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Short report

Parental age and offspring leukocyte telomere length and attrition in midlife: Evidence from the 1946 British birth cohort

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ABSTRACT

Background: There is evidence that paternal age may influence offspring telomere length, but the joint effects of father's and mother's age are unclear. We evaluated whether parental ages, individually and jointly, were associated with offspring telomere length and shortening.

Methods: We included 2305 British birth cohort participants with measured leukocyte telomere length (LTL) at age 53, among whom 941 had a second measurement at age 60–64. Linear regressions were performed to assess the associations of father's and mother's age at birth and the parental age gap, i.e. the difference between maternal and paternal age with LTL and LTL change.

Results: A one year increase in father's age corresponded to a 0.26% (95% CI: 0.04–0.47%) increase in offspring LTL at age 53 in the sex-adjusted model. No association was observed for mother's age. Associations of father's or mother's age with offspring LTL at age 53 went to opposite directions when both parental ages were included together. For the difference in parental age, every year that fathers were older than mothers corresponded to a 0.94% (95% CI, 0.38–1.50%) increase in LTL at age 53 after adjustment for potential confounders. Neither parental ages nor the difference in parental ages were correlated with LTL change.

Conclusion: There was a joint effect of parental ages on offspring telomere length, further denoting a complex role of reproductive age in offspring health and ageing.

1. Introduction

Telomeres are the terminal part of the chromosomes containing tandem repeats of DNA sequences which maintain genomic stability (Blackburn, 2001). Telomere shortening is regarded as a hallmark of ageing and shorter leukocyte telomeres correlate to higher mortality risk in several studies (Huzen et al., 2014; Kimura et al., 2008). Telomere maintenance is determined by genetic and nongenetic factors from early life onwards (Charakida et al., 2014). Among early life factors, paternal age has been suggested as a determinant of adult telomere length, with approximately 15 to 20 base pairs longer leukocyte telomere length in the offspring for each year of paternal age at conception (Aviv and Susser, 2013).

It has been suggested that this association between paternal age and offspring telomere length may be biologically driven by elongation of sperm telomere length observed in older compared to younger men (Eisenberg, 2011). One potential explanation is that the number of sperm produced decreases with age, thereby the amount of telomerase, a key enzyme for telomere maintenance, which is divided for each remaining sperm would be greater with advancing age. The effect of maternal age is less consistent (Unryn et al., 2005; De Meyer et al., 2007). Potential biological explanations may include effects of maternal age on intrauterine stress and maternal hormonal status as these factors have been linked to telomere length in infants (Entringer et al., 2011; Entringer et al., 2015). There is a lack of knowledge of whether these associations remain when taking into account confounders such as socioeconomic position, and whether parental age influences the rate of telomere shortening. Additionally, since parental age may be correlated, associations between mother's age and telomere length may be influenced by father's age and vice versa. Therefore, it would be interesting to further assess the gap between father's and mother's age in relation to telomere length in offspring.

We investigated father's and mother's ages at birth and the difference between father's and mother's age at birth as potential predictors of leukocyte telomere length at age 53 and 60–64 in the Medical Research Council (MRC) National Survey of Health and Development (NSHD). Using two repeated measurements, we also examined telomere shortening to further gain insight into the role of parental reproductive age on offspring health and ageing.

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Table 1
Characteristics of study participants.

	All participants (N = 2162)	Participants with LTL measures at follow-up (N = 897)	Participants without LTL measures at follow-up (N = 1265)
Sex, male – N(%)	1075 (49.72)	426 (47.69)	649 (51.30)
Childhood socioeconomic position – N(%)			
Professional	139 (6.43)	63 (7.02)	76 (6.01)
Intermediate	434 (20.07)	203 (22.63)	231 (18.26)
Skilled (non-manual)	342 (15.82)	138 (15.38)	204 (16.13)
Skilled (manual)	707 (32.70)	282 (31.44)	425 (33.60)
Partly skilled	414 (19.15)	166 (18.51)	248 (19.60)
Unskilled	126 (5.83)	45 (5.02)	81 (6.40)
Father's education, higher than primary – N(%)	653 (30.20)	300 (33.44)	353 (27.91)
Mother's education, higher than primary – N (%)	475 (21.97)	214 (23.86)	261 (20.63)
Any parent smoked, yes – N(%)	851 (39.36)	334 (37.24)	517 (40.87)
Region – N(%)			
Scotland	235 (10.87)	105 (11.71)	130 (10.28)
Wales	122 (5.64)	60 (6.69)	62 (4.90)
Northern	171 (7.91)	85 (9.48)	86 (6.80)
East and West Ridings	154 (7.12)	94 (10.48)	60 (4.74)
North Western	228 (10.55)	146 (16.28)	82 (6.48)
North Midland	191 (8.83)	79 (8.81)	112 (8.85)
Midland	169 (7.68)	71 (7.92)	98 (7.75)
Eastern	166 (7.68)	55 (6.13)	111 (8.77)
London and South Eastern	486 (22.48)	131 (14.60)	355 (28.06)
Southern	111 (5.13)	24 (2.68)	87 (6.88)
South Western	129 (5.97)	47 (5.24)	82 (6.48)
Father's age at birth – Mean (SD), range	31.93 (6.40), 17–61	31.91 (6.30), 18–61	31.95 (6.47), 17–61
Mother's age at birth – Mean (SD), range	29.03 (5.66), 16–48	29.07 (5.68), 17–47	29.01 (5.65), 16–48
Parental age gap – Mean (SD)	2.90 (4.05)	2.85 (3.87)	2.94 (4.16)
LTL at age 53 (kbp) – Mean (SD)	5.66 (1.93)	5.68 (1.95)	5.65 (1.91)
LTL at age 60–64 (kbp) – Mean (SD)	–	4.30 (1.31)	–
Annual change in LTL (%) – Mean (SD)	–	−1.62 (4.49)	–

2. Methods

2.1. Study population

The NSHD is based on a nationally representative sample of 5362 births out of all the single births to married mothers that occurred in one week in March 1946 in England, Scotland, and Wales. Details on the NSHD and its follow-up have been published elsewhere (Kuh et al., 2011). Ethical approval was obtained from the Greater Manchester Local Research Ethics Committee and the Scotland Research Ethics Committee. Written informed consent was obtained from the study members.

We included 2305 study members who had follow-up assessment at age 53 and complete information on both father's and mother's age at birth, father's occupation and telomere length. Of those, 941 had a second telomere length assessment at age 60–64. Parental age gap was calculated by subtracting mother's age from father's age.

2.2. Leukocyte telomere length

DNA was extracted from frozen EDTA blood samples using Puregene DNA isolation kits (Flowgen, Leicestershire, UK). Absolute leukocyte telomere length (LTL) was measured in the same laboratory according to a previously validated real-time polymerase chain reaction technique in a blinded fashion. Measurements were performed in quadruplicate on an Applied Biosystems 7900HT Fast Real Time PCR system with 384-well plate capacity. The intra-assay coefficient of variation was 2.7% while the inter-assay coefficient of variation was 5.1%. Internal DNA controls were used to normalise assays in different runs. For participants with repeated measurements, we calculated telomere attrition as the annual percentage change in LTL (ΔLTL) as follows: $[(LTL_{60–64} - LTL_{53}) \times 100/LTL_{53})]$/interval (years).

2.3. Potential confounders

Parental sociodemographic factors were considered potential confounders in the study. The Registrar General's social class classification was used as a measure of parental socioeconomic position (SEP), based on father's occupation when the study member was aged 4, and included 6 occupational classes ranging from unskilled (class V) to professional (class I; Table S1). In addition, mother's and father's highest levels of education were dichotomised into up to or higher than primary school. Region of place of residence at birth corresponded to the civil regions used in 1946. Information on whether a parent smoked when they lived with study members was reported by adult study members.

2.4. Statistical analysis

LTL was not normally distributed and was logarithmically transformed. We ran linear regression analyses with father's and mother's ages at birth included separately as predictors of log-transformed absolute LTL at age 53, age 60–64, or ΔLTL adjusted for sex of offspring (Model 1). We repeated the analysis for LTL at age 53 in the sample with second measurements of LTL at age 60–64. We further adjusted for other potential confounders including father's social class, father's and mother's education, region of residence, and parental smoking (Model 2).

To evaluate joint parental ages effect, we first included both father's and mother's age in the same model and adjusted for the same covariates (Model 3). The variance inflation factor was estimated to check whether there was multicollinearity between mother's and father's ages, with a value above 10 commonly regarded to reflect substantial collinearity (O'Brien, 2007). Secondly, we assessed parental age gap. This analysis was subsequently adjusted for father's age and then all covariates.