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Supplementary Material

Potential risks to offspring of intrauterine exposure to maternal age-related obstetric complications

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Table S1. Effects of delayed motherhood on offspring

- Women aged ≥ 35 years are more likely to experience a term stillbirth in singleton pregnancies than women < 35 years (crude OR:1.3, 95% CI: 1.1-1.5), mainly due to a higher risk of major congenital anomalies (crude OR:1.5, 95% CI: 1.05-2.1) (Walker *et al.*, 2015).
- Infants with no recognized or strongly suspected chromosomal abnormalities, or single gene disorders born to mothers ≥ 40 years display higher risk of both isolated and multiple congenital defects, including cardiac defects (see below), esophageal atresia (adjusted OR: 2.9, 95% CI: 1.7-4.9), hypospadias (adjusted OR: 2.0, 95% CI: 1.4-3.0), and craniosynostosis (adjusted OR:1.6, 95% CI: 1.1-2.4) compared with offspring born to mothers 25-29 years (Gill *et al.*, 2012). Note that a previous study based on data from 15 European countries found no convincing evidence of the presence of an effect of advanced maternal age on non-chromosomal congenital anomalies in live births, fetal deaths with gestational age ≥ 20 weeks, and terminations of pregnancy following prenatal diagnosis of a congenital anomaly (Loane *et al.*, 2009).
- Advanced maternal age is associated with offspring's congenital heart defects including atrial septal defect, coarctation of the aorta, Ebstein's anomaly, transposition of the great arteries, tetralogy of Fallot, and ventricular septal defect, in the absence of recognized or strongly suspected chromosomal abnormalities or single gene conditions (crude OR or RR ranges from 1.2, 95% CI: 1.1-1.3 to 4.0, 95% CI: 1.7-9.2 when analyzing different databases) (for review, see Patel and Burns, 2013).
- Children born to mothers aged ≥ 35 years have increased risk of congenital ureter, bladder, and urethra anomalies in the absence of chromosomal abnormalities relative

to mothers 20-34 years (adjusted OR: 1.20, 95% CI: 1.06-1.35) (Shnorhavorian *et al.*, 2011).
- Compared with children born to mothers aged 25-30 years, children born to mothers aged ≥ 35 years have a higher risk of childhood-onset type 1 diabetes mellitus (crude OR: 1.18, 95% CI: 1.06-1.32) (for systematic review and meta-analysis, see Cardwell *et al.*, 2010).
- Adult fasting plasma glucose concentrations (i.e., 6.1 mmol/L or greater but less than 7 mmol/L) is higher by 0.06 mmol/L (95% CI: -0.01 to 0.12) in offspring of mothers ≥ 35 years compared with the reference group of mothers age 20-24 years, but not adult impaired glucose tolerance, diabetes (fasting plasma glucose concentration of 7·0 mmol/L or greater), high blood pressure, and overweight or obesity (Fall *et al.*, 2015).
- Although there are some contradictory results, advanced maternal age is likely associated with increased risk (adjusted OR per 5-year increment in maternal age) of the most frequent childhood cancer including leukemia (1.06, 95% CI: 1.01-1.10), brain tumor (1.08, 95% CI: 1.03-1.14), neuroblastoma (1.10, 95% CI: 1.02-1.19), and Wilm's tumor (1.25, 95% CI: 1.14-1.36) (Johnson *et al.*, 2009).
- Women born to mothers aged ≥ 36 years have increased risk for breast cancer (HR: 1.12; 95% CI: 1.01-1.25) compared with women born to mothers aged ≤ 20 years (for review, see Nassar and Usta, 2009).
- Men born to mothers aged > 30 years exhibit higher risk of seminoma (adjusted OR: 2.00, 95% CI: 1.20-3.60) relative to men born to mothers aged 24-29 years. This effect is particularly high for the first child of the mother (adjusted OR: 4.1, 95% CI: 1.10-14.60) (Møller and Skakkebaek, 1997). Taking into account the two main types of testicular cancer (seminomas and non-seminomas), the adjusted OR per 1-year

increment in maternal age is 1.03, 95% CI: 1.01-1.05 (for review, see Nassar and Usta, 2009).
- Maternal age is associated with offspring's male infertility. Taking into account all causes of male infertility together, the adjusted OR per 1-year increment in maternal age is 1.24, 95% CI: 1.10-1.39 (Tarín *et al.*, 2001) (note that the estimated adjusted OR per 10-year increment in maternal age would be $1.24^{10} = 8.59$).
- Compared with women born to mothers aged 26-35 years, women born to mothers aged ≥ 40 years display increased risk of suffering from menstrual disorders (adjusted OR: 3.24, 95% CI: 1.27-8.30) (for review, see Nassar and Usta, 2009).
- Despite mixed data, literature suggests a protective effect of increased maternal age on offspring's cognitive and behavioral outcomes (for review, see Tearne, 2015). In addition, the majority of studies indicates that maternal age is not directly implicated in the etiology of affective and psychotic disorders (for review, see Tearne, 2015). Notwithstanding, other studies suggest that advanced maternal age may increase the offspring risk for severe psychiatric outcomes including autism spectrum disorders (adjusted RR: 1.52, 95% CI: 1.12-1.92 in offspring born to mothers aged ≥ 35 years versus offspring born to mothers aged 25-29 years) (Sandin *et al.*, 2012), schizophrenia, schizotypal, and delusional disorders (compared with offspring born to mothers aged < 25 years, offspring born to mothers aged 25-29, 30-34, 35-39 years have a crude OR of 1.98, 95% CI: 1.30-3.03, 1.79, 95% CI: 1.08-2.95, and 2.17, 95% CI: 1.21-3.91, respectively) (Lopez-Castroman *et al.*, 2010), and bipolar disorder (compared with offspring born to mothers aged 20-24 years, offspring born to mothers aged 30-34 and 35-39 years have an adjusted OR of 1.08, 95% CI: 1.01-1.16 and 1.16, 95% CI: 1.06-1.26, respectively) (Frans *et al.*, 2008).

Table S2. Potential risks and epigenetic changes in offspring associated with obstetric the complications present at time of delivery in hospital discharges among women aged ≥ 35 years

Obstetric complications (ICD-9-CM codes)[A]	Potential risks to offspring[B]	Epigenetic changes in offspring
Fetal growth restriction (656.5x)[C]	- At birth, small-for-gestational-age infants [i.e., newborns with an actual birth weight below 10th percentile for gestational age- and sex-specific references, a proxy for fetal growth restraint (Chauhan *et al.*, 2009)] have low circulating insulin and insulin-like growth factor-1 (IGF1) concentrations. Thereafter, by 48 h after birth they are more insulin-sensitive and have higher plasma free non-esterified fatty acid levels than average-for gestational-age infants. Consequently, they undergo a period of accelerated post-natal growth which is associated with negative long-term effects later in life including increased risk of developing glucose intolerance, insulin resistance, type 2 diabetes, obesity, poorer sleep (defined by a lower sleep efficiency and more awakenings during the sleep period), cardiovascular disease, systolic hypertension, and impaired	- In-vitro *NOS3* expression of endothelial cells isolated from umbilical arteries and veins of intrauterine growth restricted fetuses is altered by differential DNA methylation (note that *NOS3* is a crucial gene in the nitric oxide system) (Krause *et al.*, 2013). - DNA from umbilical cord blood samples of infants exhibiting prenatal growth restriction, as indicated by rapid post-natal catch-up growth, display CpG loci differentially methylated compared with DNA from control infants who have normal post-natal growth. These CpG loci represent many genes relevant to metabolic disease or growth and development (Quilter *et al.*, 2014). These data are supported by another recent study analyzing DNA from umbilical cord blood samples of fetal

	renal and lung function (for reviews, see Morrison *et al.*, 2010, Salam *et al.*, 2014, and Yiallourou *et al.*, 2015). - Decreasing birthweight raises the risk of hepatic tumors (OR per 0.5 kg increase in birthweight: 0.77, 95% CI: 0.69-0.85) (O'Neill *et al.*, 2015). - Birthweights < 2500 g are associated with 3.5 times higher prevalence of congenital birth defects compared with normal birthweight infants (Kim *et al.*, 2012), seminoma (adjusted OR for term infants: 2.69, 95% CI: 1.40-5.17) (English *et al.*, 2003) and non-seminoma (adjusted OR: 7.62; 95% CI: 1.59-36.60) (Akre *et al.*, 1996) testicular cancer, and schizophrenia (fixed-effects pooled OR: 1.67, 95% CI: 1.22-2.29) (for review and meta-analysis, see Cannon *et al.*, 2002). - Children born small for gestational age, likely irrespective of whether they are born preterm or at term (Bassan *et al.*, 2011), have lower intelligence quotient scores than their peers, poorer language skills, impaired spatial learning and memory, higher risks for behavioral and attentional problems, and consequently poorer	growth restricted infants born at term versus DNA from appropriated grown for gestational age neonates (Hillman *et al.*, 2015). - DNA methylation of three CpG sites within the *AHRR* gene promoter from umbilical cord blood samples is negatively associated with birth weight for gestational age (note that AHRR is involved in mediating xenobiotic metabolism and cell growth and differentiation) (Burris *et al.*, 2015).

	academic outcomes. Catch-up growth, however, is associated with better visuomotor and problem solving skills, intelligence quotient and academic performance in children and adults compared with growth-restricted children with failure of catch-up growth (Hunter *et al.*, 2015 and references cited therein).	
Preterm labor (644.x)	- Preterm infants when reach the age of term exhibit lower bone mineral density, bone mass, bone mineral content, body weight, and ponderal index compared with infants born at term. However, there are conflicting data on later bone strength during childhood. While some studies do not find an association between premature birth and later bone strength during childhood, others report lower bone mineral density and bone mineral content in preterm children (Quintal *et al.*, 2014; for review, see Wood *et al.*, 2013 and Embleton and Wood, 2014). - Babies born very early (< 35 weeks) are at increased risk of neuroblastoma (crude OR: 1.64, 95% CI: 1.01-2.68) (for review, see Heck *et al.*, 2009).	- DNA from leukocytes from dried blood spots of preterm individuals born at less than 31 weeks of gestational age exhibit numerous autosomal locations with significant differences in methylation at birth compared with individuals born at term. Despite most of these differences disappear at 18 years of age, 10 genome loci still show persistent methylation differences between 18-year-old preterm and tern individuals (Cruickshank *et al.*, 2013). - Methylation of CpG sites from leukocytes of umbilical cord blood samples of fetuses born preterm at 24-34 weeks of gestational age associates with methylation of CpG sites from leukocytes of their respective mothers. The methylated CpG sites are more likely to be located in genes whose expression levels are

	- Shorter gestational duration is weakly but significantly associated with risk for type 1 diabetes (for review, see Stene and Gale, 2013). - Preterm delivery is related to reduced insulin sensitivity during childhood. Data on adults, however, are conflicting with some studies showing no effect of gestation on insulin sensitivity, whereas others report persisting effects of preterm birth (for systematic review, see Tinnion *et al.*, 2014). - Purchase of prescription asthma medication in infancy increases by degree of immaturity (OR: 3.86, 95% CI: 2.46-6.04 in gestational-age 23-27 weeks; OR: 2.37, 95% CI: 1.84-3.04 in gestational-age 28-31 weeks; and OR: 1.59, 95% CI: 1.43-1.77-6.04 in gestational-age 32-36 weeks compared to term infants with gestational-age 37-42 weeks). This association weakens during childhood and adolescence and is non-significant in young adulthood (Damgaard *et al.*, 2015). In contrast, survivors of prematurity-associated bronchopulmonary dysplasia have impaired respiratory function during infancy, childhood, and adulthood compared with full control subjects. Differences, however, are less apparent when	also correlated in maternal-fetal pairs and involved in metabolic, cardiovascular, and immune pathways (Parets *et al.*, 2015). - Preterm birth at less than 36 weeks gestational age is linked with hypermethylation of the *OXTR* gene and increased protein production in chorio-amniotic membranes compared with term-labor and term-not-in-labor births (note that methylation of *OXTR* gene is associated with autism spectrum disorders) (Behnia *et al.*, 2015). - DNA methylation of three CpG sites within the *AHRR* gene promoter in samples from umbilical cord blood is negatively associated with the length of gestation (Burris *et al.* 2015).

	comparing preterm children with or without bronchopulmonary dysplasia suggesting that bronchopulmonary dysplasia is not the only factor accounting for the long-term pulmonary morbidity observed in premature infants (for review, see Islam *et al.*, 2015). - Although mortalities rates have fallen steadily for all gestational ages, infant mortality and expectation of survival times decreases with decreasing gestational age (in children born between 1967 and 1983, survival at the age of 5 years drops from 99% for children born at term to 20% for children born at 23-27 weeks of gestation) (Moster *et al.*, 2008; D'Onofrio *et al.*, 2013). Men generally have higher absolute mortality rates than women, and women are at increased risk of having preterm offspring (Swamy *et al.*, 2008). Concomitantly, a lower gestational age at birth is associated with increased risk of cerebral palsy (adjusted RR for birth at 23-27 weeks of gestation: 78.9, 95% CI: 56.5-110.0; P value for trend < 0.001), mental retardation (adjusted RR for birth at 23-27 weeks of gestation: 10.3, 95% CI: 6.2-17.2; P value for trend < 0.001), psychotic or bipolar disorders (HR for birth at 23-27 weeks of	

	gestation: 3.2, 95% CI: 2.3-4.4) (D'Onofrio *et al.*, 2013), autism spectrum disorders (adjusted RR for birth at 23-27 weeks of gestation: 9.7, 95% CI: 1.5-36.2; P value for trend < 0.002), and disorders of psychological development, behavior, and emotion (adjusted RR for birth at 23-27 weeks of gestation: 10.5, 95% CI: 5.6-19.9; P value for trend < 0.001), as well as of other major disabilities including blindness or low vision, hearing loss, and epilepsy (adjusted RR for birth at 23-27 weeks of gestation: 19.6, 95% CI: 11.9-32.2; P value for trend < 0.001), or any other medical disability severely affecting working capacity (adjusted RR for birth at 23-27 weeks of gestation: 7.5, 95% CI: 5.5-10.0; P value for trend < 0.001). Likewise, among preterm people without medical disabilities, a lower gestational age at birth is associated with (1) reduced likelihood of completing high school (P value for trend = 0.003), receiving a bachelor's degree (P value for trend = 0.009), receiving a post-graduate degree (P value for trend = 0.006), having a high job-related income (P value for trend < 0.001), finding a life partner (P value for trend < 0.001), and	

	having biological children (P value for trend < 0.001); and (2) increased likelihood of having a low job-related income (P value for trend < 0.001) and receiving social security benefits (P value for trend < 0.001) (Moster *et al.*, 2008). The risks of psychotic or bipolar disorders, academic problems, and receiving social security benefits, however, are attenuated when controlling for both statistical covariates and shared familial confounds (D'Onofrio *et al.*, 2013). - Accelerated neonatal gain in weight compared with gain in length immediately after preterm birth and during the first three months after term age is associated with future risk factors for cardiovascular disease and type 2 diabetes at 21 years of age (Kerkhof *et al.*, 2012). - Preterm labor is associated with higher systolic and diastolic blood pressure in adult life, with women appearing to be at greater risk than men; increased plasma low-density lipoprotein (for systematic review and meta-analysis, see Parkinson *et al.*, 2013), and structural and functional cardiac, macrovascular, and microvascular	

	complications in young adults (for review, see Lewandowski and Leeson, 2014). However, the vascular phenotype of young adults depends on whether or not mothers suffered from hypertensive pregnancies. In particular, compared with preterm offspring of normotensive pregnancies which have greater arterial stiffness, preterm offspring exposed to hypertensive pregnancies display impaired endothelial function and greater subclinical atherosclerosis (increased carotid intima-media thickness) (Lazdam *et al.*, 2010).	
Cervical incompetence (654.5x)	- Cervical incompetence is a contributing factor to preterm birth even taking into account the significant prolongation of pregnancy and greater gestational age at delivery after cerclage (for systematic review and meta-analysis, see Ehsanipoor *et al.*, 2015) (see above for epigenetic changes and potential long-term risks to offspring of preterm labor).	
Premature rupture of membranes (658.1x)	- When premature rupture of membranes occurs at term, most women will go into labor spontaneously or induced within 12 to 24	

	h (for review, see Caughey *et al.*, 2008). In contrast, women with preterm premature rupture of membranes display a larger interval between rupture of membranes and the onset of labor (latency period). Notwithstanding, spontaneous or induced labor may also take place < 24 h after premature rupture of membranes when there are absolute contraindications to expectant management including intra-amniotic infection (chorio-amnionitis), non-reassuring fetal testing, and active labor (for review, see Caughey *et al.*, 2008) (see above for epigenetic changes and potential long-term risks to offspring of preterm labor).	
Placental abruption (641.2x)	- Placental abruption is associated with increased risks of fetal growth restriction, anemia, hyperbilirubinemia, low birthweight (46% of neonates), preterm labor (40-60% of neonates), intrapartum asphyxia (3.7-fold higher risk compared with control newborns), cystic periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, major congenital anomalies (adjusted OR: 1.92, 95% CI 1.6-2.52) (Riihimäki *et al.*, 2013), perinatal mortality (even term babies with normal birthweight have 25-fold	

	higher mortality with abruption compared with term babies without abruption), stillbirth (more than 50% of all perinatal deaths among abruption cases are stillborns), and sudden infant death syndrome (for review, see Tikkanen, 2011). All these perinatal outcomes may lead to long-term consequences among survivors (see above for epigenetic changes and potential long-term risks to offspring of fetal growth restriction and preterm labor). - Male adolescents whose mothers suffered from placental abruption or pre-eclampsia at the time of delivery by cesarean section exhibit increased risk of severe atopy compared with children of control women that did not experience placental abruption or pre-eclampsia (adjusted RR for skin prick tests positive for ≥ 3 allergens: 4.03, 95% CI: 1.40-11.58; adjusted RR for inhalant allergen-specific immunoglobulin E: 15.28, 95% CI: 1.28-182.01) (Keski-Nisula *et al.*, 2009).	
Placenta previa (641.0-641.1x)	- Placental previa is linked with increased risk of major congenital anomalies (1.6-fold higher risk compared with unaffected women) (Kancherla *et al.*, 2015), preterm delivery (random-effects pooled	

	RR: 5.30, 95% CI: 4.39-6.45), neonatal intensive care unit admission (random-effects pooled RR: 4.09, 95% CI: 2.80-5.97), neonatal death (random-effects pooled RR: 5.44, 95% CI: 3.03-9.78), perinatal death (random-effects pooled RR: 3.01, 95% CI: 1.41-6.43) (for systematic review and meta-analysis, see Vahanian *et al.*, 2015), and delivery of a small-for-gestational-age newborn in multiparous (adjusted OR: 2.08, 95% CI: 1.50-2.89) but not nulliparous women (Räisänen *et al.*, 2014) (see above for epigenetic changes and potential long-term risks to offspring of fetal growth restriction and preterm labor).	
Cesarean delivery (74.x, except 74.91 and DRG codes 765 and 766)	- Cesarean delivery (likely prelabor elective cesarean delivery rather than emergency cesarean delivery after the onset of labor) (Romero and Korzeniewski, 2013) versus vaginal birth is associated with increased risk of developing asthma in children and adults (≈ 20% higher risk), higher body mass index in adulthood (pooled-gender unadjusted mean difference: 0.44 $kg \cdot m^2$, 95% CI: 0.17-0.72), overweight in adulthood (pooled-gender unadjusted OR: 1.26, 95% CI: 1.16-1.38), obesity in adulthood (pooled-gender unadjusted	- Neonatal CD34+ hematopoietic stem cells from infants delivered by elective cesarean section are globally more DNA methylated than DNA from infants delivered vaginally. In addition, differential DNA methylation involves genes/gene regions related to later immune-mediated diseases (Almgren *et al.*, 2014). Likewise, infants born by elective cesarean section have higher global DNA methylation in cord-blood leukocytes at birth compared with those born by vaginal delivery although

	OR: 1.22, 95% CI: 1.05-1.42), allergic rhinitis and atopy in children, childhood-onset type 1 diabetes mellitus (random-effect OR: 1.23, 95% CI: 1.15-1.32), increased hospitalization for gastroenteritis in infancy, aseptic necrosis of the femoral head in childhood (36% higher risk), systemic connective tissue disorders in children [adjusted IRR: 1.11, 95% CI: 1.04-1.19], juvenile arthritis in children (adjusted IRR: 1.10, 95% CI: 1.02-1.18), and immune deficiencies in children (adjusted IRR: 1.46, 95% CI: 1.32-1.62) (Sevelsted *et al.*, 2015; for reviews, see Hyde and Modi, 2012 and Cho and Norman, 2013; for systematic reviews and meta-analyses, see Li *et al.*, 2013 and Darmasseelane *et al.*, 2014). Reports on the effects of cesarean delivery on food allergy, celiac disease, inflammatory bowel disease, lower blood pressure, dentition, neurodevelopmental delay, and cancer (leukemia, neuroblastoma and testicular cancer) in children and young adults are not consistent (Sevelsted *et al.*, 2015; for reviews, see Hyde and Modi, 2012 and Cho and Norman, 2013).	methylation levels of leukocytes from peripheral blood decreases on post-natal days 3-5 (Schlinzig *et al.*, 2009). In contrast, other study (Virani *et al.*, 2012) has found no differences in global DNA and repetitive element methylation of cord-blood leukocytes between infants delivered via elective or emergency cesarean section and those delivered vaginally.

	- Emergency cesarean section is linked with offspring's schizophrenia later in life (fixed-effects pooled OR: 3.24, 95% CI: 1.40-7.50) (for review and meta-analysis, see Cannon *et al.*, 2002).	
Pre-eclampsia, eclampsia, gestational hypertension (642.3x-642.7x)	- Pre-eclampsia, eclampsia, and gestational hypertension are associated with adverse changes in cardiovascular risk in children, adolescents, and adult offspring including raised body mass index, overweight, obesity, insulin resistance, and higher systolic and diastolic blood pressure (Lim *et al.*, 2015; for reviews, see Davis *et al.*, 2012 and Lin *et al.*, 2015; for systematic review and meta-analysis, see Thoulass *et al.*, 2016). - Chronic hypertension, pre-eclampsia, and gestational hypertension may be associated with lower cognitive ability of offspring (for systematic review, see Tuovinen *et al.*, 2014). In addition, female offspring born to pregnancies complicated by hypertension even without proteinuria are at 1.19-fold higher risk of mental disorders (95% CI: 1.01-1.14) and increased risk of mood and anxiety disorders (95% CI: 1.11-1.88) (for review, see Lin *et al.*, 2015).	- Peripheral blood mononuclear cells from young-adult men with higher systolic pulmonary artery pressure, born to women suffering from hypertensive complications of pregnancy, display differentially methylated regions in three genes (*SMOC2*, *ARID1B*, and *CTRHC1*) relevant to vascular function compared with young-adult men born to women having a normotensive pregnancy. The transcriptional activity of two of these genes (*ARID1B*, and *CTRHC1*) is inversely related to methylation status (Julian *et al.*, 2015).

	- Pre-eclampsia is linked with stillbirth, neonatal mortality, preterm birth (established pre-eclampsia is responsible for 15% of all preterm births), placental abruption, oligohydramnios, non-reassuring fetal surveillance, intrauterine growth restriction (RR: 4.2, 95% CI: 2.2-8.0), neurodevelopmental delay, cerebral palsy, metabolic disorders (IRR: 1.2, 95% CI: 1.5-1.7), and respiratory disorders (IRR: 1.2, 95% CI: 1.1-1.2) in children born at term (for review, see Lin *et al.*, 2015). - Infants born to mothers with hypertension during pregnancy have an approximate twofold increased risk of congenital heart defects. However, it remains to be ascertained whether the responsible for the increased risk is the underlying maternal hypertension or the medications used to treat hypertension (for review, see Patel and Burns, 2013). - Reports on the potential association between fetal exposure to maternal pre-eclampsia and offspring's bone mineral density are contradictory. In particular, whereas one study (Hannam *et al.*, 2015) shows a modest but significant negative association of	

	maternal pre-eclampsia and hip and total body bone mineral density in adolescent offspring, another paper (Miettola *et al.*, 2013) reports a protective effect of maternal pre-eclampsia on lumbar spine, femoral neck, and whole body bone mineral density in young-adult offspring born preterm at very low birth weight (< 1500 g), and likely also among those born at term not being small for gestational age. A third study (To and Wong, 2011) failed to find any significant association between gestational hypertensive disorders and offspring's bone mineral density measured at the os calcis before 20 weeks and after 36 weeks of pregnancy. - Female intrauterine exposure to maternal pre-eclampsia and eclampsia is associated with decreased risk of breast cancer (RR: 0·48, 95% CI: 0·30–0·78) (Qiu *et al.*, 2015; for systematic review and meta-analysis, see Xue and Michels, 2007).	
Gestational diabetes (648.8x)	- Gestational diabetes is associated with spontaneous preterm birth, macrosomia, hypertrophic cardiomyopathy (for review, see Mitanchez *et al.*, 2015), and congenital renal (adjusted OR: 1.42, 95% CI 1.09-1.85) and urinary tract anomalies including the ureter,	- Maternal glucose levels, within the normal range, are associated with DNA methylation changes at genes associated with gestational diabetes mellitus and related to energy metabolism

	bladder, and urethra (adjusted OR: 1.25, 95% CI 1.01-1.56) (Shnorhavorian *et al.*, 2011). - Children exposed to gestational hyperglycemia tend to be heavier and taller, and have increased incidence of gross and fine motor abnormalities, attention deficit hyperactivity disorder, learning difficulties, and likely autism spectrum disorder, as well as increased risk of schizophrenia (fixed-effects pooled OR: 7.76, 95% CI: 1.37-43.9) (for review and meta-analysis, see Cannon *et al.*, 2002), renal disease, cardiovascular morbidity, and metabolic syndrome including obesity, type 2 diabetes mellitus, and elevated systolic and diastolic blood pressure (only in men) later in life (for reviews, see Hiersch and Yogev, 2014, Ma *et al.*, 2015, Mitanchez *et al.*, 2015, and Ornoy *et al.*, 2015; for systematic review and meta-analysis, see Aceti *et al.*, 2012). - Despite maternal diabetes often results in macrosomia, in some cases of gestational diabetes, fetal insulin resistance may develop. This may attenuate the trophic effect of insulin and result in intrauterine growth retardation (for review, see Szostak-Wegierek	suggesting that maternal glycemia may be involved in fetal metabolic programming (Houde *et al.*, 2015). - Higher maternal hyperglycemia is associated with lower DNA methylation levels near *LEP* gene in cord blood samples and higher cord blood leptin levels, likely contributing to long-term programming of excessive adiposity later in life (note that leptin is an adipokine that has a key role in appetite regulation by inhibiting hunger, fat storage, and weight set point) (Allard *et al.*, 2015). - Analysis of DNA from umbilical cord blood samples and peripheral blood leukocytes shows many differentially methylated CpG loci and genes involved in cardiovascular and metabolic disease pathways, including cholesterol efflux and atherosclerosis, adiposity, pancreatic development, □-cell response to glucose, and insulin secretion in infants, children, and adolescents exposed to maternal gestational diabetes mellitus compared with those not exposed to maternal gestational diabetes (for review, see Ma *et al.*, 2015).

	et al., 2014) which may increase the risk of metabolic and cardiovascular diseases later in life (see above for epigenetic changes and potential long-term risks to offspring of fetal growth restriction).	
Macrosomia (656.6x)[D]	- A high birth weight predisposes to childhood-onset type 1 diabetes, independent of maternal diabetes (for review, see Stene and Gale, 2013), and later overweight and obesity, glucose intolerance, insulin resistance, and impaired insulin secretion resulting in increased risk of diabetes and cardiovascular diseases in adult life (for review, see Szostak-Wegierek *et al.*, 2014). - Increasing birthweight raises the risk of breast cancer (RR: 1.15, 95% CI: 1.09-1.21) regardless of whether women are premenopausal or postmenopausal (for systematic reviews and meta-analyses, see Xue and Michels, 2007 and Park *et al.*, 2008), and childhood cancer including leukemias, myeloproliferative and myelodysplastic diseases (OR per 0.5 kg increase in birthweight in USA: 1.10, 95% CI: 1.06-1.13), tumors of the central nervous system (OR per 0.5 kg increase in birthweight in USA: 1.05, 95%	

	CI: 1.01-1.08), renal tumors (OR per 0.5 kg increase in birthweight in USA: 1.17, 95% CI: 1.10-1.24), soft tissue and other extraosseous sarcomas (OR per 0.5 kg increase in birthweight in USA: 1.12, 95% CI: 1.05-1.20), neuroblastoma and other peripheral nervous cell tumors (OR per 0.5 kg increase in birthweight in USA: 1.21, 95% CI: 1.02-1.44), germ cell tumors, trophoblastic tumors, and neoplasms of gonads (OR per 0.5 kg increase in birthweight in USA: 1.10, 95% CI: 1.01-1.20), and other malignant epithelial neoplasms and malignant melanomas (OR per 0.5 kg increase in birthweight in UK: 1.17, 95% CI: 1.07-1.29) (O'Neill *et al.*, 2015). - Data on the presence of an association between macrosomia and psychiatric disorders later in life are mixed and no solid conclusions can be drawn (Wegelius *et al.*, 2011; for review, see Van Lieshout and Boyle, 2011).	

[A]Obstetric events associated (adjusted ORs with p-values ranging from 0.029 to < 0.0001) with advanced maternal age reported by Grotegut *et al.* (2014) after analyzing 10,768,536 and 1,860,210 women < 35 and ≥ 35 years of age, respectively, from The Nationwide Inpatient Sample, the largest all-payer inpatient database in the United States, for years 2008-2010. Note that Grotegut *et al.* (2014) used International

Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to identify preexisting medical conditions and medical and obstetric complications at time of delivery. Cesarean deliveries were also identified by diagnosis-related group (DRG) codes. In order to estimate the independent role of maternal age alone on obstetric (and medical) events, multivariate logistic regression analyses were controlled for insurance status, multiple gestation and pre-existing medical conditions including chronic hypertension, chronic renal failure, cardiomyopathy, valvular heart disease, cardiac conduction disorders, history of myocardial infarction/chronic myocardial ischemia, asthma, diabetes, thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis/collagen vascular disease, thrombophilia/antiphospholipid antibody syndrome, anemia, thrombocytopenia, drug use, alcohol use and smoking. We have not included other obstetric events reported by Grotegut *et al.* (2014) because (1) the risk among women ≥ 35 years of age were lower compared to women < 35 years (operative vaginal delivery and chorio-amnionitis); and (2) the events were not directly related with maternal-age-associated changes in fetal intrauterine environment with potential long-term consequences for offspring (fetal chromosomal anomaly, fetal demise and post-partum hemorrhage).

[B]OR, RR, or IRR to offspring of some obstetric complications at time of delivery are missing because of reviewed data come from literature narrative syntheses.

[C]Women aged ≥ 45 years only (Grotegut *et al.*, 2014).

[D]Macrosomia is mainly associated with maternal diabetes (whatever its type), obesity, and/or gestational weight gain (for review, see Mitanchez *et al.*, 2015). It is a consequence of fetal overnutrition likely due to greater transfer of glucose, amino acids, and free fatty acids to the fetus. This leads to increased fetal production of insulin which plays a role of fetal growth factor (for review, see Szostak-Wegierek *et al.*, 2014).

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