Effect of parental age at birth on the accumulation of deficits, frailty and survival in older adults

RUTH E. HUBBARD, MELISSA K. ANDREW, KENNETH ROCKWOOD

Geriatric Medicine Research Unit, Dalhousie University and QEII Health Sciences Centre, 5955 Veterans’ Memorial Lane, Halifax, Nova Scotia, B3H 2E1, Canada

Address correspondence to: R. E. Hubbard. Tel: (+1) 902 473 3973; Fax: (+1) 902 473 1050.
Email: Ruth.Hubbard@cdha.nshealth.ca

Abstract

Introduction: parental age at conception may affect life expectancy. Adult daughters of older fathers seem to live shorter lives and, in one study, being born to a mother aged <25 was an important predictor of exceptional longevity. The effect of parental age on fitness/frailty in late life is unknown.

We aimed to investigate the relationships between parental age and frailty and longevity in older adults.

Methods: in the Canadian Study of Health and Aging (CSHA), data was collected on individuals aged ≥65 using a Self-Assessed Risk Factor Questionnaire and screening interview. In this secondary analysis, 5112 participants had complete data for parental age, frailty status and 10-year survival. Parental age was divided into three groups, with cut-offs at 25 and 45 for fathers and at 25 and 40 for mothers. Frailty was defined by an index of deficits. Survival was analysed using Kaplan-Meier curves and Cox regression with analyses adjusted for subject’s age, sex and age of the other parent.

Results: mean maternal age at subject’s birth was 29.2y (SD 6.8) and mean paternal age 33.3y (SD 7.8). There was no effect of maternal or paternal age on survival for either sons or daughters. Similarly, there was no association between parental age and subject frailty in old age.

Conclusion: we did not identify an association between parental age and frailty or longevity in older adult participants in the CSHA.

Keywords: frail elderly, longevity, parents

Introduction

There is increasing interest in the health and lifespan of children born to older parents. Societal, economic and technological changes in the developed world have lead to postponement of childbirth. The age at which women first become mothers is increasing: in the United Kingdom over 80% of women born in 1940 had given birth by the age of 30 compared with less than 60% of those born in the early 1970s [1]. In the United States, between 1991 and 2001, the number of first births for women 35–39 years of age increased by 36% and that for women 40–44 years increased by 70% [2].

Increased maternal age (35 years and older) is associated with adverse outcomes including higher miscarriage rates [3], increased obstetric interventions and perinatal mortality [4] and increased risk of chromosomal abnormalities [5]. Men too are delaying parenthood, also with a higher risk of adverse outcomes. In the UK, births to fathers aged 35–54 years increased from 25 to 40% of total births between 1993 and 2003 [1]. Increasing paternal age is associated with both pregnancy complications and birth defects [6]: pre-eclampsia, cleft lip and palate, neural tube defects and autosomal dominant diseases, particularly achondroplasia. Advanced parental age is also associated with diseases of complex aetiology arising in childhood (leukaemias and brain cancers [7]) and young adulthood (schizophrenia [8]).

All this has prompted interest in the effect of late reproduction on adult progeny. In Gavrilov and Gavrilova’s pioneering analyses of genealogical data on 18th- and 19th-century European nobility, parental age did not affect the lifespans of sons but adult daughters born to mothers aged older than 40 years [9] or to fathers older than 45 years [10] lived significantly shorter lives. Amongst centenarians and their siblings, exceptional longevity has been linked to birth order, a relationship driven mostly by young maternal age (>25 years) at the person’s birth [11]. Other studies
have reported contradictory results. No difference was found between the ages of parents of centenarians and controls born at the same place and time [12]. British aristocracy data contained no significant relationship between paternal age and the longevity of either sons or daughters [13].

The aims of this study were to investigate the relationship between parental age and longevity in later life and to explore the effect of parental age on fitness and frailty in older people.

Methods

Sample

The Canadian Study of Health and Aging (CSHA) is a representative study of dementia and related conditions in Canadians aged 65 years and older. Baseline assessments were conducted for 10,263 individuals in 1991, with follow-up interviews at 5 and 10 years [14]. The current study is a secondary analysis of data collected on the subsets of individuals who participated in a screening interview and completed a self-administered risk factor questionnaire. The screening interview was done for all individuals who were community-dwelling at baseline, while the risk factor questionnaire was completed only by community-dwellers without dementia. The sample for this study includes 5,112 individuals who completed the risk factor questionnaire and the screening interview, and who had complete data regarding age of each parent at the subject’s birth, the subject’s frailty status and 10-year survival (Figure 1).

Measures

Parental age (both mother’s and father’s age) at the subject’s birth was recorded as part of the risk factor questionnaire. In this analysis, parental age was divided into three groups, with cut-offs at 25 and 45 for fathers and at 25 and 40 for mothers.

Frailty was defined by an index of deficits, constructed from a list of 40 self-reported variables [15]. Briefly, potential deficits including functional impairments, illnesses, symptoms and health attitudes are scored from 0 to 1, with 0 indicating the absence of the deficit and 1 indicating its presence. For example, an individual with heart disease would be assigned 1 point for having ‘heart and circulation problems’, while another individual without such problems would be assigned 0 points for that item. Each individual’s deficit points are then summed and divided by the total number of deficits considered (here, 40), to yield a frailty index (FI) with theoretical range 0–1, with higher values indicating a greater number of problems, and hence greater frailty.

Survival was analysed using Kaplan–Meier curves and Cox regression to adjust for subject’s age, sex and age of the other parent. Analyses were done using STATA 8.1 statistical
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Figure 2. 10-year survival by parental age at birth. Panel A: survival by the mother’s age at birth. Panel B: survival by the father’s age at birth.

Participants had a mean age of 74.5 years (standard deviation 6.7); 60% were women. Those for whom parental ages were missing were older and frailer: 78.5 (SD 7.6) versus 75.3 (SD 7.2) years and mean FI 0.18 (SD 0.11) versus 0.15 (SD 0.09) (both P < 0.001). Those missing the FI were also more likely to be older: their mean age was 81.4 (SD 8.1) years versus 75.6 (SD 7.0) for those with frailty data (P < 0.001).

The mean maternal age at subject’s birth was 29.2 years (SD 6.8) and the mean paternal age was 33.3 years (SD 7.8). The mean maternal age was 29.2 years (SD 6.6) among survivors and 29.1 years (SD 7.0) among those who died during the follow-up period. The mean paternal age was 33.2 years (SD 7.6) for survivors and 33.3 years (SD 8.2) for those who died. There was no association between maternal age and survival; compared with maternal age <25, mortality HR was 0.99 (95% CI 0.87–1.12) for mothers aged 26–40 and 1.04 (95% CI 0.83–1.29) for maternal age >40. Nor was there a survival difference by paternal age; compared with paternal age <25, HR was 0.85 (95% CI 0.71–1.01) for fathers aged 25–45 and 0.92 (95% CI 0.71–1.20) for paternal age >45 (Figure 2).

Figure 3. Frailty status at baseline by parental age at birth. Panel A: mean frailty index by the mother’s age at the subject’s birth. Panel B: mean frailty index by the father’s age at the subject’s birth.

To examine the effect of parental age on frailty status at baseline (CSHA-1), participants were categorised into six groups by age: group 1 was 65–70 years, 2 = 70–75 years, 3 = 75–80 years, 4 = 80–85 years, 5 = 85–90 years and 6 = 90–95 years. Mean FI as a proportion of deficits was determined for each age group by maternal and paternal ages (Figure 3). There was no clear association between parental age and subject frailty in old age in this population.

Conclusion

Our objectives were to test whether parental age at birth could explain differences in frailty status and life expectancy at late ages. These hypotheses had been suggested by recent studies reporting an adverse effect of increased parental age on longevity of adult daughters. Our study did not identify an association between parental age and frailty or longevity in older adult participants in the CSHA.

Our data must be interpreted with caution. As in other studies investigating this field [16], parental age was self-reported by participants. Genealogical databases have been more widely used to study the influence of parental age on longevity [9, 10, 13] though this methodology also has limitations. Individuals and events may be under-registered and
females not bearing male heirs are frequently excluded [12]. Furthermore, the contemporaneous approach employed here minimised effects of secular health changes and facilitated an assessment of participant health status. Misattribution of parental age by participants raised by grandparents as if they were parents is difficult to quantify and remains a limitation of both self-reported and genealogical parental age studies.

Animal studies have provided tentative evidence for a detrimental effect of higher maternal age on offspring performance. In a study of over 200,000 Austrian cows, milk yield of daughters decreased with age of dam though other traits including functional longevity and fertility were unaffected [17]. In this study, the effect of parental age on health was measured by constructing a FI for each subject. While this is not the only approach to frailty [18], it has much to recommend it. The model conceptualises frailty as a result of multiple interacting factors [19], employing a well-defined methodology to create an index as a proportion of deficits [20]. Frailty indices can be constructed from different numbers and types of variables, allowing comparisons between datasets [21]. For example, analysis of data for 36,424 older people in four developed countries found FI values to be closely comparable across countries, increasing with age at ~3% per year in community-dwellers and correlating highly with mortality [22]. Further studies confirm that the risk of adverse outcomes is defined more precisely by deficit indices than by phenotypic definitions of frailty [23, 24]. A FI approach translates meaningfully from an epidemiological perspective to small clinical studies [25]. There is, therefore, strong evidence that the FI is a valid construct for assessing heterogeneity in the health of older people. In this study, there was no clear association between frailty in older age and parental age at birth.

Data for paternal and maternal ages for males and females were explored separately (data not shown). Previous studies reported the paternal contribution to longevity to be confined to daughters [10]. Similarly, the inheritable component of longevity seems substantially larger for daughters compared to sons [13, 26]. The reasons for this are incompletely understood, but differential genomic imprinting or an X-linked factor has been hypothesised [13, 26]. Loci on the X chromosome are protected in the germ line (they spend two-thirds of their time in oocytes rather than in sperm cells which may account for their slower mutation rate), yet vulnerable in the soma (because only one X chromosome is active in each human female cell, they lack a partner for repair by homologous recombination) [27]. Thus, the X chromosome is theoretically attractive as a site of crucial longevity genes, representing the trade-off between germ-line propagation and somatic maintenance [27]. The paternal X chromosome is inherited by daughters rather than sons which would explain the detrimental effect of high paternal age on daughters [10]. However, in this study, there was no association between advanced paternal age and survival at older ages for either sons or daughters.

There are several mechanisms by which parental age at conception may affect offspring longevity. The high initial damage load hypothesis of the reliability theory of ageing [28] predicts that differences in lifespan are linked to the rates of DNA damage in parental germ cells. Between the ages of 20 and 60, DNA repair activity decreases at a rate of 0.61% per annum [29] which may result in an accumulation of persistent DNA damage. There is experimental evidence to support this: reporter genes such as hypoxanthine-guanine phosphoribosyl transferase exhibit mutation frequency increases of 1.7% per year [30]. Furthermore, sperm of older men exhibit increase sperm DNA damage [31]. The degree of initial damage, according to reliability theory, determines ageing-related deterioration accumulating during the rest of the entire lifespan.

There are conflicting factors which may be beneficial to children born to older parents. The ability to bear children later in life is associated with increased longevity in both sexes. Women who lived to at least 100 were four times more likely to have had children while in their 40s than women who survived until age 73 [32], and daughters born to longer lived fathers were not affected by late paternal age at conception [10]. Increased longevity has a moderate to strong heritable component [33]. The increased longevity of older parents may be inherited by offspring to compensate for adverse effects of any parental germ cell damage.

Maternal age and, even more strongly, parity are positively correlated with birth weight [34]. Low birth weight is a significant determinant of many adult diseases, particularly coronary artery disease and diabetes mellitus [35]. Thus, children born to older mothers may have health and longevity advantages according to Barker’s fetal origins of disease hypothesis [35].

Currently, older parents are more affluent with higher educational attainment [6]. This socioeconomic profile impacts positively on child and adult health status [36]. However, there is no evidence that delayed parenthood was associated with higher socioeconomic status at the beginning of the 20th century, when participants of this study were born.

In summary, our study did not find an association between parental age at birth and survival or frailty in older adults. The pathways to frailty, like those to ageing itself, are complex and incompletely understood. An exploration of the factors that influence health in later life is the foundation of future enquiries by our group.

Key points

- Increased parental age is associated with pregnancy complications, chromosomal abnormalities and an increased risk of diseases of complex aetiology arising in childhood and young adulthood.
- Recent studies investigating the effect of parental age on longevity at older ages have yielded contradictory results.
- We found no association between parental age and frailty or longevity in older adult participants in the CSHA.
- Theoretically, the detrimental effect of higher initial load of germ cell damage of older parents may be offset by the increased longevity of those able to bear children later in
life and the pervasive positive impacts of increased birth weight and higher socioeconomic status.

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Conflicts of interest

No conflicts of interest.

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References

The course of delirium in acute stroke

JOHN MCMANUS1, ROHAN PATHANSALI1, HARDI HASSAN1, EMMA OULDRED1, DEREK COOPER2, ROBERT STEWART3, ALASTAIR MACDONALD1, STEPHEN JACKSON1

1Department of Clinical Gerontology, Clinical Age Research Unit, King’s College Hospital NHS Foundation Trust, Denmark Hill, Bessemer Road, London, SE5 9PJ, UK
2Graduate Training Office, Franklin-Wilkins Building, King’s College, Stamford Street, London, SE1 9NH, UK
3King’s College London (Institute of Psychiatry), De Crespigny Park, Denmark Hill, London, SE5 8AF, UK

Address correspondence to: J. McManus. Tel: (+44) 203 2993420; Fax: (+44) 203 2993441. Email: john.mcmanus@kch.nhs.uk

Abstract

Background and purpose: several studies have assessed delirium post-stroke but conflicting results have been obtained. Also, the natural history and outcome of delirium post-stroke need to be fully elucidated.

Methodology: eligible stroke patients were assessed for delirium on admission and for four consecutive weeks using the Confusion Assessment Method (CAM). Risk factors for delirium were recorded. Our outcome measures were length of stay, inpatient mortality and discharge destination.

Results: of 110 eligible patients, 82 were recruited over 7 months. Delirium was detected in 23 patients (28%); 21 of these were delirious on their first assessment. Sixty-nine per cent of patients who had four weekly assessments were delirious at 4 weeks. Multivariate logistic regression analysis was performed, and two models were identified. With unsafe swallow in the analysis, delirium was associated with an unsafe swallow on admission (OR 28.4, \( P < 0.001 \)), Barthel score \(< 10 \) (OR 32.1, \( P = 0.004 \)) and poor vision pre-stroke (OR 110.8, \( P = 0.01 \)). With unsafe swallow removed from the analysis, delirium was associated with an admission C-reactive protein (CRP) \( > 5 \) mg/l (OR 10.2, \( P = 0.009 \)), Barthel score \(< 10 \) (OR 46.5, \( P = 0.001 \)) and poor vision pre-stroke (OR 85.2, \( P = 0.01 \)). Delirious patients had a higher mortality (30.4% vs. 1.7%, \( P < 0.001 \)), longer length of stay (62.2 vs. 28.9 days, \( P < 0.001 \)) and increased risk of institutionalisation (43.7 vs. 5.2%, OR 14, \( P < 0.001 \)).

Conclusions: delirium is common post-stroke. Most cases develop at stroke onset and remain delirious for an appreciable period. Delirium onset is associated with stroke severity (low admission Barthel), unsafe swallow on admission, poor vision pre-stroke and a raised admission CRP. Delirium is a marker of poor prognosis.

Keywords: stroke, delirium, cognition, elderly

Background

Although stroke is a known predisposing factor for delirium, there have only been a few prospective studies of delirium in the acute stroke setting and these have given conflicting results with prevalence estimates ranging from 13 to 48% [1–5]. In addition, different independent risk factors for delirium post-stroke have been identified including left-sided...