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**Milk intake across adulthood and muscle strength decline from mid- to late
life: the MRC National Survey of Health and Development**

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Short title: Milk intake and muscle strength decline

22 **Abstract**

23 Milk is a source of several nutrients which may be beneficial for skeletal muscle. Evidence that links
24 lower milk intake with declines in muscle strength from midlife to old age is lacking. We used data from
25 the MRC NSHD to test sex-specific associations between milk consumption from age 36 to 60-64 years,
26 low grip strength (GS) or probable sarcopenia, and GS decline from age 53 to 69 years. We included 1340
27 men and 1383 women with at least one measure of both milk intake and GS. Milk intake was recorded in
28 5-day food diaries (ages 36, 43, 53 and 60-64), and grand mean of total, reduced-fat and full-fat milk each
29 categorised in thirds (T1 (lowest) to T3 (highest), g/day). GS was assessed at ages 53, 60-64, and 69, and
30 probable sarcopenia classified at age 69. We employed logistic regression to examine the odds of
31 probable sarcopenia, and multilevel models to investigate decline in GS in relation to milk intake thirds.
32 Compared with T1, only T2 (58.7-145.2g/day) of reduced-fat milk was associated with lower odds of sex-
33 specific low GS at age 69 (OR (95% CI): 0.59 (0.37, 0.94), p=0.03). In multilevel models, only T3 of
34 total milk (≥ 237.5 g/day) was associated with stronger GS in midlife in men (β (95% CI) = 1.82 (0.18,
35 3.45)kg, p=0.03) compared with T1 (≤ 152.0 g/day), but not with GS decline over time. A higher milk
36 intake across adulthood may promote muscle strength in midlife in men. Its role in muscle health in late
37 life needs further examination.

38

39 **Key words:** skeletal muscle, grip strength, probable sarcopenia, milk, reduced-fat milk, full-fat milk, cohort
40 study, ageing.

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45 **Introduction**

46 Recent evidence from nutritional epidemiology and intervention studies supports a protective role
47 of nutrient-rich whole foods in skeletal muscle ageing⁽¹⁾. Milk is a whole food that, as part of a healthy
48 diet throughout the life course, provides a combination of nutrients and non-nutrients beneficial for
49 health⁽²⁾. Specifically, milk is a source of fast and slow digestible proteins, and contains 20% whey and
50 80% of caseins, that have been shown to stimulate muscle protein synthesis (MPS) via the mammalian
51 target of rapamycin (mTOR) pathway, alone or in combination with resistance exercise, in both young
52 and older adults^(3,4). Whilst whey proteins are rapidly digested and release essential amino acids (EAA)
53 such as leucine—the main regulator of MPS⁽⁵⁾—casein proteins are absorbed slowly and may support
54 extended hyperaminoacidemia prolonging the anabolic response⁽⁶⁾. We have recently hypothesised about
55 the myoprotective potential of other milk constituents beyond pro-anabolic effects of milk proteins,
56 including anti-oxidative, anti-inflammatory, and immunomodulating capacity of milk bioactive
57 components⁽⁷⁾, which may act cumulatively and synergistically in increasing the importance of milk for
58 skeletal muscle health in older adults. For example, several milk-derived peptides, minerals, lipids and
59 fatty acids have anti-oxidative and anti-inflammatory properties thus contributing to the antioxidant
60 capacity of a healthy diet by reducing oxidative damage to key organelles and molecules in ageing
61 myofibers⁽⁸⁾, and attenuating inflammaging—a chronic low-grade inflammation that underlies the ageing
62 process and contributes to the pathology of many age-related diseases, including those of muscle⁽⁹⁻¹³⁾.

63 Cellular processes of oxidative stress and inflammation have been implicated in the
64 pathophysiology of sarcopenia⁽¹¹⁾, a condition characterised by a progressive and generalised loss of
65 skeletal muscle strength and mass⁽¹²⁾. Based on the current European consensus definition of sarcopenia,
66 reduced muscle strength—assessed by grip strength (GS)⁽¹²⁾ or chair stands⁽¹³⁾—is the primary indicator of
67 probable sarcopenia (e.g., defined as sex-specific low GS) in older adults, which can occur both acutely
68 (e.g., after hospitalisation with an acute illness) or progressively (e.g., with ageing). GS, a primary and
69 easily obtained measure of muscle strength, increases steadily across early adulthood, peaks in the third or

70 fourth decade of life, plateaus thereafter, and declines rapidly after the fifth decade in both men and
71 women^(14,15). Midlife is recognised as a critical period of life when individuals experience a change in
72 muscle strength from relative stability to progressive decline⁽¹⁵⁾, whilst better midlife health⁽¹⁶⁾ and
73 healthier lifestyle (e.g., healthier diets) have been linked to better muscle health and function in later
74 life⁽¹⁷⁾. Investigating the variability in muscle strength (GS) and associated modifiable lifestyle factors
75 such as milk intake during this period of life could inform primary prevention strategies for sarcopenia.

76 We have recently highlighted a gap in knowledge in nutritional epidemiology from observational
77 studies, that is the role of whole foods, including milk, in muscle health (defined in terms of muscle
78 strength, mass, function, and sarcopenia), and utilising a life course approach^(1,7). Although nutrition plays
79 a key role in several disorders of muscle, surprisingly little is known about how nutrient-rich foods (e.g.,
80 milk, meat, seafood, eggs, whole grains, legumes) that are consumed over adulthood and provide a mix of
81 beneficial micro- and macronutrients and biologically active components⁽¹⁸⁾ may influence muscle health
82 parameters in late life. In particular, there is a lack of prospective studies investigating the association
83 between milk intake across adulthood and sex-specific changes in muscle strength from mid- to late life—
84 here midlife being identified as a starting point of GS decline⁽¹⁵⁾ in both sexes. Our objective was to
85 address this important evidence gap, by using available longitudinal data from the Medical Research
86 Council (MRC) National Survey of Health and Development (NSHD) to test whether milk intake from
87 age 36 to 60-64 years was associated with risk of probable sarcopenia (i.e., sex-specific low grip GS) and
88 GS decline from age 53 to 69 years in men and women.

89

90 **Materials and methods**

91 *Study population*

92 The MRC NSHD, also known as the 1946 British Birth Cohort, is a social-class-stratified random
93 sample of all singleton births in England, Wales, and Scotland during the first week of March 1946. The
94 5362 participants (2815 male, and 2547 female) have been followed up prospectively since birth^(19,20).
95 Medical, social, educational, and other data, including tests of functional capacity (from mid- to late life),
96 anthropometry, and diet have been collected throughout life via home visits by research nurses, medical
97 examinations during clinical visits, and postal questionnaires^(19,20). The cohort has been assessed on up to
98 24 occasions most recently in 2015 at age 69 years (for details see Supplementary Methods in
99 Supplementary Material)⁽²¹⁾.

100 ***Ethics***

101 The MRC NSHD study was conducted according to the guidelines laid down in the Declaration
102 of Helsinki. Relevant ethical approvals have been obtained for each data collection, with the most recent
103 data collection at age 68-69 years approved by Queen Square Research Ethics Committee (13/LO/1073)
104 and Scotland A Research Ethics Committee (14/SS/1009) and participants provided written informed
105 consent. Written informed consent was obtained from each participant at each data collection. No
106 additional ethical approvals were required for these secondary analyses of the MRC NSHD data.

107 ***Dietary assessment***

108 Details about dietary assessments for this cohort have been published previously^(22,23). Briefly,
109 dietary data were collected using 5-day diet diaries on four occasions when participants were age 36
110 (1982), 43 (1989), 53 (1999), and 60-64 years (2006-2011). All foods and drinks consumed, including
111 animal milks by fat content and type (whole milk, semi-skimmed milk, 1% fat milk, other animal milk
112 except cow's (e.g., goat), flavoured milk (e.g., chocolate milk)), were coded by MRC Human Nutrition
113 Research, Cambridge with the in-house programmes based on McCance and Widdowson's The
114 Composition of Foods and its Supplements⁽²⁴⁾, and gram per day (g/day) calculated. For the present study,
115 dietary data of participants who completed at least 3 days of food diary at any one age were included, and

116 intakes of each milk type at each age were calculated. A total of 3126 participants had at least one dietary
117 assessment from 36 to 60-64 years (n = 2085 at age 36, 2040 at age 43, 1742 at age 53, and 1892 at age
118 60-64 years) (**Figure 1**).

119 *Milk intake.* Only animal milks were used to calculate total milk, reduced-fat milk, and full-fat
120 milk intake (g/day) for each assessment from age 36 to 60-64 years. For reduced-fat milk, daily intakes of
121 skimmed, semi-skimmed, and 1% fat milk were combined. For full-fat milk, daily intakes of whole milk,
122 flavoured milk, and other animal milk were combined. For total milk, reduced-fat and full-fat milk intake
123 were combined for each assessment. For an average milk intake over ~28 years, grand means of intake for
124 total, reduced-fat, and full-fat milk were calculated (g/day; continuous) in 3126 participants, taking into
125 account the number of dietary assessments each participant provided. All grand mean milk variables
126 (total, full-fat, and reduced-fat milk) had a positive skew so were each categorised in thirds (T1 (lowest)
127 to T3 (highest) intake). Milk intake (g/day) by milk fat content in the analytic sample and by sex over ~28
128 years is presented in Supplementary Table 1 (Supplementary Material). Using the same approach, we
129 also calculated grand means of total milk protein and total dietary protein intake (g/day), and their
130 difference at each age to estimate the grand mean of protein intake from other foods (i.e., grand mean of
131 non-milk protein) in the analytic sample and by sex from age 36 to age 60-64 years (details in
132 Supplementary Methods and Supplementary Table 1).

133 ***Grip strength***

134 Grip strength (kg), a recommended measure of muscle strength for assessment of probable
135 sarcopenia by the European Working Group for Sarcopenia in Older People (EWGSOP2)⁽¹²⁾, was
136 assessed by nurses following standardised measurement protocols at ages 53, 60-64 and 69 years. At ages
137 53 and 60-64 years a Nottingham electronic handgrip dynamometer was used, and at age 69 years a Jamar
138 Plus+ Digital Hand dynamometer was used^(25,26), and the measurements across the two devices were
139 comparable⁽²⁷⁾. For each GS assessment from age 53 to 69 years, we used the maximum of the first four
140 measurements (two in left and two in right hand)⁽²⁶⁾ to define the outcome at each age as recommended by

141 established protocols for muscle strength (GS)⁽²⁸⁾ if at least two measurements were available⁽²⁶⁾. A total
142 of 2516 (age 53 years), 1954 (age 60-64 years), and 1944 (age 69 years) participants had valid GS
143 measures at each age (Figure 1) and those with <4 measurements were excluded.

144 We used sex-specific cut-offs for low GS (<16kg (women), <27kg (men)) to define probable
145 sarcopenia as recommended by the EWGSOP2 in 2019⁽¹²⁾. Maximum GS (kg) with absolute mean change
146 for men and women, and by sex-specific cut-offs (percentages) for low GS (probable sarcopenia) at each
147 age are presented in Supplementary Table 2 (Supplementary Material).

148 *Analytic sample*

149 Longitudinal data for both the exposure (milk) and outcome (GS) available for analyses from age
150 36 to 69 years is presented in **Supplementary Figure 1**. The maximum sample (i.e., ‘analytic sample’)
151 comprised 2723 participants (1340 (49.2%) men, and 1383 (50.8%) women) with at least one exposure
152 (milk intake from age 36 to 60-64 years) and one outcome (GS from age 53 to 69 years) (Figure 1). Risk
153 factors of muscle strength for the analytic sample were measured at midlife (age 53 years), a period in the
154 life course identified as a starting point for GS decline⁽¹⁵⁾. Age 53 years was used as baseline for change
155 in GS over time.

156 >>>Insert Figure 1 <<<<

157 *Covariates*

158 The following characteristics (variables) were included in univariable and multivariable analyses.
159 Socio-demographic factors comprised of sex, highest educational level attained (up to age 26 years), and
160 occupational class of the head of household (at age 53 years or at age 43 years if missing at 53 years).
161 Health and lifestyle factors included health conditions, BMI (kg weight/m² height, continuous), smoking
162 status, and leisure-time physical activity at age 53 years⁽²⁹⁾. We also included a variable indicating
163 attrition after age 53 years which distinguished those participants who were assessed later in life (at ages
164 60-64 and/or 69 years) from those participants assessed at age 53 who did not participate at ages 60-64

165 and 69 years to account for losses to follow-up, and calculated intakes of total milk protein at each
166 assessment and grand means of total milk protein and non-milk protein in the analytic sample and by sex
167 over ~28 years (Supplementary Methods in Supplementary Materials; Supplementary Table 1).

168 ***Statistical analysis***

169 IBM SPSS v25 (SPSS, IBM Corporation, Armonk, NY, USA) and R version 4.0.2 (R Foundation
170 for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>) were used for the analyses. The
171 analytic sample was described using descriptive statistics across key socio-demographic, health and
172 lifestyle variables. To compare men and women, we used a Student t-test for normally distributed
173 continuous variables, a Mann-Whitney U test for non-normally distributed and ordered variables, and a
174 Chi-square test for categorical variables at $\alpha < 0.05$ (Table 1). Data normality was determined by
175 examining normality statistics (skewness, kurtosis, the Shapiro-Wilk test, and Q-Q plots).

176 To examine the association between grand mean milk thirds (for total, reduced-fat, and full-fat
177 milk) and the risk of probable sarcopenia (sex-specific low GS) at age 69 years, we used logistic
178 regression (odds ratio (OR) 95% CI) (Table 2). T1 (low milk intake) was used as a reference group in all
179 models. Model 1 was unadjusted. Model 2 was adjusted for sex and occupational class; Model 3 (i.e.,
180 parsimonious model) was further adjusted for health and lifestyle variables (health conditions, BMI,
181 leisure-time physical activity).

182 To investigate the associations between grand mean milk thirds and GS initial level (at age 53
183 years) and the rate of change over 16 years, we conducted multilevel linear modelling⁽³⁰⁾, and fitted the
184 following linear growth curve models in men and women in the analytic sample (Table 3). Model 1 was a
185 ‘time’ only model and included age centred at 53 years (continuous (in years)) to test the linear trend of
186 time. Model 2 included grand milk thirds of either total, reduced-fat, or full-fat milk (to test whether
187 initial status (intercept) varied by milk thirds), and an interaction term for milk and time to test for
188 varying rates of change (slope) in GS by milk thirds. Model 3 was further adjusted for the same set of
189 covariates as described above.

190 Further details about logistic and mixed models and rationale for the inclusion of covariates (i.e.,
191 known influences of GS) are described in Supplementary Methods (Supplementary Materials).

192 *Supplementary analysis*

193 The analytic sample was further described by grand mean of total milk thirds and sex across key
194 socio-demographic, health and lifestyle variables. For comparison, we used Chi-squared tests for
195 categorical variables, Kruskal-Wallis for ordinal and non-normally distributed variables, and one-way
196 ANOVA for normally distributed, continuous variables $\alpha < 0.05$ (Supplementary Table 3). Multivariable
197 supplementary analyses employed, and the results are presented in Supplementary Methods
198 (Supplementary Methods and Supplementary Tables 4 to 10, respectively). We examined the robustness
199 of the main findings using additional covariates, imputation, and subsample analyses (Supplementary
200 Table 4 to Supplementary Table 7). We also conducted a series of regression analyses to explore the
201 cross-sectional associations between milk intake and GS (Supplementary Table 8 to Supplementary Table
202 10).

203 **Results**

204 *Sample characteristics at age 53 years*

205 The characteristics of participants in the analytic sample across a set of socio-demographic,
206 health, and lifestyle factors at age 53 years are presented in Table 1. Of 2723 participants in the sample
207 (50.8% women), over half belonged to low social class based on the occupation of the head of household,
208 whilst 10.7% had high educational attainment. Over 50% had no health conditions (from the list), and
209 34.6% reported engaging in leisure-time vigorous physical activity 5 or more times a month. Women
210 were more likely to belong to lower occupational classes ($p = 0.008$), and to have contributed to data at
211 age 60-64 and/or 69 years ($p = 0.005$) after age 53 years, whilst men had stronger GS, higher levels of
212 educational attainment ($p < 0.001$), and had fewer health conditions ($p < 0.001$) compared with women.

213 Table 1. Characteristics of the analytic sample^a by sex at age 53 years (unless otherwise stated)

Characteristics ^b	Men	Women	p ^c
Grip strength (kg), M (SD)	47.7 (12.1)	28.08 (7.8)	<0.001
<i>Socio-demographic</i>			
Sex, n (%)	1340 (49.2)	1383 (50.8)	
Highest educational level attained (by age 26)			<0.001
none	451 (35.5)	450 (34.4)	
less than O-levels	74 (5.8)	120 (9.2)	
O-levels or equivalents	187 (14.7)	354 (27.0)	
A-levels or equivalents	360 (28.3)	311 (23.7)	
Degree or higher	200 (15.7)	75 (5.7)	
Occupational class ^d			0.008
high	133 (10.1)	186 (13.7)	
intermediate	477 (36.1)	498 (36.7)	
low	710 (53.8)	674 (49.6)	
<i>Health</i>			
health conditions ^e , M (SD)	0.6 (0.7)	0.7 (0.8)	<0.001
0	731 (57.4)	654 (48.1)	
1	398 (31.2)	500 (37.3)	
2	129 (10.1)	147 (11.0)	
≥3	16 (1.3)	50 (3.7)	
BMI (kg/m ²), M (SD)	27.3 (3.9)	27.4 (5.4)	0.002
<i>Lifestyle</i>			
Smoking status, n (%)			
current	269 (21.1)	283 (21.1)	
never or former	1004 (78.9)	1059 (78.9)	
Physical activity ^f , n (%)			
none (inactive)	588 (46.2)	655 (48.8)	
1-4 times/month (intermediate)	238 (18.7)	229 (17.1)	
≥5 times/month (active)	446 (35.1)	458 (34.1)	
Grand mean of total milk, n (%)			0.02
T1 (≤153.0g/day)	421 (47.8)	460 (52.2)	
T2 (153.01-237.51g/day)	434 (46.8)	494 (53.2)	
T3 (≥237.52g/day)	485 (53.1)	429 (46.9)	
Grand mean of reduced-fat milk, n (%)			<0.001
T1 (≤58.75g/day)	423 (55.1)	354 (44.9)	
T2 (58.76-145.25g/day)	472 (48.4)	504 (51.6)	
T3 (≥145.26g/day)	445 (45.5)	534 (54.5)	
Grand mean of full-fat milk, n (%)			<0.001
T1 (≤48.22g/day)	416 (43.6)	538 (56.4)	
T2 (48.23-107.0g/day)	461 (47.9)	501 (52.1)	
T3 (≥107.01g/day)	463 (57.4)	344 (42.6)	
Attrition after age 53, n (%)			0.005
participated at age 60-64 and/or age 69	1194 (89.1)	1276 (92.3)	
did not participate at age 60-64 or age 69	146 (10.9)	107 (7.7)	

214 ^aMRC NSHD participants with at least one exposure (milk intake from age 36 to 60-64 years) and one outcome (grip strength
215 from age 53 to 69 years).

216 ^bn varies because of missing data in some variables.

217 ^cBased on adjusted residuals for categorical variables.

218 ^dBased on the head of household occupation (at age 53 and, if missing, at age 43 years) and categorised using the Registrar
219 General's Social Classification.

220 ^eKnee osteoarthritis and hand osteoarthritis, severe respiratory symptoms, and other disabling or life-threatening conditions.

221 ^fAny sports or vigorous leisure activities in the last month at age 53 years.

222

223 The characteristics of participants in the analytic sample by grand mean of total milk thirds and
224 sex are reported in Supplementary Table 3. Briefly, participants in T3 (highest intake) were more likely to
225 be men ($p = 0.02$), to have higher educational attainment ($p < 0.001$), whilst participants in T1 (lowest
226 intake) belonged to lower occupational class, were more likely to be current smokers, and had higher BMI
227 ($p < 0.001$) compared with participants in T1 and T2. Women in T1 had lower occupational class ($p =$
228 0.001), were current smokers ($p = 0.01$), and had higher BMI ($p = 0.002$) compared with women in other
229 milk thirds.

230 ***Milk intake across adulthood in the analytic sample***

231 Milk intake (total, reduced-fat, and full-fat) across adulthood (from age 36 to 60-64 years) in all
232 participants, men, and women in the analytic sample is presented in Supplementary Table 1. Total milk
233 intake was the lowest at age 36 years (M (mean) SD (standard deviation) = 195.16 (119.63) g/day), and
234 the highest at age 53 years (237.08 (141.0) g/day), and was in general higher in men than in women
235 corresponding to higher milk protein intake in men at each age. Reduced-fat milk intake increased, and
236 full-fat milk intake decreased over ~28 years, a trend reported previously in this cohort⁽²²⁾. Grand means
237 (SD) of total, reduced-fat, and full-fat milk intake across adulthood were 205.6 (104), 121.6 (96.2), and
238 86.6 (79.4) g/day, respectively. Men were more likely to belong to T3 of both total ($p = 0.02$) and full-fat
239 milk ($p < 0.001$), and to belong to T1 of reduced-fat milk ($p < 0.001$) compared with women (Table 1). In
240 general, men had higher total protein and non-milk protein intakes compared with women
241 (Supplementary Table 1).

242 ***Muscle strength from age 53 to 69 years in the analytic sample***

243 Supplementary Table 2 describes mean levels of GS and the prevalence of probable sarcopenia
244 (i.e., low sex-specific GS) at each age in the analytic sample. GS declined in both men and women
245 between ages 53 and 69 years, an absolute change in mean maximum GS (SD) of -8.06kg (11.53) in men,

246 and -4.30kg (7.95) in women. At age 69 years, the prevalence of probable sarcopenia was 6.9%, and was
 247 comparable in men and women and across other assessments (age 53, and 60-64 years) in the analytic
 248 sample (all $p \geq 0.2$; details not shown).

249 ***Milk intake across adulthood and muscle strength from age 53 to 69 years***

250 *Milk intake and probable sarcopenia at age 69 years.* Participants in T1 (≤ 58.75 g/day) of grand
 251 mean reduced-fat milk were more likely to have probable sarcopenia at age 69 years ($p = 0.049$) (details
 252 not shown). Table 2 presents the results from logistic regression models. In the parsimonious model
 253 (Model 3), only T2 (58.7-145.2g/day) of grand mean reduced-fat milk was associated with lower odds of
 254 probable sarcopenia at age 69 years (OR (95% CI): 0.59 (0.37, 0.94), $p = 0.03$) compared with T1, after
 255 adjusting for key covariates at midlife (sex, occupational class, health conditions, BMI, leisure-time
 256 physical activity). The odds for T2 remained lower (0.60 (0.37, 0.98), $p = 0.04$) after further adjustment
 257 for education, smoking status, and attrition after age 53 years in the saturated models, and after further
 258 adjustment for grand mean intakes of protein from other foods (non-milk protein) (Supplementary Table
 259 4). No associations with other types of milk (grand mean of total and full-fat thirds) were observed (Table
 260 2).

261 Table 2. The odds ratios of probable sarcopenia^a at age 69 years by grand mean milk intake thirds in the
 262 analytic sample

263

Grand mean of milk in thirds	Model 1: OR (95% CI)	p	Model 2: OR (95% CI)	p	Model 3: OR (95% CI)	p
n	1944		1924 ^b		1854 ^b	
Total milk, g/day						
T1 (≤ 153.00)	1		1		1	
T2 (153.01–237.51)	0.69 (0.44, 1.08)	0.1	0.69 (0.44, 1.08)	0.1	0.67 (0.42, 1.07)	0.1
T3 (≥ 237.52)	1 (0.66, 1.5)	0.99	0.99 (0.65, 1.51)	0.99	1.00 (0.65, 1.55)	0.99
Reduced-fat milk						
T1 (≤ 58.75)	1		1		1	
T2 (58.76–145.25)	0.59 (0.38, 0.91)	0.02	0.58 (0.37, 0.90)	0.02	0.59 (0.37, 0.94)	0.03
T3 (≥ 145.26)	0.68 (0.44, 1.04)	0.08	0.68 (0.44, 1.05)	0.08	0.69 (0.44, 1.09)	0.12
Full-fat milk						
T1 (≤ 48.22)	1		1		1	
T2 (48.23–107.00)	1.06 (0.71, 1.59)	0.77	1.07 (0.71, 1.61)	0.75	1.14 (0.75, 1.73)	0.55
T3 (≥ 107.01)	0.92 (0.58, 1.44)	0.71	0.90 (0.57, 1.42)	0.66	0.82 (0.50, 1.33)	0.42

264 ^abased on the sex-specific cut-offs for low grip strength (<27 kg in men, and <16 kg in women) [15]. 1944 participants had grip
265 strength data at age 69 years.
266 ^bMissing data for covariates: occupational class (n = 20), health conditions (n = 60), BMI (n = 7), leisure-time physical activity (n
267 = 3).
268 Model 1 is unadjusted.

269 Model 2 is adjusted for socio-demographic variables (sex and occupational class).

270 Model 3 is further adjusted for health and lifestyle variables (health conditions, BMI, and leisure-time physical
271 activity).

272 *Milk intake and change in GS over time.* Table 3 presents estimates from mixed effect models for
273 GS change (kg) over 16 years in men and women, and GS trajectories by grand mean milk thirds for
274 significant results were plotted graphically (**Figure 2, Supplementary Figure 2**).

275 In Model 3, which included the fixed effect of time (age centred at 53 years; midlife), grand mean
276 milk thirds (T1 (lowest) and T3 (highest) intake, g/day), milk × time interaction term, and key covariates
277 (occupational class, health conditions, BMI, and physical activity), T3 of total milk (≥ 237.52 g/day) was
278 associated with higher GS in midlife (β (95% CI) = 1.82 (0.18, 3.45)) in men compared with T1
279 (≤ 153.0 g/day). Trajectory of GS by grand mean total milk thirds (Model 3) in men over 16 years (i.e.,
280 between age 53 and 69) is presented in Figure 2, showing an overall decline over time, but no difference
281 in the rate of change across the milk thirds. However, these associations were not robust to additional
282 adjustments for education, smoking status, attrition after age 53 years (Saturated Model 1: 1.66 (0.01,
283 3.33), $p = 0.052$), and grand mean of non-milk protein (Saturated Model 2: 1.49 (-0.20, 3.17), $p = 0.08$)
284 (Supplementary Table 6).

285 No fixed effects of grand mean milk thirds (total milk, reduced-fat milk, full-fat milk) on GS
286 were found in women, and GS slopes did not vary by grand mean milk thirds in any of the parsimonious
287 models (Model 3; Table 3), except for T3 of reduced-fat milk in the saturated model (Supplementary
288 Table 6), showing a slower rate of GS decline compared with T1 (Supplementary Figure 2). Because of
289 large confidence intervals, the result should be interpreted with caution.

290 Table 3. β estimates of mixed models for muscle strength (grip strength) decline^a from age 53 to 69 years in by grand mean milk intake^b from mid-
 291 to late life in men and women in the analytic sample

Exposure	Effect	Model 1	p	Model 2	p	Model 3	p
Men		β (95% CI)		β (95% CI)		β (95% CI)	
<i>Total milk</i>	Time	-0.47 (-0.51, -0.42)	<0.001	-0.44 (-0.52, -0.36)	<0.001	-0.44 (-0.52, -0.36)	<0.001
<i>g/day</i>	T1 (≤ 153.0) (ref)			0		0	
	T2 (153.01-237.51)			1.30 (-0.39, 2.99)	0.13	1.07 (-0.61, 2.75)	0.21
	T3 (≥ 237.52)			1.54 (-0.1, 3.18)	0.06	1.82 (0.18, 3.45)	0.03
	Slope						
	T1 \times Time (ref)			0		0	
	T2 \times Time			-0.03 (-0.14, 0.09)	0.66	-0.02 (-0.13, 0.09)	0.72
	T3 \times Time			-0.05 (-0.16, 0.06)	0.33	-0.06 (-0.17, 0.05)	0.29
<i>Reduced-fat milk</i>	Time	-0.47 (-0.51, -0.42)	<0.001	-0.43 (-0.51, -0.34)	<0.001	-0.44 (-0.52, -0.35)	<0.001
<i>g/day</i>	T1 (≤ 58.75) (ref)			0		0	
	T2 (58.76-145.25)			1.68 (0.02, 3.33)	0.05	1.25 (-0.40, 2.9)	0.14
	T3 (≥ 145.26)			1.44 (-0.23, 3.11)	0.09	1.23 (-0.44, 2.89)	0.15
	Slope						
	T1 \times Time (ref)			0		0	
	T2 \times Time			-0.07 (-0.18, 0.05)	0.25	-0.05 (-0.17, 0.06)	0.34
	T3 \times Time			-0.05 (-0.16, 0.07)	0.40	-0.04 (-0.16, 0.07)	0.45
<i>Full-fat milk</i>	Time	-0.47 (-0.51, -0.42)	<0.001	-0.50 (-0.58, -0.42)	<0.001	-0.50 (-0.58, -0.42)	<0.001
<i>g/day</i>	T1 (≤ 48.22) (ref)			0		0	
	T2 (48.23-107.0)			-0.90 (-2.57, 0.76)	0.29	-1.02 (-2.67, 0.64)	0.23
	T3 (≥ 107.01)			0.90 (-0.77, 2.57)	0.29	1.21 (-0.45, 2.87)	0.15
	Slope						
	T1 \times Time (ref)			0		0	
	T2 \times Time			0.09 (-0.02, 0.2)	0.11	0.08 (-0.03, 0.19)	0.15
	T3 \times Time			0.01 (-0.1, 0.13)	0.80	0.01 (-0.10, 0.12)	0.86
Women							
<i>Total milk</i>	Time	-0.25 (-0.28, -0.22)	<0.001	-0.24 (-0.29, -0.19)	<0.001	-0.25 (-0.30, -0.20)	<0.001
<i>g/day</i>	T1 (ref)			0		0	
	T2			0.55 (-0.47, 1.57)	0.29	0.24 (-0.78, 1.27)	0.65
	T3			-0.15 (0.54); -1.21, 0.91	0.78	-0.21 (-1.27, 0.85)	0.70
	Slope						
	T1 \times Time (ref)			0		0	
	T2 \times Time			-0.03 (-0.10, 0.04)	0.41	0.01 (-0.06, 0.09)	0.71
	T3 \times Time			0.01 (-0.06, 0.09)	0.70	-0.03 (-1.0, 0.05)	0.48
<i>Reduced-fat milk</i>	Time	-0.25 (-0.28, -0.22)	<0.001	-0.31 (-0.37, -0.24)	<0.001	-0.31 (-0.38, -0.25)	<0.001

<i>g/day</i>	T1 (ref)			0		0	
	T2			-0.04 (-1.15, 1.06)	0.94	-0.26 (-1.37, 0.86)	0.65
	T3			-0.39 (-1.49, 0.70)	0.48	-0.45 (-1.55, 0.66)	0.43
	Slope						
	T1 × Time (ref)			0		0	
	T2 × Time			0.07 (-0.01, 0.15)	0.09	0.07 (-0.01, 0.15)	0.09
	T3 × Time			0.08 (-0.0003, 0.16)	0.051	0.08 (-0.001, 0.16)	0.053
<i>Full-fat milk</i>	Time	-0.25 (-0.28, -0.22)	<0.001	-0.24 (-0.29, -0.19)	<0.001	-0.24 (-0.29, -0.20)	<0.001
<i>g/day</i>	T1 (ref)			0		0	
	T2			0.29 (-0.68, 1.26)	0.56	0.28 (-0.69, 1.25)	0.57
	T3			-0.34 (-1.43, 0.75)	0.54	-0.26 (-1.35, 0.84)	0.65
	Slope						
	T1 × Time			0		0	
	T2 × Time			-0.02 (-0.09, 0.05)	0.52	-0.03 (-0.10, 0.04)	0.37
	T3 × Time			0.003 (-0.07, 0.08)	0.95	0.004 (-0.07, 0.08)	0.92

292 ref, reference.

293 ^aMaximum grip strength measured four times in both hands for each assessment.

294 ^bGrand mean milk thirds of total, reduced-fat, and full-fat milk from age 36 (1982) to age 60-64 (2006/2011) in participants who had complete data for milk intake (g/day) for at
295 least 3 days of a 5-day diet diary at each diet assessment.

296 Negative coefficients for grip strength indicate poorer performance.

297

298

299 Model 1 was unadjusted and included liner trend of time (age centred at 53 years), random intercepts and slopes.

300 Model 2 was further adjusted for grand mean milk thirds (total, reduced-fat, and full-fat milk, respectively) and interaction terms (grand mean milk thirds ×

301 Time).

302 Model 3 was further adjusted for socio-demographic (occupational class), health and lifestyle variables (health conditions, BMI, and leisure-time physical

303 activity).

304 >>>Insert Figure 2<<<

305 ***Supplementary analysis***

306 *Multivariate analyses with imputed covariates and in complete covariates subsample.* For
307 imputed analyses, similar results were observed in logistic models (parsimonious and saturated) showing
308 40% decreased odds of probable sarcopenia being associated with T2 (58.76-145.25g/day) of reduced-fat
309 milk in the analytic sample (Supplementary Table 4). The results were also very similar for mixed linear
310 models compared with the main analyses. T3 of total milk was associated with higher GS at baseline (age
311 53 years) in men in both the parsimonious (Model 3) and saturated models, but not with GS decline over
312 time (Supplementary Table 7). For women, T3 of reduced-fat milk showed a slower rate of GS decline in
313 both the parsimonious and saturated model (Supplementary Table 7). Large confidence intervals preclude
314 the certainty of the estimates. Over 89% of participants (n = 2445) in the analytic sample had complete
315 data for covariates. Both ORs and β estimates in the subsample were comparable to those in the main and
316 imputed analyses (Supplementary Table 5 and Supplementary Table 7, respectively).

317 *Linear regression models for milk intake and GS.* In multivariable linear regression models with
318 milk intake transformed (\sqrt{x}), we observed the following statistically significant effects sizes (β
319 coefficients) for GS (kg). Total milk intake at age 60-64 years was associated with higher GS at the same
320 age (a 0.09kg per unit increase in total milk ($\sqrt{g/day}$), $p = 0.04$) in the saturated model (Model 3;
321 Supplementary Table 8). Similar associations were found for reduced-fat milk intake after adjustment for
322 key covariates (Model 2). Total milk intake at age 36 (Model 2: $\beta = 0.04$, $p = 0.04$), 43 ($\beta = 0.02$, $p =$
323 0.02), and 60-64 years ($\beta = 0.07$, $p = 0.03$) was positively associated with GS at age 69 years. Significant
324 positive associations were also observed with full-fat milk intake at age 43 ($\beta = 0.07$, $p = 0.02$) and
325 reduced-fat milk at age 60-64 years ($\beta = 0.08$, $p = 0.009$) and GS at age 69 years (Supplementary Table
326 9). However, the grand means of milk intake across adulthood (total, reduced-fat, and full-fat) were not
327 associated with GS in late life in the adjusted models (Model 2 and 3; Supplementary Table 10).

328 **Discussion**

329 *Summary of results*

330 We investigated the relationship between milk intake across adulthood (from age 36 to 60-64
331 years) and grip strength (GS) from mid- (age 53 years) to late life (age 69 years) in 2723 participants from
332 the MRC NSHD. In multivariate analyses higher grand mean (≥ 237.5 g/day) of total milk intake was
333 associated with higher GS in midlife in men and this was maintained after adjustment for key covariates
334 including known influences on muscle strength (including sex, occupational class, BMI, health
335 conditions, physical activity)^{25,26, S1-S5}, but not with GS decline over 16 years. Additionally, higher total
336 milk intake at ages 36, 43, and 60-64 years was associated with stronger GS in late life (age 69 years). For
337 reduced-fat milk, T2 of grand mean (58.8-145.2g/day) was associated with a 40% lower risk of probable
338 sarcopenia at age 69 years after including key covariates in all participants and was robust to additional
339 adjustments, including protein intake from other food sources. No clear associations were found in
340 women.

341 *Comparison with existing literature and interpretation of results*

342 To our knowledge, this is one of a few prospective studies investigating the link between milk
343 intake (at any point in life) and muscle-related outcomes (mass, strength, physical performance,
344 sarcopenia) in late life, thus making the comparison of the findings across studies challenging. Our recent
345 narrative synthesis of epidemiological evidence revealed only three prospective studies with both milk
346 intake and muscle health parameters assessed only once throughout the life course⁽⁷⁾. The studies were
347 heterogenous and differed greatly by the period in life when milk intake was measured (from childhood to
348 late life) and how muscle health was determined in late life. Validated food frequency questionnaires
349 (FFQ) were the commonest way to estimate milk intakes (total or by fat content), which, because of
350 skewed distributions, were expressed in medians (g/day) or categories (e.g., quartiles of intake, pints in
351 categories, and per diet score category). Briefly, in the Boyd Orr study of 405 older adults (aged ≥ 70

352 years), no associations were found between total milk intake (type not specified) in midlife (none, <1/2
353 pint, 1/2 to 1 pint, >1 pint) and walking times, and higher milk intake was associated with poorer balance
354 in late life⁽³¹⁾, whilst a unit increase (1/2 pint milk/day) of full-fat milk at age 59-73 years was associated
355 with 21% lower risk of poor balance at age 66-86 years in >1000 men in the Caerphilly Prospective
356 Study⁽³¹⁾. In the Helsinki Birth Cohort Study of over 1000 adults aged ≥60 years at baseline, low
357 consumption of reduced-fat milk (<2% fat and fat-free in sex-specific quartiles of average daily intakes
358 (g/day) and as a part of a healthy Nordic diet score (NDS)) was independently associated with better
359 physical performance assessed by the Senior Fitness Test (SFT; including chair stands and arm curls) at
360 10-year follow-up in men, but not in women⁽³²⁾. However, a separate study from this cohort has shown
361 that GS was 5% and leg extension strength 7% greater in women (but not in men) who belonged to the
362 highest quartile of the NDS score compared with those in the lowest quartile, but milk was not the
363 component that contributed to these association⁽³³⁾.

364 Taken together, the results regarding the amount and type of milk (by fat content) and muscle
365 health from mid- to late life from the aforementioned observational studies were inconclusive. Similarly,
366 our results on the relationships between milk (by types and amounts in thirds) and GS in men and women
367 from mid- to late adulthood were mixed. We have found some evidence for lower risk of probable
368 sarcopenia in later life in participants consuming 59-145g/day of reduced-fat milk across adulthood (age
369 36 to 60/64 years), and not in those with higher intake. However, no clear dose-response was observed,
370 and the results need to be interpreted with caution. Associations for full-fat milk were not consistent, and
371 the total milk intake was associated with stronger GS initially (age 53 years) but not over time in men,
372 and not in women. Although we adjusted for occupational (social) class, physical activity, and disease
373 burden, the latter could be explained by marked sex differences in occupations and types of physical
374 activities undertaken by men compared to women which may benefit muscle strength, and by
375 uncontrolled confounding (e.g., differences in change in key covariates over time). Experimental evidence
376 in young adults has shown that milk with higher content of milk fats might be beneficial for muscles by
377 aiding better absorption of EAA for muscle anabolism after resistance exercise⁽³⁴⁾. Although full-fat milk

378 may be relatively easy to incorporate into a balanced diet of an older person as a nutritious and affordable
379 whole food, little is known about how milk consumption in amounts providing >20g of protein/day
380 needed to overcome anabolic resistance⁽³⁵⁾ may affect muscle health in late life.

381 Regarding reduced-fat milk intake, the results from the Helsinki cohort of older adults were
382 mixed; only lower consumption (~137g/day in the lowest quartile of the NDS, and not amounts
383 >226g/day in higher NDS quartiles) in early late life (≥ 60 years) was associated with better fitness score
384 (including muscle strength) in men a decade later, but reduced-fat milk was not a component of the NDS
385 contributing to greater GS and leg extension strength in older women⁽³²⁾. We have found some positive
386 associations between reduced-fat milk and GS, which need to be interpreted with caution as specified
387 below. Along with T2 (59-145g/day) of reduced-fat milk being associated with 40% lower odds of
388 probable sarcopenia (sex-specific low GS), other significant associations were found with higher intake at
389 age 60-64 years and greater GS at the same age and at age 69 years. However, the fixed effects estimates
390 for women belonging to T3 of reduced-fat milk (>145.3g/day) experiencing slower rate of GS decline
391 compared to those in the lowest third (saturated and imputed models; Supplementary Figure 2) were
392 uncertain although being robust to additional adjustments (including attrition and non-milk protein
393 intake). Also, the non-linear association observed in reduced-fat milk and probable sarcopenia
394 relationship (i.e., T2 of milk intake significantly associated but T3 not) may have resulted from residual
395 confounding, bias sample, or spurious findings.

396 Aside from observational studies synthesised in our previous narrative review⁽⁷⁾, we have found
397 only one additional study that investigated the association between total milk intake frequency (from FFQ
398 and 24-hour recall), muscle mass and GS in Korean adults aged 19 to 69 years belonging to three
399 population-based cohorts, including the 2008-2011 and the 2014-2016 Korean National Health and
400 Nutrition Examination Survey (KNHANES)⁽³⁶⁾. Milk intake frequencies were dichotomised to <1 a day
401 or ≥ 1 a day from ten categories (from rarely to 2-3 times a month to 3 times a day), but no amounts
402 (servings) were estimated (per the Korean Dietary Reference Intake, one serving of milk/dairy product is

403 the amount of food providing 125kcal). In the 2014-2016 KNHANES in over 13,500 individuals, those in
404 the ≥ 1 a day milk group had on average 0.8kg greater GS compared with those in < 1 a day group after
405 multiple adjustments, including age, sex, lifestyle, and number of chronic diseases. We have found some
406 evidence for the associations with total milk intake defined as either grand mean (habitual intake across
407 adulthood) or milk intake (g/day) at each time point over ~ 28 years. For grand mean in thirds, men
408 consuming ≥ 237.5 g/day (T3) had higher GS in midlife compared to those in T1 (≤ 153 g/day) in the model
409 adjusted for known influences of GS (e.g., health conditions, BMI, physical activity) reported in
410 this^(25,26,55) and other cohorts of middle aged and older adults^(S1-S4). However, the results were not robust to
411 additional adjustments (education, attrition, smoking, non-milk protein intake), and these covariates were
412 not independently associate with GS (details not shown). No associations were found for GS change over
413 16 years (from mid- to late life) or in women. Higher total milk intake at age 60-64 years was positively
414 associated with GS at the same age and at age 69 years.

415 Taken together, it could be postulated that habitual intake of milk across the life course providing
416 an exceptional mixture of nutrients, including fast-acting soluble proteins—easily delivered in a liquid
417 form and essential for muscle anabolism—may represent an important part of a balanced diet for muscle
418 health in older adults. However, the lack of prospective studies for pooled analysis and the heterogeneity
419 of the existing ones makes any assumptions about the strength of this association challenging.

420 ***Relevance of results***

421 Here we used longitudinal data from the 1946 British Birth Cohort and a broad life course
422 approach⁽³⁷⁾ to study the relationship between milk intake and muscle strength. Life course epidemiology
423 of health and disease risk posits that numerous biological and social factors throughout the life course
424 influence health and disease trajectory in adult life by acting either independently, cumulatively, or
425 interactively⁽³⁷⁾. We used milk as a cumulative exposure assessed over ~ 28 years during the period in life
426 characterised by muscle strength peak (early 30s), followed by plateau (40s), and decline (50s and later),

427 and linked it to a specific time window of progressive change in skeletal muscle with ageing (through 50s
428 to late 60s). The accumulation of exposure (milk) may result in long-term changes in biological systems
429 (muscle) and exert either positive or negative influence on the system as the duration, type and intensity
430 of exposure changes (e.g., total versus reduced-fat versus full-fat milk).

431 Using data from the birth cohort, both time in terms of lifetime (i.e., chronological age of
432 individuals) for examining GS trajectories, and historic time/period at the population level (as indexed by
433 the birth cohort membership) become important in understanding the association between milk and
434 muscle strength. Changes in the milk type preference over ~28 years in this cohort have been described
435 previously; with full-fat milk being the most commonly consumed type at age 36 years and declining
436 thereafter and reduced-fat milk intake increasing over time⁽²²⁾. Because of the prospective nature of the
437 study, it is hard to disentangle the age effect from the time/period effect, and in the case of preferring
438 reduced-fat milk over full-fat milk, this change could be explained by both availability of the new food
439 (milks with low fat content) and dietary recommendations favouring low-fat diet. With current growth in
440 consumption of plant-based milks⁽³⁸⁾, it should be acknowledged that the time/period effect on food
441 choices and consumption of new milk alternatives in the later cohorts of older adults might be greater.

442 Changes in nutrient intake from age 36 to 53 years have been also described in this cohort (e.g.,
443 decrease of fat and potassium, but increase in calcium, folic acid, vitamins C, D, and E), and explained by
444 change in the consumption of several key whole foods (e.g., increased consumption of fruits and
445 vegetables; decreased consumption of full-fat milk, butter, and red meats), which were socioeconomically
446 patterned⁽²⁴⁾. These changes need to be considered when interpreting the associations reported in this
447 study. Proposed beneficial associations between reduced-fat milk and muscle strength could be
448 confounded by or contributed to a simultaneous increase in other healthy foods and reduction of those
449 negatively associated with overall health.

450 We have chosen midlife as a potentially important period in the life course postulating that
451 midlife factors may exert strong effects on muscle health with long-lasting consequences in late life. The

452 importance of midlife, especially for modifiable lifestyle factors influencing health and disease
453 development in late life⁽³⁹⁾, including those of muscle^(16,17,40), has been recognised in a number of studies.

454 ***Strength and weaknesses***

455 This study has several strengths, including (a) longitudinal design of the NSHD with long-term
456 follow-up allowing for a life course approach; (b) repeated measures for muscle strength (GS) and diet
457 from mid to late life, including different types of milk for more complex analyses between exposure and
458 outcome); (c) prospective ascertainment of a number of potential confounders and inclusion of known
459 influences of GS; (d) representativeness of the population born in England, Scotland and Wales in the late
460 1940s⁽⁴¹⁾; (e) robust analyses of change in GS (e.g., within- and between-person change) in the maximised
461 sample to increase power. However, several weaknesses should be considered when interpreting the
462 results, including (a) bias introduced by attrition and higher rates of mortality being previously reported in
463 participants with low GS at age 53 years over 13 years of follow-up⁽⁴²⁾, and (b) higher health
464 consciousness in those completing diet diaries⁽²⁴⁾; (c) spurious findings because of a large number of
465 associations tested; (d) residual confounding such as change in key covariates (occupational class,
466 BMI, physical activity, health conditions) from mid to late life; and uncontrolled confounding (e.g.,
467 change in daily activities and quality of life close to retirement) possibly contributing to inconsistent
468 results across milk types and sexes, and (e) only linear trends being explored because of three data points
469 being available for GS change.

470 **Conclusions**

471 We aimed to investigate the associations between milk intake (total, reduced-fat, and full-fat)
472 across adulthood and change in muscle strength (GS) in mid- to late life using a birth cohort with long-
473 term follow-up. We found some evidence to suggest that a higher total milk intake was associated with
474 greater muscle strength in midlife (age 53 years) in men, and higher reduced-fat milk intake predicted
475 lower odds of probable sarcopenia (sex-specific low GS) in later life (age 69 years) compared with low

476 intake in all participants. Milk intake was not associated with change in muscle strength over time and no
477 clear associations were found in women. The results need to be corroborated in other birth cohorts of
478 ageing born in different decades and from other countries to understand the nutritional value of milk for
479 muscle health in late life and to aid future causal inference work.

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487 **Conflict of Interest**

488 None.

489 **Authorship**

490 AG: Conceptualization, Methodology, Formal analysis, Investigation, Data interpretation,
491 Writing – original draft, Visualization, Project administration; RC: Methodology, Data
492 interpretation, Writing – review & editing; RMD: Data interpretation, Writing – review & editing;
493 SJH: Formal analysis, Data interpretation; AAS: Funding acquisition, Supervision, Resources,
494 Writing – review & editing; SMR: Supervision, Data interpretation, Writing – review & editing.
495 All authors approved the final version of the manuscript.

496

497 **Figure legend**

498 **Figure 1** Flow chart of participants in the analytic sample.

499 Of 5362 singleton births recruited to the MRC National Survey of Health and Development in 1943, 3126
500 participants had at least one milk assessment across adulthood (age 36 to 60-64 years), and 2069
501 participants had at least one grip strength assessment from mid- to late life (age 53 to 69 years). Of those,
502 2723 had data for at least one measure of both and comprised the analytic sample.

503

504 **Figure 2** Estimated 16-year trajectory of grip strength by grand mean of total milk thirds across
505 adulthood in men.

506 In the model adjusted for key covariates (Model 3), only the highest intake of grand mean of total milk
507 was associated with grip strength (GS) in midlife in men, but not with GS decline over 16 years.

508 Although men in T3 ($\geq 237.52\text{g/day}$; blue line) had higher GS (kg) in midlife (age 53 years) compared
509 with those in T1 ($\leq 153.0\text{g/day}$; black line), no differences in the rate of decline in GS across the milk
510 thirds were observed over time.

511

512 **Supplementary material**

513 Additional supporting information is available at the *British Journal of Nutrition* online.

514 **Supplementary methods**

515 **Supplementary univariable analyses** (Supplementary Table 1, Supplementary Table 2, Supplementary
516 Table 3)

517 **Supplementary multivariable analyses** (Supplementary Table 4 to Supplementary Table 10)

518 **Supplementary Figures** (Supplementary Figure 1, Supplementary Figure 2)

519 Supplementary References

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