Original Research Article

Increasing Parental Age at Childbirth is Associated with Greater Insulin Sensitivity and More Favorable Metabolic Profile in Overweight Adult Male Offspring

BENJAMIN B. ALBERT,[1] MARTIN DE BOCK,[1] JOSÉ G.B. DERRAIK,[1] CHRISTINE M. BRENNAN,[1] JANENE B. BIGGS,[1] PAUL L. HOFMAN,[1,2] AND WAYNE S CUTFIELD[1,2]*
[1]*Liggins Institute, University of Auckland, Auckland, New Zealand*
[2]*Gravida: National Centre for Growth and Development, Auckland, New Zealand*

Objective: To assess the effect of parental age at childbirth on insulin sensitivity and other metabolic outcomes in overweight middle-aged males.

Methods: We studied 73 men aged 46.0±5.4 years, who were overweight (body mass index, BMI 25–30 kg/m^2) but otherwise healthy. Insulin sensitivity was assessed by the Matsuda method from an oral glucose tolerance test. Other assessments included dual-energy X-ray absorptiometry-derived body composition, lipid profile, 24-hour ambulatory blood pressure, and carotid intima-media thickness. Maternal and paternal ages were highly correlated ($r = 0.71$; $P < 0.0001$), and the main parameter of interest in this study was the mean parental age at childbirth (MPAC), calculated as the average of maternal and paternal ages.

Results: Increasing MPAC was associated with a continuous increase in insulin sensitivity ($\beta = 0.193$; $P = 0.008$), as well as reductions in insulin resistance (HOMA-IR; $\beta = -0.064$; $P = 0.011$), fasting insulin ($\beta = -0.221$; $P = 0.018$) and fasting glucose ($\beta = -0.030$; $P = 0.033$) concentrations. Increasing MPAC was also associated with reductions in night time systolic ($\beta = -0.500$; $P = 0.020$) and diastolic ($\beta = -0.325$; $P = 0.047$) blood pressure, as well as with improved (greater) nocturnal diastolic blood pressure dipping ($\beta = 0.413$; $P = 0.046$). Subgroup analyses on participants of European descent ($n = 64$) showed that increasing MPAC was associated with reduced carotid intima-media thickness ($\beta = -0.008$; $P = 0.018$) and lower low-density lipoprotein cholesterol concentrations ($\beta = -0.042$; $P = 0.028$).

Conclusions: Increasing parental age at childbirth was associated with a more favorable metabolic phenotype in overweight middle-aged males. However, it is unknown whether the effect was maternal, paternal, or both. Future studies on the effects of parental age at childbirth on the metabolism of males and females across the BMI range are required. Am. J. Hum. Biol. 27:380–386, 2015.

There has been a progressive increase in parental age at childbirth in most western societies, so that more couples are having children in their thirties and forties (Mills et al., 2011). In the United States, the proportion of births occurring to women over 35 years has increased from 9% in 1990 to 14% in 2008 (Livingston and Cohn, 2010). Data from OECD countries show a considerable shift in the mean maternal age at first childbirth over the last 40 years, for example, rising by 5.2 years in Iceland and 4.8 years in the Czech Republic (Mills et al., 2011).

Although much attention has been given to the increase in maternal age at childbirth, an upwards shift in paternal age is also taking place (Savage et al., 2014). However, paternal age at childbirth is not routinely recorded in birth registries, and such data are consequently scarce. In England and Wales, mean paternal age reportedly increased from 29.2 years in 1980 to 32.1 in 2002 (Bray et al., 2006). In Germany, the median age of married fathers increased from 31.3 to 33.1 years between 1991 and 1999 (Kuhnert and Nieschlag, 2004).

Increasing parental age at childbirth has been linked to adverse outcomes in the offspring, including genetic disease (Bray et al., 2006), malignancy and mental health disorders (Mintziori et al., 2013). Further, there is strong evidence that older paternal age also has important long-term effects on offspring health (Curley et al., 2011), such as increased risk of autism (Hultman et al., 2011). A variety of mechanisms could mediate the health effects of greater parental age, including epigenetic changes (Curley et al., 2011; Hamatani et al., 2004) and direct effects of the pre- and postnatal environments.

There are limited and conflicting data on the effects of parental age at childbirth on offspring body composition and metabolism. Recently, increasing parental age at childbirth was found to be associated with taller stature and reduced central adiposity in children (Savage et al., 2013, 2014). Further, girls born to older mothers appeared to have improved insulin sensitivity as assessed by HOMA-IR (Savage et al., 2013). However, increased maternal age at childbirth has been linked to higher blood pressure in childhood (Lawlor et al., 2004), and increased paternal age was associated with a less favorable lipid profile in prepubertal children (Savage et al., 2014). In young adults, a large cross-sectional study in men found a greater rate of obesity with increasing paternal age (Eriksen et al., 2013), while increasing maternal age was associated with higher risk of type 2 diabetes (Lammi et al., 2007).

Contract grant sponsor: University of Auckland (TECHNZ grant); Contract grant number: UniS 30475.001); Contract grant sponsor: New Zealand Ministry of Science and Innovation; The Douglas Charitable Trust.

*Correspondence to: Wayne Cutfield, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand.
E-mail: w.cutfield@auckland.ac.nz

Received 17 July 2014; Revision received 16 September 2014; Accepted 15 October 2014

DOI: 10.1002/ajhb.22654
Published online 13 November 2014 in Wiley Online Library (wileyonlinelibrary.com).

Thus, although there is some evidence suggesting older parenthood may have favorable metabolic effects in the offspring, the evidence is conflicting and the long-term metabolic implications for the offspring of older parents remain unclear. In particular, there are no data on associated metabolic outcomes in the offspring in adulthood. It is important to assess whether the differences observed in childhood studies (Savage et al., 2013, 2014) persist into adult life. Therefore, we assessed the impact of parental age at childbirth on insulin sensitivity and other metabolic outcomes in a cohort of overweight middle-aged males.

Methods

Ethics approval

Ethics approval was provided by the Central and Northern Y Regional Ethics Committees (Ministry of Health, New Zealand) and the University of Auckland Human Participants Ethics Committee. Written informed consent was obtained from all participants. This study was performed in accordance with all appropriate institutional and international guidelines and regulations for medical research, in line with the principles of the Declaration of Helsinki.

Participant and recruitment

Participants were recruited for two clinical trials investigating the metabolic effects of nutritional supplementation with olive leaf extract (de Bock et al., 2013) or krill oil (Fig. 1). This study encompasses a *post hoc* analysis of their pretrial baseline data. Volunteers were recruited in 2011 and 2012 using advertisements in local newspapers that circulate freely in the central Auckland metropolitan area (New Zealand). Middle-aged men (35–55 years) who were overweight [body mass index (BMI) 25–30 kg/m^2] were eligible to participate. Only males were recruited to avoid the effects of the menstrual cycle and/or oral contraceptives on the primary outcome (insulin sensitivity). Exclusion criteria were: diabetes mellitus, hypertension (systolic blood pressure >145 mmHg or diastolic blood pressure >95 mmHg), known dyslipidemia, the use of tobacco, or prescription medications likely to affect blood pressure, lipid profile, or insulin sensitivity. From this group, all participants born at term (37–41 weeks of gestation) from singleton pregnancies, who knew the age of both parents when they were born, were included.

Clinical assessments

Clinical assessments were carried out at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Insulin sensitivity was assessed via an oral glucose tolerance test using the Matsuda method (Albert et al., 2014; Matsuda and DeFronzo, 1999). The Matsuda index is strongly correlated with the hyperinsulinemic euglycemic clamp (Lorenzo et al., 2010) and it is highly reproducible during multiple measures (Maki et al., 2010). Fasting blood samples were used to measure triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations. Assays were as described in Albert et al. (2014).

Height was measured with a Harpenden stadiometer. Weight and body composition were assessed using whole-body dual-energy X-ray absorptiometry (DXA, Lunar Prodigy 2000, General Electric, Madison, WI). Body composition data of interest were total percentage body fat and the ratio of android fat to gynoid fat (a marker of abdominal adiposity).

Twenty-four-hour ambulatory blood pressure monitoring was carried out prior to the clinical assessment using a Spacelabs 90207 or 90217 monitor (Spacelabs Medical, Redmond, WA). Carotid artery intima-media thickness was measured using a M-Turbo ultrasound system (Sonosite, Bothel). Protocols for both assessments were as per Albert et al. (2014). Physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ) (Hagstromer et al., 2006). Socioeconomic status was determined by geo-coded deprivation scores derived from current address, using the New Zealand Index of Deprivation 2006 (NZDep2006) (Salmond et al., 2007).

Statistical analysis

Maternal and paternal ages are highly correlated, and in this relatively small cohort it would not be possible to differentiate their individual effects on study outcomes. Thus, the main parameter of interest was the mean parental age at childbirth (MPAC), calculated as the average of maternal and paternal ages. However, it was important to account for the age gap between parents, and whether the father or the mother was older. Thus, another parameter was calculated, which was the age difference between mother and father, where a negative difference indicated a mother who was older than the father.

Descriptive statistics were obtained in Minitab v.16 (Pennsylvania State University, State College, PA) and are presented as means ± standard deviations. Multivariate linear regression models were carried out in SAS v.9.3 (SAS Institute, Cary, NC). All models accounted for important confounding factors, namely age of the offspring at assessment, physical activity levels (IPAQ), socioeconomic status (NZDep2006), birth order, as well as parental age difference. In addition, BMI was controlled for when assessing potential differences in lipid concentrations and outcomes associated with glucose homeostasis. Subgroup analyses were carried out solely on data for participants of European ethnicity. Where necessary, outcome parameters were log-transformed to approximate normality. All statistical tests were two-tailed and significance level maintained at 5%.

Results

Demographics

There were 97 subjects in both trials, but since five men took part in both studies, there were 92 individuals enrolled. We consequently studied a total of 73 men who met the inclusion criteria and knew the age of both biological parents. When study participants were compared to the 19 excluded subjects, there were no significant differences in age, ethnic composition, socioeconomic status, body composition, insulin sensitivity, blood pressure, or lipid profile between groups.

Participants were aged 46.0 ± 5.4 years (range 34.5–55.6 years), and most (88%) were of European ethnicity. The characteristics of the study cohort are provided in Table 1.

Maternal age at childbirth was 27.6 ± 5.3 years (range 18–45 years) and paternal age was 30.7 ± 5.7 years (range 19–45 years) (Fig. 1), with maternal and paternal

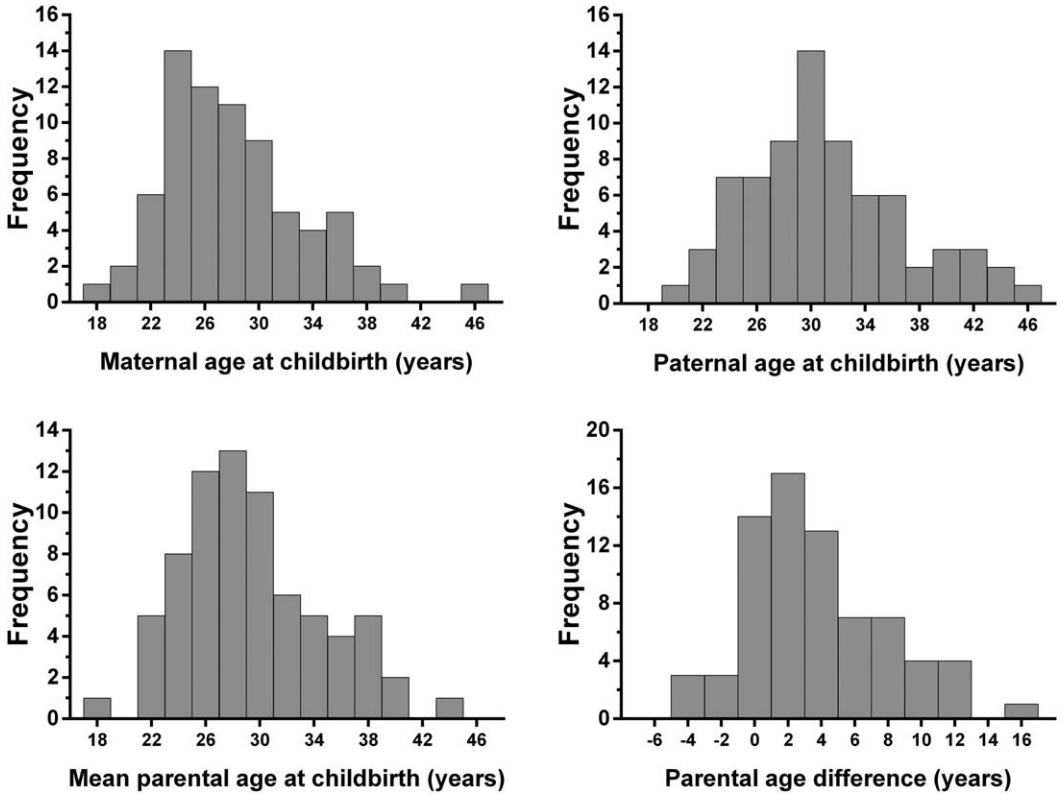

Fig. 1. Distribution of parental ages at childbirth in the studied cohort (n = 73). For parental age difference, negative values indicate a mother older than the father.

TABLE 1. Characteristics of the study population (n = 73)

Outcome response	Mean	SD	Range
Diet and lifestyle			
Physical activity levels (IPAQ)	3,716	3,728	66–19,490
Total energy intake (kJ/day)	9,875	2,798	3,313–17,378
Saturated fat intake (g/day)	32.3	13.1	6.2–64.5
Anthropometry			
Weight (kg)	88.6	9.5	66.2–111.8
BMI (kg/m^2)	27.6	1.8	25.0–30.0
Glucose homeostasis			
Insulin sensitivity (Matsuda index)	6.82	3.85	1.31–17.0
HOMA-IR	1.74	1.27	0.37–6.42
HOMA-β (%)	80.2	43.6	13.7–198
Fasting insulin (mU/l)	7.20	4.79	1.68–24.3
Fasting glucose (mmol/l)	5.33	0.56	4.16–7.57
Glucose 120 min (mmol/l)	5.70	1.70	2.47–10.8
Cardiovascular parameters			
Daytime systolic blood pressure (mmHg)	126.4	9.1	107.0–160.0
Daytime diastolic blood pressure (mmHg)	80.2	6.6	69.0–107.0
Night time systolic blood pressure (mmHg)	110.5	8.9	89.0–138.0
Night time diastolic blood pressure (mmHg)	67.0	6.7	53.0–88.0
Night time systolic blood pressure dip (%)	12.6	5.7	1.6–30.0
Night time diastolic blood pressure dip (%)	16.5	7.4	0.0–41.2
Carotid intima-media thickness (mm)	0.800	0.165	0.459–1.436
Lipid profile			
Total cholesterol (mmol/l)	5.06	0.90	3.21–7.75
LDL-C (mmol/l)	3.42	0.79	1.83–5.67
HDL-C (mmol/l)	1.09	0.30	0.61–2.23
Triglycerides (mmol/l)	1.20	0.47	0.53–3.10

ages being highly correlated (r = 0.71; $P < 0.0001$) (Fig. 2). MPAC was 29.2 ± 5.1 years (range 18.5–44.5 years) (Fig. 1). For the majority of participants, the father was older than the mother, with a mean parental age difference of 3.2 ± 4.2 years, ranging from −5 to 16 years (Fig. 1). MPAC was highly correlated with both maternal (r = 0.92; $P < 0.0001$) and paternal (r = 0.93; $P < 0.0001$) ages at childbirth, but it was not correlated with parental age difference (r = 0.12; P = 0.32).

Effects of parental age at childbirth

Multivariate models showed that increasing MPAC was associated with a continuous increase in insulin sensitivity (Matsuda index) (P = 0.008) and a reduction in insulin resistance as assessed by HOMA-IR (P = 0.011) in our cohort of overweight middle-aged men (Table 2). In addition, increasing MPAC was associated with lower fasting insulin (P = 0.018) and glucose (P = 0.033) concentrations (Table 2).

Greater MPAC was associated with reductions in night time systolic (P = 0.020) and diastolic (P = 0.047) blood pressure, as well as with improved (increased) nocturnal diastolic blood pressure dipping (P = 0.046) (Table 2). Increasing MPAC also trended to be associated with a subtle reduction in carotid intima-media thickness (P = 0.068). MPAC was not associated with any parameter of body composition or lipid profile (Table 2).

Note that MPAC was not associated with birth weight (P = 0.20), physical activity levels (P = 0.79), energy

intake ($P = 0.23$), or saturated fat consumption ($P = 0.58$). Further, in light of their very strong correlations with MPAC, when assessed separately, maternal and paternal ages yielded continuous associations with study outcomes that were very similar to those obtained for MPAC.

Europeans

Subgroup analyses were carried out on the 64 participants of European ethnicity. Despite a 12% reduction in n, these data corroborated the findings obtained for the whole cohort (Table 3). Increasing MPAC was associated with greater insulin sensitivity (Matsuda index; $P = 0.007$), lower insulin resistance (HOMA-IR; $P = 0.009$), lower fasting insulin concentrations ($P = 0.009$), lower nocturnal systolic blood pressure ($P = 0.032$), and greater nocturnal diastolic dip ($P = 0.039$) (Table 3). However, this subgroup analyses also indicated that increase MPAC was associated with a reduction in carotid intima-media thickness ($P = 0.035$) and a more favorable lipid profile, namely lower LDL-C ($P = 0.028$) and a trend toward lower total cholesterol ($P = 0.054$) concentrations (Table 3).

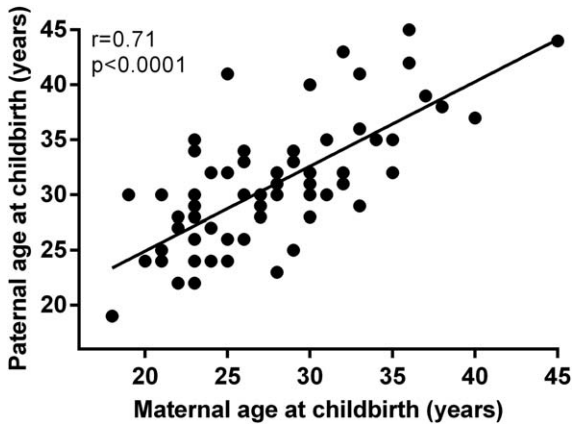

Fig. 2. The association between maternal and paternal ages at childbirth in the studied cohort ($n = 73$).

Discussion

We showed in a cohort of overweight middle-aged men that increasing MPAC was associated with improved insulin sensitivity and a more favorable nocturnal blood pressure profile. In addition, there was evidence of an association between increased MPAC and a subtle reduction in carotid artery intima-media thickness (which may indicate a slower rate of atherosclerosis (Hodis et al., 1998) and a more favorable lipid profile. Our study cohort is a group at moderately increased risk of insulin resistance, hypertension, dyslipidemia and early atherosclerosis (Eckel et al., 2005), and it appears that parental age could theoretically assist in the modulation of such risks. Importantly, the statistical models controlled for the effects of age, BMI, socioeconomic status, and physical activity, so that our findings suggest that parental age at childbirth may have long-term effects on the metabolic health of the offspring.

Our findings are particularly surprising, and somewhat in contrast with the existing literature. The recent EMAS position statement on late parenthood warns that advanced parental age may adversely impact on long-term offspring health (Mintziori et al., 2013). Increasing parental age has been associated with a number of adverse effects on offspring, particularly in the rate of genetic disease (Bray et al., 2006). Mintziori et al. listed numerous long-term adverse outcomes, such as increased rates of childhood asthma, autism, neurocognitive disorders, CNS tumors, leukemia and type 1 diabetes in association with advanced maternal age, and schizophrenia, autism, bipolar disorder, and cancer in association with

TABLE 2. Results from multivariate regression models showing the estimated mean change in the outcome response per year increase in mean parental age at childbirth (β), with associated standard error and 95% confidence interval

Outcome response	β	Standard error	Lower 95% confidence limit	Upper 95% confidence limit	P
Anthropometry					
BMI (kg/m^2)	0.074	0.044	−0.015	0.163	0.10
Total body fat (%)	0.183	0.146	−0.110	0.475	0.22
Glucose homeostasis					
Insulin sensitivity (Matsuda index)	0.193	0.078	0.038	0.349	**0.008**
HOMA-IR	−0.064	0.024	−0.112	−0.015	**0.011**
HOMA-β (%)	−0.997	0.923	−2.838	0.853	0.29
Fasting insulin (mU/l)	−0.221	0.091	−0.403	−0.039	**0.018**
Fasting glucose (mmol/l)	−0.030	0.014	−0.058	−0.003	**0.033**
Glucose 120 min (mmol/l)	−0.034	0.042	−0.119	0.051	0.42
Cardiovascular parameters					
Daytime systolic blood pressure (mmHg)	−0.208	0.229	−0.667	0.252	0.37
Daytime diastolic blood pressure (mmHg)	−0.080	0.158	−0.396	0.235	0.61
Night time systolic blood pressure (mmHg)	−0.500	0.213	−0.928	−0.073	**0.020**
Night time diastolic blood pressure (mmHg)	−0.325	0.168	−0.661	0.011	**0.047**
Night time systolic blood pressure dip (%)	0.241	0.156	−0.072	0.554	0.13
Night time diastolic blood pressure dip (%)	0.413	0.202	0.008	0.818	**0.046**
Carotid intima-media thickness (mm)	−0.006	0.003	−0.013	0.001	0.068
Lipid profile					
Total cholesterol (mmol/l)	−0.025	0.021	−0.066	0.017	0.24
LDL-C (mmol/l)	−0.028	0.019	−0.066	0.009	0.13
HDL-C (mmol/l)	0.003	0.007	−0.012	0.018	0.73
Triglycerides (mmol/l)	−0.007	0.011	−0.030	0.016	0.54

P values in bold are statistically significant at $P < 0.05$.

TABLE 3. Results from multivariate regression models among participants of European ethnicity (n = 64)

Outcome response	β	Standard error	Lower 95% confidence limit	Upper 95% confidence limit	*P*
Anthropometry					
BMI (kg/m^2)	0.089	0.046	−0.002	0.180	0.056
Total body fat (%)	0.165	0.145	−0.126	0.457	0.26
Glucose homeostasis					
Insulin sensitivity (Matsuda index)	0.204	0.084	0.036	0.372	**0.007**
HOMA-IR	−0.070	0.026	−0.122	−0.019	**0.009**
HOMA-β (%)	−1.397	0.919	−3.238	0.445	0.13
Fasting insulin (mU/l)	−0.256	0.095	−0.447	−0.066	**0.009**
Fasting glucose (mmol/l)	−0.021	0.013	−0.047	0.005	0.11
Glucose 120 min (mmol/l)	−0.042	0.046	−0.135	0.050	0.36
Cardiovascular parameters					
Daytime systolic blood pressure (mmHg)	−0.232	0.202	−0.638	0.175	0.26
Daytime diastolic blood pressure (mmHg)	−0.106	0.144	−0.394	0.183	0.46
Night time systolic blood pressure (mmHg)	−0.513	0.232	−0.978	−0.047	**0.032**
Night time diastolic blood pressure (mmHg)	−0.338	0.182	−0.704	0.028	0.070
Night time systolic blood pressure dip (%)	0.240	0.148	−0.058	0.537	0.11
Night time diastolic blood pressure dip (%)	0.377	0.178	0.020	0.734	**0.039**
Carotid intima-media thickness (mm)	−0.008	0.004	−0.015	−0.001	**0.035**
Lipid profile					
Total cholesterol (mmol/l)	−0.040	0.020	−0.081	0.001	0.054
LDL-C (mmol/l)	−0.042	0.019	−0.080	−0.005	**0.028**
HDL-C (mmol/l)	0.004	0.008	−0.013	0.020	0.65
Triglycerides (mmol/l)	−0.012	0.012	−0.036	0.011	0.30

Data are the estimated mean change in the outcome response per year increase in mean parental age at childbirth (β), with associated standard error and 95% confidence interval. *P* values in bold are statistically significant at $P < 0.05$.

advanced paternal age (Mintziori et al., 2013). In contrast, our study suggests that the offspring of older parents may have a more favorable metabolic phenotype, indicative of a lower risk of type 2 diabetes mellitus and cardiovascular disease. Thus, we speculate that, if our findings are corroborated by other studies, increasing parental age at childbirth may help mitigate the metabolic effects of the high rates of overweight and obesity in western countries.

As maternal and paternal ages were highly correlated, it was not possible to determine whether just one or both were responsible for the more favorable metabolic phenotype with increasing parental age at childbirth. Nonetheless, in principle, the effect of both maternal and paternal ages could be mediated through epigenetic changes (Godfrey et al., 2011), or via effects on the fetal (Odibo et al., 2006) or postnatal environment.

Increased paternal age has been shown to be associated with long-term cognitive and psychiatric outcomes, including greater incidence of schizophrenia, autism, early-onset bipolar disorder, and reduced IQ and social functioning in adolescents (Curley et al., 2011). Confirmation of similar effects in rodents (Curley et al., 2011) suggests that these effects are caused by age itself, rather than environmental factors. The mechanisms underpinning such paternal age effects are unknown, but they may be associated with epigenetics, i.e., those processes that alter gene expression without changing the sequence of DNA base pairs, including DNA methylation, histone acetylation and noncoding RNAs passed from the sperm to oocyte at fertilization (Curley et al., 2011). Indeed, the sperm of aging rats show hypermethylation of ribosomal DNA, suggesting a possible effect on cellular metabolism (Oakes et al., 2003). Another potential mechanism for paternal age to affect the metabolism of adult offspring is through increased telomere length. The sperm of older men have longer telomeres and these are inherited by the offspring (Eisenberg et al., 2012). Telomere length is thought to influence the changes associated with aging, and the rate of telomere attrition has been associated with insulin resistance (Gardner et al., 2005). However, whether insulin resistance causes telomere shortening or longer telomeres have a role in maintaining insulin sensitivity is unclear (Gardner et al., 2005).

Increasing maternal age is associated with changes in gonadotrophins (Ebbiary et al., 1994) and sex steroids (Panagiotopoulou et al., 1990; Troisi et al., 2003). Such maternal hormonal changes have been associated with alterations in postnatal growth (Wang and vom Saal, 2000) and metabolism (Crespi et al., 2006) in offspring. Thus, it is possible that age-related changes in maternal hormones lead to programmed changes in offspring phenotype. In addition, increasing maternal age has also been associated with epigenetic changes (Hamatani et al., 2004) and altered gene expression (Grøndahl et al., 2010) in oocytes, which could mediate long-term effects on offspring metabolism. Further, there is compelling evidence that environmental influences can result in highly specific epigenetic changes in the germline, which alter phenotype and persist through generations (Dias and Ressler, 2014). This evidence provides additional support for the hypothesis that the effects of parental age at childbirth on offspring metabolism could be mediated through epigenetic changes.

It is important to consider the possibility that the effect we have described may be due to differences in the postnatal environment. One major environmental factor that varies with parental age is socioeconomic status, as parents who delay fertility tend to be wealthier (Australian Bureau of Statistics, 2010). Socioeconomic status may affect factors such as nutrition (Galobardes et al., 2001), physical activity (Ford et al., 1991), and body composition (McLaren, 2007). Although we adjusted for current socioeconomic status in our analysis, we could not adjust for possible socioeconomic differences in childhood. Indeed, variation in the postnatal child-rearing environment across the socioeconomic spectrum does affect childhood

growth and body composition (Whitley et al., 2008), leading to a taller and slimmer phenotype in those of higher socioeconomic status (Whitley et al., 2008). However, Stringhini et al. compared the effects of socioeconomic status in childhood and adulthood on the risk of chronic inflammation and type 2 diabetes, showing that the adult status was the more important determinant of risk (Stringhini et al., 2013). This suggests that the differences we have described in this study cannot be solely attributed to differences in socioeconomic status in childhood.

However, irrespective of current socioeconomic status, it is possible that older parents may have greater wisdom about the importance of lifestyle factors such as breastfeeding, healthy eating, and/or physical activity; thus, creating a healthier child-rearing environment. In support of this contention, older mothers are more likely to breastfeed (Meedya et al., 2010), and there is evidence that breastfeeding may be protective against obesity in childhood and beyond (Anzman et al., 2010). In addition, older parents are more likely to actively control their children's diet, although this has not been shown to have an effect on BMI (Brown et al., 2008). Further, while there is evidence that parental support increases physical activity levels in their children (Anderssen and Wold, 1992), it is not clear if this support varies with parental age. Importantly, older parents may impart their knowledge regarding healthier lifestyles to their offspring, which could improve the offspring's adult environment. In our study, physical activity, energy, and saturated fat intake did not vary with parental age, findings that are not suggestive of a persistent effect of parental age on lifestyle in adulthood. Nonetheless, it is plausible that the observed effects of parental age on adult metabolism could be mediated through differences in the child-rearing environment.

The major strength of this study is the detailed metabolic assessment. However, our study has limitations, including the *post hoc* analysis. Because maternal and paternal ages were highly correlated, it was not possible to tease out the individual effects of either variable on study outcomes. Future studies in larger cohorts with parents of more discrepant ages would likely enable isolation of these effects. In addition, our study involved a relatively small sample size of 73 individuals, so that it is not possible to ascertain whether non-significant associations actually did not exist or were undetectable due to a lack of sufficient statistical power. Lastly, we studied a relatively narrow range of individuals (overweight males living in a large urban center, mostly of New Zealand European ethnicity), which may limit wider applicability of our findings, especially to females.

In conclusion, increasing parental age at childbirth was associated with a more favorable metabolic profile in overweight middle-aged men. Future studies on the effects of parental age at childbirth on the metabolism of adult males and females across the BMI range are required.

Acknowledgments

The authors acknowledge the Paykel Trust for long-term support of the Maurice & Agnes Paykel Clinical Research Unit at the Liggins Institute, University of Auckland. They also thank Eric Thorstensen (Liggins Institute) and his group for assistance with laboratory work, and Yannan Jiang (Department of Statistics, University of Auckland) for valuable statistical input.

Disclosure Statement

The authors have no financial or nonfinancial conflicts of interest to disclose that may be relevant to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript.

LITERATURE CITED

Albert BB, de Bock M, Derraik JGB, Brennan CM, Biggs JB, Hofman PL, Cutfield WS. 2014. Among overweight middle-aged men, first-borns have lower insulin sensitivity than second-borns. Sci Rep 4:3906.

Anderssen N, Wold B. 1992. Parental and peer influences on leisure-time physical activity in young adolescents. Res Q Exerc Sport 63:341–348.

Anzman SL, Rollins BY, Birch LL. 2010. Parental influence on children's early eating environments and obesity risk: implications for prevention. Int J Obes 34:1116–1124.

Australian Bureau of Statistics. 2010. One for the country: recent trends in fertility. Available at: www.abs.gov.au/socialtrends.

Bray I, Gunnell D, Davey Smith G. 2006. Advanced paternal age: how old is too old? J Epidemiol Community Health 60:851–853.

Brown KA, Ogden J, Vogele C, Gibson EL. 2008. The role of parental control practices in explaining children's diet and BMI. Appetite 50:252–259.

Crespi EJ, Steckler TL, MohanKumar PS, Padmanabhan V. 2006. Prenatal exposure to excess testosterone modifies the developmental trajectory of the insulin-like growth factor system in female sheep. J Physiol 572:119–130.

Curley JP, Mashoodh R, Champagne FA. 2011. Epigenetics and the origins of paternal effects. Horm Behav 59:306–314.

de Bock M, Derraik JGB, Brennan CM, Biggs JB, Morgan PE, Hodgkinson SC, Hofman PL, Cutfield WS. 2013. Olive (*Olea europaea* L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial. PLoS One 8:e57622.

Dias BG, Ressler KJ. 2014. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci 17:89–96.

Ebbiary N, Lenton E, Cooke I. 1994. Hypothalamic-pituitary ageing: progressive increase in FSH and LH concentrations throughout the reproductive life in regularly menstruating women. Clin Endocrinol (Oxf) 41: 199–206.

Eckel RH, Grundy SM, Zimmet PZ. 2005. The metabolic syndrome. Lancet 365:1415–1428.

Eisenberg DT, Hayes MG, Kuzawa CW. 2012. Delayed paternal age of reproduction in humans is associated with longer telomeres across two generations of descendants. Proc Natl Acad Sci USA 109:10251–10256.

Eriksen W, Sundet JM, Tambs K. 2013. Paternal age at birth and the risk of obesity in young adulthood: a register-based birth cohort study of Norwegian males. Am J Hum Biol 25:29–34.

Ford ES, Merritt RK, Heath GW, Powell KE, Washburn RA, Kriska A, Haile G. 1991. Physical activity behaviors in lower and higher socioeconomic status populations. Am J Epidemiol 133:1246–1256.

Galobardes B, Morabia A, Bernstein MS. 2001. Diet and socioeconomic position: does the use of different indicators matter? Int J Epidemiol 30: 334–340.

Gardner JP, Li S, Srinivasan SR, Chen W, Kimura M, Lu X, Berenson GS, Aviv A. 2005. Rise in insulin resistance is associated with escalated telomere attrition. Circulation 111:2171–2177.

Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR, Emerald BS, Gale CR, Inskip HM, Cooper C, Hanson MA. 2011. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes 60:1528–1534.

Grøndahl ML, Yding Andersen C, Bogstad J, Nielsen FC, Meinertz H, Borup R. 2010. Gene expression profiles of single human mature oocytes in relation to age. Hum Reprod 25:957–968.

Hagstromer M, Oja P, Sjostrom M. 2006. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. Public Health Nutr 9:755–762.

Hamatani T, Falco G, Carter MG, Akutsu H, Stagg CA, Sharov AA, Dudekula DB, VanBuren V, Ko MS. 2004. Age-associated alteration of gene expression patterns in mouse oocytes. Hum Mol Genet 13:2263–2278.

Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. 1998. The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 128:262–269.

Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. 2011. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. Mol Psychiatry 16:1203–1212.

Kuhnert B, Nieschlag E. 2004. Reproductive functions of the ageing male. Hum Reprod Update 10:327–339.

Lammi N, Moltchanova E, Blomstedt P, Eriksson J, Taskinen O, Sarti C, Tuomilehto J, Karvonen M. 2007. The effect of birth order and parental age on the risk of type 1 and 2 diabetes among young adults. Diabetologia 50:2433–2438.

Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Smith GD. 2004. Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age findings from the Mater-University study of pregnancy and its outcomes. Circulation 110:2417–2423.

Livingston G, Cohn D. 2010. The New Demography of American Motherhood. Pew Research Center. Available at: http://www.pewsocialtrends.org/files/2010/10/754-new-demography-of-motherhood.pdf.

Lorenzo C, Haffner SM, Stancakova A, Laakso M. 2010. Relation of direct and surrogate measures of insulin resistance to cardiovascular risk factors in nondiabetic Finnish offspring of type 2 diabetic individuals. J Clin Endocrinol Metab 95:5082–5090.

Maki KC, Rains TM, Dicklin MR, Bell M. 2010. Repeatability of indices of insulin sensitivity and secretion from standard liquid meal tests in subjects with type 2 diabetes mellitus or normal or impaired fasting glucose. Diabetes Technol Ther 12:895–900.

Matsuda M, DeFronzo RA. 1999. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470.

McLaren L. 2007. Socioeconomic status and obesity. Epidemiol Rev 29:29–48.

Meedya S, Fahy K, Kable A. 2010. Factors that positively influence breastfeeding duration to 6 months: a literature review. Women Birth 23:135–145.

Mills M, Rindfuss RR, McDonald P, te Velde E, on behalf of the ESHRE Reproduction Society Task Force. 2011. Why do people postpone parenthood? Reasons and social policy incentives. Hum Reprod Update 17: 848–860.

Mintziori G, Lambrinoudaki I, Kolibianakis EM, Ceausu I, Depypere H, Erel CT, Perez-Lopez FR, Schenck-Gustafsson K, van der Schouw Y, Simoncini T, Tremollieres F, Tarlatzis BC, Rees M, Goulis DG. 2013. EMAS position statement: late parenthood. Maturitas 76:200–204.

Oakes CC, Smiraglia DJ, Plass C, Trasler JM, Robaire B. 2003. Aging results in hypermethylation of ribosomal DNA in sperm and liver of male rats. Proc Natl Acad Sci USA 100:1775–1780.

Odibo AO, Nelson D, Stamilio DM, Sehdev HM, Macones GA. 2006. Advanced maternal age is an independent risk factor for intrauterine growth restriction. Am J Perinatol 23:325–328.

Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. 1990. Maternal age, parity, and pregnancy estrogens. Cancer Causes Control 1:119–124.

Salmond C, Crampton P, Atkinson J. 2007. NZDep2006 Index of Deprivation. Wellington: Department of Public Health, University of Otago.

Savage T, Derraik JGB, Miles HL, Mouat F, Hofman PL, Cutfield WS. 2013. Increasing maternal age is associated with taller stature and reduced abdominal fat in their children. PLoS One 8:e58869.

Savage T, Derraik JGB, Miles HL, Mouat F, Hofman PL, Cutfield WS. 2014. Increasing paternal age at childbirth is associated with taller stature and less favourable lipid profiles in their children. Clin Endocrinol 80:253–260.

Stringhini S, Batty GD, Bovet P, Shipley MJ, Marmot MG, Kumari M, Tabak AG, Kivimäki M. 2013. Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II Prospective Cohort Study. PLoS Med 10:e1001479.

Troisi R, Potischman N, Roberts J, Siiteri P, Daftary A, Sims C, Hoover RN. 2003. Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). Cancer Causes Control 14:347–355.

Wang M-H, vom Saal FS. 2000. Maternal age and traits in offspring. Nature 407:469–470.

Whitley E, Gunnell D, Davey Smith G, Holly JM, Martin RM. 2008. Childhood circumstances and anthropometry: the Boyd Orr cohort. Ann Hum Biol 35:518–534.