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Persistence of the effect of birth size on dysglycaemia and type 2 diabetes in old age: AGES-Reykjavik Study

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ABSTRACT

We studied the effect of birth size on glucose and insulin metabolism among old non-diabetic individuals. We also explored the combined effect of birth size and midlife body mass index (BMI) on type 2 diabetes in old age. Our study comprised 1682 Icelanders whose birth records included anthropometrical data. The same individuals had participated in the prospective population-based Reykjavik Study, where BMI was assessed at a mean age of 47 years, and in the AGES-Reykjavik Study during 2002 to 2006, where fasting glucose, insulin, and HbA_{1c} were measured and HOMA-IR calculated at a mean age of 75.5 years. Type 2 diabetes was determined as having a history of diabetes, using glucose-modifying medication, or fasting glucose of >7.0 mmol/l. Of the participants, 249 had prevalent type 2 diabetes in old age. Lower birth weight and body length were associated with higher fasting glucose, insulin, HOMA-IR, and HbA_{1c} among old non-diabetic individuals. Higher birth weight and ponderal index at birth decreased the risk for type 2 diabetes in old age, OR 0.61 (95% CI 0.48-0.79) and 0.96 (95% CI 0.92-1.00), respectively. Compared with those with high birth weight and low BMI in midlife, the odds of diabetes was almost five-fold for individuals with low birth weight and high BMI, (OR 4.93, 95% CI 2.14-11.37). Excessive weight gain in adulthood might be particularly detrimental to the health of old individuals with low birth weight.

INTRODUCTION

The rapid increase in type 2 diabetes, reaching the magnitude of a worldwide epidemic, is expected to have a large impact on health, functioning, and premature mortality among the aging population (Preis et al. 2009, Danaei et al. 2011). Type 2 diabetes is thought to originate in fetal adaptations to undernutrition *in utero* during certain critical periods in the development (Hales et al. 1991, Barker 1994). This has been confirmed by numerous studies in which small body size at birth has been identified as one of the risk factors for type 2 diabetes in adulthood (Whincup et al. 2008). Furthermore, the prevalence of diabetes is particularly high among adults who were thin at birth but had a high body mass index (BMI) later in life (Eriksson et al. 2003, Bhargava et al. 2004). It has been suggested that the rapid increase in the prevalence of type 2 diabetes, witnessed particularly in developing countries, is driven by the combined effect of undernutrition *in utero* and overnutrition in later life (Chan et al. 2009). Relatively little is known about the effects of these phenomena among individuals aged 70 years and over.

Glucose tolerance, and in particular the body's ability to secrete insulin, often decreases with age, leading to an imbalance in insulin and glucose metabolism and subsequently dysglycaemia or type 2 diabetes (Szoke et al. 2008). These changes are often exacerbated by the increasing prevalence of obesity, co-morbidity, and sedentary behaviour, all of which are associated with older age (Imbault et al. 2003). Given the known changes in glucose and insulin metabolism with older age and the increase in the prevalence of type 2 diabetes among the older population, it is important to establish whether the effects of these fetal exposures track throughout life and have an effect on the distal end of the lifespan.

An earlier study in an Icelandic population, known to have a high mean birth weight, showed that higher birth weight protected from glucose intolerance in midlife (Birgisdottir et al. 2002). As part of the AGES-Reykjavik Study, we followed up the effects of body size at birth on

glucose and insulin metabolism in old age among non-diabetic individuals. We also explored the combined effect of birth weight and BMI in midlife on type 2 diabetes at a mean age of 75.5 years.

METHODS

Study population

The study population comprised 1682 individuals born as singletons and for whom birth record data were available. They had participated in the Reykjavik Study in midlife, and at a mean age of 75.5 years, in the Age, Gene/Environment Susceptibility – Reykjavik Study (AGES-Reykjavik) conducted during 2002 to 2006 (Harris et al. 2007). In the Reykjavik Study, initiated in 1967 by the Icelandic Heart Association (Sigurdsson et al. 1995), data on body size at birth were extracted from the original birth records of midwives for 4828 individuals born in the greater Reykjavik area in 1914-35 and still alive and residing in Reykjavik (Gunnarsdottir et al. 2002). Of these individuals, 1682 participated in the extensive clinical assessments of the multidisciplinary epidemiologic AGES-Reykjavik Study. The AGES-Reykjavik was approved by the Icelandic National Bioethics Committee (VSN 00-063) and by the Institutional Review Board of the U.S. National Institute on Aging, National Institutes of Health. All participants signed an informed consent.

Birth record data

Data on birth weight, body length, information on singleton or multiple births, mother's age at parity and marital status were extracted from the birth records obtained from the National Archives of Iceland. Birth weight was recorded to the nearest 50 g and length in centimeters from crown to heel. Ponderal index was calculated as weight (kg) divided by height (m) raised to the power of three to measure body leanness at birth. Data on gestational age was not clearly documented, but at the time of birth, preterm birth was defined as birth length less than 48 cm (Gunnarsdottir et al. 2002). Excluding these 22 preterm births in the analyses presented in this paper did not change the results. Compared to the 4648 individuals with birth record data in the Reykjavik Study cohort (Birgisdottir et al. 2002), the individuals in the analytical sample of this study had similar birth weight, adult body mass index and fasting glucose level in midlife.

Clinical assessment in midlife

As part of the Reykjavik Study, these individuals participated in a clinical assessment at the Icelandic Heart Association Heart Preventive Clinic at a mean age of 46.9 years (standard deviation [SD] 7.4) (Gunnarsdottir et al. 2002). Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. At the clinical examination, participants were asked about their educational attainment, which was dichotomized into primary and secondary education vs. college or university education. The participants had an oral glucose challenge test in which they ingested 50 g of glucose after fasting for ten hours. Capillary blood glucose was measured from the ear lobe at 60 and 90 minutes after the glucose load as described in detail previously (Vilbergsson et al. 1997, Gunnarsdottir et al. 2002).

Clinical assessment in old age

As part of the AGES-Reykjavik Study, at a mean age of 75.5 years, the participants took part in an extensive clinical examination and interview (Harris et al. 2007). Smoking history was categorized into never smoked vs. used to smoke regularly or current smoker. Physical activity was assessed as self-reported level of physical activity during the life course and categorized as moderate or high level vs. occasionally physically active at most. Family history of diabetes was defined as mother, father, or a sibling with diagnosed diabetes. Systolic and diastolic blood pressure was measured with a mercury sphygmomanometer. Fasting glucose and HbA_{1c} were measured on a Hitachi 912, using reagents from Roche Diagnostics. Insulin was measured with a Roche Elecsys 2010 instrument (Olafsdottir et al. 2009). The homeostasis model assessment for the degree of insulin resistance (HOMA-IR) was calculated with the formula [insulin (mU/L x glucose (mmol/l) / 22.5] (Matthews et al. 1985). Prevalent coronary heart disease was defined as having a history of coronary artery disease or coronary artery bypass surgery or angioplasty or angina pectoris or evidence on ECG of myocardial infarction. The presence of type 2

diabetes was determined as having a history of diabetes, using glucose-modifying medication or fasting glucose of >7.0 mmol/l. 17 individuals had diabetes in midlife, defined as self-reported physician-diagnosed diabetes or use of insulin, glucose-modifying medication, or diet for diabetes. Excluding these individuals from the analyses did not change the results, and hence they were included in the analyses.

Statistical methods

For comparing the characteristics of the study sample, birth weight was categorized into gender-specific quartiles for men of <3.5 kg, ≥3.5 to <3.80 kg, ≥3.8 to <4.2 kg, and ≥4.2 kg and for women of <3.25 kg, ≥3.25 to <3.65 kg, ≥3.65 to <4.0 kg, and ≥4.0 kg. Pearson's chi-square test was used for comparing proportions for categorical variables and analyses of variance and Kruskal-Wallis test for comparing means for continuous variables. The bivariate age- and gender-adjusted differences were compared for the dichotomized variables using logistic regression and for the continuous variables using analysis of covariance. The effect of body size at birth on glucose and insulin levels among those individuals free from type 1 or type 2 diabetes in old age were investigated with multiple linear regression models. The associations between body size at birth and BMI in midlife and type 2 diabetes was analyzed with logistic regression models. Lastly, the combined effect of birth weight and BMI in midlife on type 2 diabetes was analyzed. In this analysis, birth weight and BMI in midlife were categorized gender-specifically into three categories: low (first quartile), medium (two intermediate quartiles), and high (last quartile). The BMI cut-offs were ≤23.45, >23.45 to <27.55, and ≥27.55 for men and ≤22.37, >23.37 to <26.95, and ≥26.96 for women. The analyses were adjusted first for age and gender and then for education, smoking history, and physical activity. The tests were performed two-tailed and the level of significance was set at $p<0.05$.

RESULTS

The mean age of the participants at follow-up was 75.5 years (SD 5.1, range 66 to 90 years) and 44.1% were men. Mean birth weight was 3820 g (SD 563) for men and 3668 g (SD 516) for women. Of the 1682 individuals in the analytical sample, 249 (14.8%) had prevalent type 2 diabetes at the end of the follow-up.

Table 1 presents the associations across the birth weight quartiles with respect to the participants' anthropometrical characteristics at birth, midlife and old age. Consistent linear associations were observed across the birth weight quartiles, showing that those with low birth weight had lower mean weight and shorter stature in midlife and old age. Age at participation in the study was linearly associated with birth weight, those with the lowest birth weight being the youngest. Low birth weight was associated with higher fasting glucose and HbA_{1c} in old age and a similar but non-significant trend was found for insulin and insulin resistance assessed by HOMA-IR. A significant linear increase in the prevalence of type 2 diabetes, but not coronary heart disease was observed in old age among participants with lower birth weight.

The effects of birth size on fasting glucose, insulin, HOMA-IR, and HbA_{1c} in old age studied among non-diabetic individuals are presented in Table 2. In the age- and gender-adjusted bivariate models, birth weight and length were inversely associated with fasting glucose, insulin, HOMA-IR and HbA_{1c} at a mean age of 75.5 years. Adjustment for BMI in midlife, education, smoking, and physical activity did not materially change these associations. Ponderal index at birth was not associated with glucose or insulin metabolism among old non-diabetic individuals.

The bivariate effects of body size at birth and BMI in midlife on the risk of prevalent type 2 diabetes in old age are shown in Table 3. The risk for type 2 diabetes at a mean age of 75.5 years was increased for individuals who were born small. Higher birth weight, length and

ponderal index decreased the risk for type 2 diabetes, odds ratio (OR) 0.61 (95% confidence interval [CI] 0.48-0.79), 0.93 (95% CI 0.88-0.98), and 0.96 (95% CI 0.92-1.00), respectively. Adjusting for BMI in midlife, education, smoking, and physical activity did not alter these associations (Model 3). Further adjustment for family history of diabetes did not change the results. Higher BMI in midlife increased the odds of type 2 diabetes in old age (age- and gender-adjusted OR 1.16, 95% CI 1.13-1.18). The association between birth weight and type 2 diabetes was similar when the analyses were stratified into ≤75 and >75 years of age (data not shown).

Finally, we investigated the combined effect of birth weight and BMI in midlife (both measures were divided into: high=highest quartile, medium=two intermediate quartiles, and low= lowest quartile) on the risk for type 2 diabetes in old age, see Table 4. Among those with high BMI in midlife, we found a graded increase with lower birth weight in the risk for diabetes in old age compared to those with high birth weight and low BMI in midlife (referent group). When compared to the referent group, the age- and gender-adjusted odds for type 2 diabetes for individuals with low birth weight and high BMI in midlife was 4.93 (95% CI 2.14-11.37), for those with medium birth weight and high BMI in midlife 3.47 (95% CI 1.63-7.35) and for those with high birth weight and high BMI in midlife 2.30 (95% CI 1.01-5.23). The odds were significantly increased for those with low birth weight and medium BMI in midlife, OR 2.60 (95% CI 1.17-5.80) compared to those with high birth weight and low BMI in midlife. Adjusting for education, smoking, and physical activity increased these odds. Similar associations between birth weight and BMI in midlife and prevalent diabetes in old age were found when using the conventional cut-off of 30 for BMI indicating obesity.

To further investigate the association between combined birth weight and BMI in midlife with type 2 diabetes in old age, we conducted sensitivity analyses (data not shown). First, the

analyses were confined to those aged 76 to 90 years (45.8% of the study population) to investigate whether the effect was different among the oldest individuals, but the association was even more pronounced. To investigate the risk of incident type 2 diabetes, we excluded individuals with type 1 or 2 diabetes in midlife (n=17); however, the effect was similar. Finally, we adjusted the model with midlife plasma glucose concentration measured 90 min after a glucose load to see whether it would decrease the effect, but the odds were only slightly attenuated.

DISCUSSION

In a population with a mean age of 75.5 years, we showed for the first time that small body size at birth, as an indicator of unfavourable conditions during prenatal life, is related to higher fasting glucose and insulin levels among non-diabetic individuals. In addition, we found gradients in the risk for type 2 diabetes in old age across groups differing in birth weight and midlife body mass index. Compared to those with high birth weight and low BMI in midlife, the individuals with low birth weight and high BMI in midlife had approximately a five-fold risk and those with medium birth weight and high midlife BMI a 3.5-fold risk for type 2 diabetes in old age.

Our findings on the effect of small body size at birth on higher fasting glucose and insulin levels and increased risk for type 2 diabetes parallel earlier findings in this population (Birgisdottir et al. 2002) and other adult populations (Hales et al. 1991, Lithell et al. 1996, Forsen et al. 2000, Lawlor et al. 2006, Tian et al. 2006). However, to our knowledge there are only two smaller studies that have reported similar findings among old individuals (Eriksson et al. 2004, Lapidus et al. 2008). Twin studies have further shown that monozygotic twins discordant for diabetes in adulthood differed in birth weight, the diabetic twin having lower birth weight than the euglycaemic co-twin (Poulsen et al. 1997).

While lifestyle factors such as sedentary behaviour and obesity are important risk factors for abnormal glucose and insulin metabolism and type 2 diabetes and also tend to increase with older age (Lindström et al. 2006), we expected these factors to dilute the effect of early body size on dysglycaemia and type 2 diabetes in old age. However, we found that birth weight was an independent and consistent predictor of glucose and insulin levels, also in the analyses confined to non-diabetic individuals. Furthermore, the association between birth weight and type 2 diabetes was strong among the oldest participants.

In our study, undernourishment *in utero,* manifested as smaller body size at birth in a population with high mean birth weight, substantially increased the risk for type 2 diabetes in old age. This indicates that such adaptations are detrimental to the glucose and insulin metabolism, and that these effects are lifelong and more pronounced among those who are heavier in adult age. Our findings are in line with the fetal programming theory, also termed developmental plasticity, which suggests that a certain genotype can produce various phenotypes depending on early fetal environment during development (Barker 1995, Bateson et al. 2004). According to the thrifty phenotype hypothesis, dysglycaemia is thought to originate in impaired fetal growth when the fetus adapts to undernourishment *in utero*, but later, if exposed to overnutrition, these adaptations will increase the risk of subsequent disease (Hales & Barker 1992). A natural human experiment, caused by famine during the Dutch Hunger Winter in 1944, showed that undernutrition particularly during late gestation was associated with glucose intolerance in adult age (Ravelli et al. 1998). Animal models have suggested that undernutrition *in utero* decreases β-cell mass and function, and reduces muscle mass, insulin sensitivity, and glucose uptake in skeletal muscle and adipose tissue (Garofano et al. 1997, Ozanne et al. 2003).

An alternative explanation has suggested that genetically determined insulin resistance underlies impaired insulin-mediated fetal growth and insulin resistance in later life (Hattersley & Tooke 1999). According to this theory, insulin secretion, which takes place in the fetus as a response to maternal glucose level, is one of the key growth factors *in utero*. Our findings, however, cannot be explained by the presence of maternal hyperglycaemia or type 2 diabetes, as the prevalence of both conditions were low in Iceland at the time when the participants were born (Vilbergsson et al. 1997). Furthermore, Iceland has one of the highest birth weights in the world (Atladottir et al. 2000). This has been attributed in earlier published research from the

Reykjavik Study to the high pre-pregnancy BMI of the women in Iceland, the universal use of cod oil which is known to lengthen gestation and the high protein diet which was common at that time (Birgisdottir et al. 2002).

The strength of our study lays in the well-characterized population-based genetically relatively homogeneous study sample. The data on body size at birth were drawn from the National Archives of Iceland and weight and height in midlife were measured at the clinical examination. Some limitations, however, also need to be considered. Birth weight is a crude measure of fetal nutrition (Harding 2001), but has been widely used in the absence of other indicators of intrauterine growth in adult populations. Gestational age was not well documented in Icelandic birth records in the early 20th century, with preterm birth defined as being shorter than 48 cm at delivery (Gunnarsdottir et al. 2002). In our analyses, excluding these persons did not change the results. Furthermore, there was limited information available on the mother's anthropometry and lifestyle which might have modified the association. The cohort under study was restricted to people who were born in the greater Reykjavik area and thus might not be representative of the general Icelandic population. The study population consists of survivors of the Reykjavik Study who were on average 75.5 years of age. Survivor bias might cause some underestimation in terms of the results, while both small size at birth (Kajantie et al. 2005) and type 2 diabetes (Preis et al. 2009) are related to premature death and thus causing drop-out from the study. It should be further noted that the prevalence of diabetes is lower in Iceland than in the other Nordic countries. In this AGES-Reykjavik cohort, at a mean age of 76 years, about 15% had prevalent diabetes. It is however in line with the prevalence reported in the Icelandic population (Vilbergsson et al. 1997 Diabetes Med).

In conclusion, small body size at birth showed a gradient in the risk for type 2 diabetes among an old population with a high mean birth weight. The risk was particularly high for those who

were born small but became overweight in midlife. The relation between birth weight and dysglycaemia in old age was consistent in spite of the many risk factors that are related to the development of the manifest disease and the long time that had elapsed between early life exposure and disease. These findings were strong among the old non-diabetic individuals, indicating that the associations were not driven by the impaired glucose and insulin metabolism of the diabetics. Identifying these individuals early on could potentially help to decrease type 2 diabetes in future generations.

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Table 1 Characteristics (mean, standard deviation unless stated otherwise) of the study population according-birth weight from the AGES-Reykjavik Study

	Birth weight quartiles[a]				
Characteristics	**1st**	**2nd**	**3rd**	**4th**	**p**[b]
Men, n (%)	158 (21.3)	207 (27.9)	195 (26.3)	182 (24.5)	
Measures at birth and childhood					
Length at birth, cm	50.4 (2.0)	51.7 (1.8)	53.2 (2.1)	53.9 (2.4)	<0.001
Ponderal index	23.5 (2.6)	25.5 (2.5)	26.1 (2.9)	27.9 (3.5)	<0.001
Age of mother at birth, y	28.7 (6.6)	28.2 (5.8)	28.5 (5.5)	30.0 (95.9)	0.001
Measures in midlife					
Weight in midlife, kg					
Men	80.3 (11.2)	82.4 (13.1)	82.1 (11.8)	85.3 (12.0)	<0.001
Women	66.7 (9.6)	67.5 (10.1)	68.6 (10.4)	68.9 (10.9)	0.148
Height in midlife, cm					
Men	177.6 (6.2)	178.1 (5.7)	179.2 (6.3)	180.7 (5.9)	<0.001
Women	163.5 (5.1)	164.7 (5.5)	164.6 (5.2)	166.4 (5.5)	<0.001
BMI in midlife					
Men	25.5 (3.3)	26.0 (3.8)	25.6 (3.2)	26.1 (3.2)	0.25
Women	25.0 (3.7)	24.9 (3.7)	25.3 (3.8)	24.9 (3.7)	0.66
University/college education, n (%)	63 (20.1)	102 (19.7)	73 (21.0)	102 (20.2)	0.49
Measures in old age					
Age at clinical examination, y	74.6 (5.0)	75.1 (5.1)	75.6 (5.0)	76.3 (5.1)	<0.001
Weight in old age, kg					
Men	83.9 (13.2)	84.8 (15.0)	85.1 (14.0)	86.5 (13.5)	0.043
Women	71.0 (14.8)	71.1 (12.9)	72.6 (13.5)	73.3 (13.8)	0.024
Height in old age, cm					
Men	174.9 (6.6)	175.6 (6.0)	176.5 (6.4)	177.9 (5.9)	<0.001
Women	160.2 (5.7)	161.6 (5.8)	160.8 (5.6)	162.9 (6.0)	<0.001
Waist circumference, cm					
Men	103.9 (10.2)	104.7 (11.7)	104.6 (11.2)	104.9 (10.4)	0.79
Women	100.6 (14.1)	100.0 (12.8)	101.8 (13.5)	100.5 (13.0)	0.58
Fasting glucose, mmol/l	6.01 (1.3)	5.96 (1.3)	5.85 (1.1)	5.73 (1.0)	0.006
Insulin, pmol/l	91.8 (156.8)	89.2 (122.4)	81.1 (67.3)	78.8 (122.4)	0.273
HOMA-IR, median (IQR)	2.32 (2.61)	2.26 (2.45)	2.28 (2.35)	2.03 (1.8)	0.158
HbA_{1c}, %	5.78 (0.6)	5.71 (0.6)	5.63 (0.4)	5.65 (0.5)	<0.001
Diabetes, n (%)	61 (19.4)	83 (16.1)	50 (14.4)	55 (10.9)	<0.001
Family history of diabetes, n (%)	65 (20.7)	68 (13.2)	34 (9.8)	58 (11.5)	0.001
Coronary heart disease, n (%)	58 (18.5)	88 (19.5)	102 (24.9)	93 (18.6)	0.95

BMI=body mass index, HbA_{1c} =glycated haemoglobin, HOMA-IR=homeostasis model assessment indicating insulin resistance, IQR=interquartile range

[a] Birth weight quartiles for men <3.5 kg, ≥3.5-<3.80 kg, ≥3.8-<4.2 kg and ≥4.2 kg and for women <3.25 kg, ≥3.25-<3.65 kg, ≥3.65-<4.0 kg and ≥4.0 kg

[b] p-values adjusted for age and gender (when analyses are not pooled by gender)

Table 2 Unstandardized regression coefficients (β**)** and 95% confidence intervals (CI) for glucose metabolism at an average age of 75.5 years according, birth anthropometrics among non-diabetic individuals in the AGES-Reykjavik Study

	Model 1		**Model 2**		**Model 3**	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
			Fasting glucose (mmol/l)			
Birth weight (kg)	-0.76 (-0.13, -0.26)	0.003	-0.08 (-0.13, -0.03)	0.002	-0.08 (-0.13, -0.03)	0.004
Birth length (cm)	-0.15 (-0.26, -0.004)	0.007	-0.02 (-0.03, -0.003)	0.010	-0.01 (-0.03, -0.003)	0.015
Ponderal index (kg/m^3)	-0.001 (-0.01, 0.01)	0.84	-0.002 (-0.01, 0.01)	0.67	-0.002 (-0.01, 0.01)	0.67
			Insulin (pmol/l)			
Birth weight (kg)	-6.05 (-11.22, -0.88)	0.022	-6.77 (-11.65, -1.68)	0.009	-6.08 (-10.39, -1.76)	0.006
Birth length (cm)	-1.05 (-2.18, 0.07)	0.066	-0.97 (-2.08, 0.13)	0.084	-0.84 (-1.78, 0.09)	0.077
Ponderal index (kg/m^3)	-0.22 (-1.07, 0.63)	0.63	-0.44 (-1.27, 0.40)	0.31	-0.44 (-1.15, 0.27)	0.22
			HOMA-IR			
Birth weight (kg)	-0.26 (-0.47, -0.06)	0.013	-0.29 (-0.49, -0.085)	0.006	-0.26 (-0.43, -0.09)	0.003
Birth length (cm)	-0.05 (-0.09, 0.000)	0.050	-0.04 (-0.09, 0.003)	0.065	-0.04 (-0.07, 0.002)	0.065
Ponderal index (kg/m^3)	-0.01 (-0.04, 0.02)	0.56	-0.07 (-0.14, 0.002)	0.057	-0.07 (-0.12, -0.007)	0.029
			HbA_{1c} (%)			
Birth weight (kg)	-0.04 (-0.07, -0.01)	0.008	-0.04 (-0.08, -0.01)	0.006	-0.04 (-0.07, -0.008)	0.014
Birth length (cm)	-0.01 (-0.01, 0.000)	0.039	-0.008 (-0.01, -0.001)	0.034	-0.007 (-0.014, 0.000)	0.057
Ponderal index (kg/m^3)	-0.002 (-0.007, 0.004)	0.57	-0.002 (-0.007, 0.006)	0.61	-0.001 (-0.01, 0.004)	0.63

BMI=body mass index, HOMA-IR=homeostasis model assessment indicating insulin resistance, HbA1c=glycated haemoglobin

Model 1 is adjusted for age and gender, Model 2 is adjusted for Model 1and BMI in midlife, and Model 3 is adjusted for Model 2 and education, smoking, and physical activity

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for type 2 diabetes at an average age of 75.5 years according-birth anthropometrics and BMI in midlife in the AGES-Reykjavik Study

	Model 1		**Model 2**		**Model 3**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Birth weight (kg)	0.61	0.48-0.79	0.60	0.47-0.78	0.56	0.42-0.74
Birth length (cm)	0.93	0.88-0.98	0.93	0.88-0.98	0.93	0.87-0.99
Ponderal index (kg/m^3)	0.96	0.92-1.00	0.99	0.92-1.00	0.94	0.90-0.99
BMI in midlife	1.16	1.13-1.18			1.17[a]	1.14-1.19

BMI=Body mass index

Model 1 is adjusted for age and gender-Model 2 is adjusted for Model 1and BMI in midlife-and Model 3 is adjusted for Model 2 and education-smoking-and physical activity

[a] Adjusted for age-gender-education-smoking-and physical activity

Table 4 Odds ratios (OR) and 95% confidence intervals (CI) for type 2 diabetes at age 75.5 years according-birth weight and body mass index in midlife in the AGES-Reykjavik Study

	OR (95% CI) *adjusted for age and gender / adjusted for age-gender-education-smoking-and physical activity*								
Birth weight[a]	**Body mass index in midlife**[b]								
	Low			**Medium**			**High**		
Low	1.17 (0.43-3.19)	/	1.60 (0.53-4.87)	2.60 (1.17-5.80)	/	3.43 (1.34-8.81)	4.93 (2.14-11.37)	/	5.77 (2.16-15.44)
Medium	1.22 (0.53-2.76)	/	1.60 (0.61-4.18)	1.74 (0.83-3.64)	/	2.18 (0.90-5.28)	3.47 (1.63-7.35)	/	4.37 (1.78-10.73)
High	1.00	/	1.00	1.07 (0.48-2.40)	/	1.18 (0.45-3.12)	2.30 (1.01-5.23)	/	2.68 (1.02-7.06)

[a] Birth weight categorized into: low (lowest quartile)-medium (two intermediate quartiles)-and high (highest quartile)-quartiles gender-specific
[b] Body mass index in midlife categorized into: low (lowest quartile)-medium (two intermediate quartiles)-and high (highest quartile)-quartiles gender-specific