25.8%)	0.12 + 0.11
64-69	542 (26.3%)	0.13 + 0.10
70-74	448 (21.8%)	0.16 + 0.12
75-79	284 (13.8%)	0.16 + 0.12
80+	254 (12.3%)	0.19 + 0.12
Smoking		
Current smoker	269 (13.1%)	0.16 + 0.12
Past smoker	827 (40.2%)	0.16 + 0.11
Never smoker	964 (46.8%)	0.14 + 0.11
Alcohol		
None or occasionally	836 (40.6%)	0.17 + 0.13
1/month-2/week	765 (37.1%)	0.13 + 0.10
almost daily or more	459 (22.3%)	0.13 + 0.10
Wealth		
Richest	433 (21.3%)	0.11 + 0.09
2nd	426 (20.9%)	0.13 + 0.10
3rd	429 (21.1%)	0.15 + 0.10
4th	389 (19.0%)	0.17 + 0.12
5th	362 (17.8%)	0.21 + 0.13
Education		
Higher education	138 (6.7%)	0.11 + 0.08
Intermediate	891 (43.3%)	0.13 + 0.10
No qualification	1,030 (50.0%)	0.17 + 0.12

* Mean $\pm$ standard deviation or n (%). Percentages may not sum to 100% due to rounding. FI: Frailty Index

Table 2. Changes in the Frailty Index over 14 years (waves 1 to 8) among 2,060 older women by the number of pregnancies.

	Estimate	SE	95% confidence interval		p value
			lower	upper	
Intercept	0.1553	0.0090	0.1377	0.1728	<0.001
Time	0.0181	0.0008	0.0165	0.0197	<0.001
$Time^2$	-0.0010	0.0001	-0.0012	-0.0008	<0.001
Number of pregnancies	0.0047	0.0014	0.0020	0.0074	0.001

SE: Standard error. Model is adjusted for age group, smoking, alcohol use, education and wealth.

Supplementary Table 1. A list of 60 deficits used to calculated the FI.

1	Difficulty with walking 100 yards	No=0, Yes=1
2	Difficulty sitting for about two hours	No=0, Yes=1
3	Difficulty getting up from a chair after sitting for long periods	No=0, Yes=1
4	Difficulty climbing several flights of stairs without resting	No=0, Yes=1
5	Difficulty climbing one flight of stairs without resting	No=0, Yes=1
6	Difficulty stooping, kneeling, or crouching	No=0, Yes=1
7	Difficulty reaching or extending arms above shoulder level	No=0, Yes=1
8	Difficulty pulling or pushing large objects like a living room chair	No=0, Yes=1
9	Difficulty lifting or carrying weights over 10 pounds, like a heavy bag	No=0, Yes=1
10	Difficulty picking up a 5p coin from a table	No=0, Yes=1
11	Difficulty dressing, including putting on shoes and socks	No=0, Yes=1
12	Difficulty walking across a room	No=0, Yes=1
13	Difficulty bathing or showering	No=0, Yes=1
14	Difficulty eating, such as cutting up your food	No=0, Yes=1
15	Difficulty getting in or out of bed	No=0, Yes=1
16	Difficulty using the toilet, including getting up or down	No=0, Yes=1
17	Difficulty using a map to figure out how to get around in a strange place	No=0, Yes=1
18	Difficulty preparing a hot meal	No=0, Yes=1
19	Difficulty shopping for groceries	No=0, Yes=1
20	Difficulty making telephone calls	No=0, Yes=1
21	Difficulty taking medications	No=0, Yes=1
22	Difficulty doing work around the house or garden	No=0, Yes=1
23	Difficulty managing money, (e.g. paying bills and keeping track of expenses)	No=0, Yes=1
24	High blood pressure or hypertension (self-reported)	No=0, Yes=1
25	Angina (self-reported)	No=0, Yes=1
26	Heart attack (including MI or coronary thrombosis) (self-reported)	No=0, Yes=1
27	Congestive heart failure (self-reported)	No=0, Yes=1
28	A heart murmur	No=0, Yes=1
29	An abnormal heart rhythm (self-reported)	No=0, Yes=1
30	Diabetes or high blood sugar (self-reported)	No=0, Yes=1
31	A stroke (cerebral vascular disease) (self-reported)	No=0, Yes=1
32	Chronic lung disease such as chronic bronchitis or emphysema (self-reported)	No=0, Yes=1
33	Asthma (self-reported) *	No=0, Yes=1
34	Arthritis (including osteoarthritis , or rheumatism) (self-reported)	No=0, Yes=1
35	Osteoporosis, sometimes called thin or brittle bones (self-reported)	No=0, Yes=1
36	Cancer or a malignant tumor (excluding minor skin cancers) (self-reported)	No=0, Yes=1
37	Parkinson's disease (self-reported)	No=0, Yes=1
38	Any emotional, nervous or psychiatric problems (self-reported) *	No=0, Yes=1
39	Alzheimer's disease (self-reported)	No=0, Yes=1
40	Dementia, organic brain syndrome, senility or any other serious memory impairment (self-reported)	excellent=0, very good=0.2, good=0.4, fair=0.6, poor=0.8, blind=1
41	Self-reported eyesight (while using lenses, if appropriate)	No=0, Yes=1, very good=0.25, good=0.5, fair=0.75, poor=1
42	Self-reported hearing (while using hearing aid if appropriate)	No=0, Yes=1
43	Whether respondent has fallen down at all /last year /last 2years	No=0, Yes=1
44	Whether respondent has fractured hip ever /in last 2 years	No=0, Yes=1
45	Whether respondent has had joint replacement ever	Yes=0, No=1
46	Identify today's date: day of month	Yes=0, No=1
47	Identify today's date: month	Yes=0, No=1
48	Identify today's date: year	Yes=0, No=1
49	Identify the day of the week?	No=0, Yes=1

50	Often troubled with severe pain	
51	Lost any urine beyond your control in last 12 months	No=0, Yes=1
52	Whether respondent has felt depressed much of the time during past week	No=0, Yes=1
53	Whether respondent felt everything they did during the past week was an effort	No=0, Yes=1
54	Whether respondent felt their sleep was restless during the past week	No=0, Yes=1
55	Whether respondent was happy much of the time during the past week	Yes=0, No=1
56	Whether respondent felt lonely much of the time during the past week	No=0, Yes=1
57	Whether respondent enjoyed life much of the time during the past week *	Yes=0, No=1
58	Whether respondent felt sad much of the time during the past week	No=0, Yes=1
59	Whether respondent could not get going much of the time during the past week	No=0, Yes=1
60	General health	Very good=0, Good=0.25, Fair=0.5, Bad=0.75, Very bad=1