

# Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring:

## The Helsinki Birth Cohort Study

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The authors report no conflict of interest.

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### Short title

*MS Kajantie*

## Abstract

**Background.** Women with hypertensive disorders in pregnancy are at an increased risk of cardiovascular disease and type 2 diabetes later in life. Offspring born from these hypertensive pregnancies have increased levels of cardiovascular risk factors; whether they are at an increased risk of type 2 diabetes is not known.

**Objective.** To study the risk of type 2 diabetes in the adult offspring exposed to maternal preeclampsia or gestational hypertension *in utero*.

**Study Design.** We studied 5335 members of the Helsinki Birth Cohort Study, who were born between 1934 and 1944 and who lived in Finland in 1995 when the National Medication Purchase Register was initiated. We ascertained gestational hypertension and preeclampsia according to modern criteria by using maternal and birth records. We defined type 2 diabetes through purchases of antidiabetic medication recorded in the comprehensive National Medication Purchase Register, excluding the 31 subjects who had purchased only insulin. We used Cox regression to assess hazard ratios for type 2 diabetes.

**Results.** 590 men (21.6%) and 433 women (16.9%) had purchased medication for diabetes. Hazard ratio for T2D for offspring exposed to any maternal hypertension in pregnancy was 1.13 (95% CI 1.00, 1.29; n=1780). For maternal gestational hypertension, it was 1.15 (95% CI 1.00, 1.33; n=1336) and for preeclampsia 0.98 (0.71, 1.34; n=231). For T2D with first medication purchase before 62 years, corresponding hazard ratios were 1.25 (1.04, 1.51); 1.28 (1.05, 1.58) and 1.18 (0.75, 1.84). The hazard ratios were similar when adjusted for birth weight SD score for gestation, length of gestation, maternal BMI in late pregnancy, height, age and parity and for childhood or adult socio-economic position. An increased risk of type 2 diabetes was also associated with low birth weight SD score, independent of the association with gestational hypertension.

**Conclusions.** Offspring exposed to maternal gestational hypertension *in utero* have an increased risk of type 2 diabetes in late adult life. This finding underlines the role of the whole spectrum of hypertensive disorders of pregnancy as risk factors of offspring disease throughout life. It also reinforces previous

suggestions that adult healthcare providers should incorporate birth histories when evaluating of an individual's risk to develop T2D.

Keywords: birth weight, cardiovascular disease, cerebrovascular disease, diabetes, gestational age, gestational hypertension, hypertension, ischemic heart disease, premature, preterm, preeclampsia

## Introduction

Hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension, are among the most common pregnancy disorders. Women with these conditions have higher levels of insulin resistance than women with normotensive pregnancy. This difference persists after pregnancy and contributes to a higher risk of type 2 diabetes (T2D) and cardiovascular disease in later life.<sup>1-3</sup> Offspring born to these women have also increased levels of cardiovascular risk factors such as higher blood pressure<sup>4-6</sup> and body mass index<sup>4,5</sup> and increased risk of manifest disease including stroke<sup>7</sup>. However, evidence on the offspring risk of diabetes is scanty. Studies on premorbid traits such as glucose metabolism remain inconclusive.<sup>4,8,9</sup>

Two studies have assessed T2D as an outcome at mean ages of 47<sup>3</sup> and 45<sup>9</sup> years in offspring of mothers with preeclampsia. The association with T2D did not reach statistical significance in either study alone<sup>3,9</sup> or a combined analysis;<sup>5</sup> neither study assessed other hypertensive disorders of pregnancy.

We used the unique data of the Helsinki Birth Cohort Study (HBCS), with maternal hypertensive disorders confirmed from pregnancy and birth records using modern criteria,<sup>7</sup> to study their effect on the risk of T2D in offspring born between 1934 and 1944.

## Subjects and methods

We studied 6410 singleton members of the HBCS, born between 1934 and 1944, who had adequate antenatal clinic and birth hospital data to confirm diagnoses of maternal pregnancy disorders by modern criteria as described.<sup>7</sup> The specific criteria are shown in Table 1. Birth weight SD score, adjusted for gestational age and sex, was based on Finnish standards.<sup>10</sup>

Of the 6410 cohort members, 5335 lived in Finland in 1995, when the National Medication Reimbursement Database was initiated. Based on this database, we defined T2D as at least one purchase of medication for diabetes between 1995 to 2011. Because the early life origins of type 1 diabetes are likely to be distinct from those of T2D, ~~W~~we excluded the 31 subjects who had purchased only insulin, who are likely to have type 1 diabetes. This left us with 5304 subjects. Comparisons of these subjects with those who had died or

emigrated from Finland before 1995 are shown in Supplementary Table 1. Those who had died or emigrated were more likely to be men, they were born to younger mothers, and had lower and more frequently unknown adult socio-economic position. There was no difference in the frequency of hypertensive disorders of pregnancy or in childhood socio-economic position.

The study was approved by the Ethics Committee at Helsinki and Uusimaa Hospital District, and data were linked with permission from the Ministry of Social and Health Affairs, National Institute for Health and Welfare, and National Social Insurance Institution. We used Cox regression, stratified for offspring sex and year of birth, to calculate hazard ratios for offspring T2D. Other censoring events were death and migration from Finland, whichever occurred first. To allow for non-linear associations with covariates, values of categorical covariates with more than two categories (childhood and adulthood socio-economic position) were contrasted against an indicator category (lowest socio-economic position). Continuous covariates were first entered as first, second and third degree polynomials. As this had virtually no effect on the association between hypertensive pregnancy disorders and offspring T2D, we report the result adjusted for linear effects of the continuous covariates.

## Results

Clinical characteristics are shown in Table 2. 590 men (21.6%) and 433 women (16.9%) had purchased medication for diabetes. Mean age at first registered purchase was 61.7 years (SD 6.0) for men and 63.0 (SD 6.0) years for women. As there was no difference in the association between maternal hypertension in pregnancy and T2D between male and female offspring (p for interaction >0.3), we report the results pooled for both sexes, stratified for sex and year of birth.

### Hypertension in pregnancy and T2D in adult offspring

Offspring of mothers with hypertension in pregnancy had a higher risk of developing T2D in adult life, compared with offspring of normotensive women (Figure 1). The risk was due to an increased risk in offspring of women with gestational hypertension. We then assessed these associations separately among

those whose first medication purchase for T2D occurred before and after 62 years, the approximate mean age of first purchase. We selected this cutoff because the medication purchase register started in 1995, when the subjects were aged 50 to 61 years. The increased risk of T2D was confined to those with first medication purchase before 62 years (Figure 1).

The re was no association between the risk of T2D ~~was not associated with and~~ maternal non-severe or severe preeclampsia (Figure 1). A post hoc analysis with any maternal preeclampsia combined showed hazard ratios of 0.98 (0.71, 1.34) for T2D; 1.18 (0.75, 1.84) for onset before and 0.83 (0.53, 1.29) after 62 years.

#### Prenatal factors and socio-economic status

A one SD higher birth weight SD score was associated with a hazard ratio of 0.87 for T2D (95% CI 0.81, 0.93). The risk of T2D was not associated with length of gestation or preterm birth (HR 1.18; 0.88, 1.58), although the association with preterm birth before 35 weeks of gestation, previously reported in the source cohort.<sup>11</sup> approached statistical significance (HR 1.60; 0.94, 2.72). The risk of T2D was also not associated with maternal age, height, BMI before delivery or parity or with childhood socio-economic position; offspring with lower adult socio-economic position had higher rates of T2D. Adjustment for these variables had a negligible effect on the association between maternal hypertensive disorders and offspring T2D (Table 3).

We then assessed the association between birth weight SD score and adult T2D separately among offspring from normotensive and hypertensive pregnancies (Table 4). The association appeared stronger among normotensive pregnancies, although the interaction was not formally statistically significant. Conversely, the association between maternal gestational hypertension and offspring adult T2D was strongest among offspring with the highest birth weight SD scores.

## Comment

We found that offspring born to mothers with gestational hypertension have higher risk of T2D treated by medication than offspring of normotensive mothers. The association was limited to T2D with medication initiated before 62 years of age. It was not confounded by maternal age or BMI in pregnancy or by childhood socio-economic status. We were unable to find any association between maternal preeclampsia and offspring T2D.

We have previously discussed the limitations of the maternal hypertension in pregnancy data in the Helsinki Birth Cohort Study.<sup>7</sup> A further limitation is that we have no information on maternal gestational diabetes or offspring adult BMI, key risk factors of offspring T2D. Adjustment for maternal BMI, however, did not change our findings. Moreover, while the use of medication purchase data enabled us to distinguish between type 1 and type 2 diabetes, we could not identify subjects with diabetes treated by diet only or subjects who died or emigrated before the register was started in 1995. However, comparisons between those who could not be included because of pre-1995 death or migration and those included raised little concern over bias. As described,<sup>7</sup> a number of mothers had no blood pressure recorded before 20 weeks of gestation. Thus the gestational hypertension group is likely also to include mothers that today would be classified as having chronic hypertension.

While gestational hypertension predicts subsequent T2D and other chronic diseases in the mother,<sup>1</sup> our study is to our knowledge the first to assess its effects on diabetes in adult offspring. The hazard ratios, 1.15 for any T2D and 1.34 for T2D before 62 years, are relatively modest. Yet, they compare with associations with established adult risk factors such as the risk ratio of 1.37 for T2D reported for current smoking.<sup>12</sup> For further comparison, previously reported hazard ratios of gestational hypertension in this same cohort include 1.4 for offspring stroke,<sup>7</sup> 1.19 for any severe mental disorder and 1.44 for severe mood disorder.<sup>13</sup>



The lack of association between maternal preeclampsia and offspring T2D should be interpreted with caution because of the smaller numbers. ~~although~~ However, it is consistent with two previous studies that have focused on preeclampsia rather than gestational hypertension as an exposure.<sup>3, 5, 9</sup> One of these studies was based on the UK 1958 Birth Cohort and reported a hazard ratio of 1.19 (95% CI 0.48, 2.96), when the outcome was self-reported T2D at 45 years.<sup>5, 9</sup> Another study assessed the offspring of mothers who had had pre-eclampsia in any of their pregnancies, identified T2D cases from medical records in a population followed up to 22 to 62 years and reported a hazard ratio of 1.38 (0.89, 2.14).<sup>3</sup> In the present study, the confidence interval of the 0.98 hazard ratio was (0.71, 1.34); it excludes ~~sd~~ any moderate or large effects with reasonable certainty.

Both low birth weight and gestational hypertension seemed to be independent, additive risk factors for offspring T2D. There was, however, some suggestion that the risk associated with gestational hypertension might be strongest among those born at high birth weight for gestation. This would be consistent with a role of maternal gestational diabetes or subthreshold hyperglycaemia, which are associated with gestational hypertension and high birth weight.

We conclude that intrauterine exposure maternal gestational hypertension is a novel risk factor of type 2 diabetes in adult life. This finding underlines the role of the whole spectrum of hypertensive disorders of pregnancy as risk factors of offspring disease throughout life. Further, it reinforces previous suggestions that adult healthcare providers should incorporate birth histories when evaluating of an individual's risk to develop T2D.

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Table 1. Definition of maternal hypertension in pregnancy according to the International Society for the Study of Hypertension in Pregnancy criteria, modified based on data available.<sup>7</sup>

	Blood pressure	Proteinuria
Normotension	All systolic measurements <140 mmHg and diastolic <90 mmHg	No
Gestational hypertension	At least one systolic measurement ≥140 mmHg or diastolic mmHg after 20 weeks of gestation, no chronic hypertension	No
Non-severe preeclampsia	At least one systolic measurement ≥140 mmHg or diastolic mmHg after 20 weeks of gestation, all systolic measurements <160 mmHg and diastolic <110 mmHg	Yes <sup>a</sup>
Severe preeclampsia	At least one systolic measurement ≥160 mmHg or diastolic mmHg after 20 weeks of gestation	Yes <sup>a</sup>
Chronic hypertension or superimposed preeclampsia	At least one systolic measurement ≥140 mmHg or diastolic mmHg before 20 weeks of gestation <sup>b</sup>	Yes/No
Any hypertension in pregnancy	Any of the above hypertensive conditions	

<sup>a</sup>Definition of proteinuria was based on a qualitative measurement, the cutoff of which approximates to 1 mg/mL of albumin

<sup>b</sup>816 of the 6410 mothers (12.7%) had blood pressure recordings before 20 weeks gestation and could be classified in relation to chronic hypertension / superimposed preeclampsia. Therefore we do not present chronic hypertension / superimposed preeclampsia as a separate exposure group but include the offspring of these mothers in the “any hypertension” category.

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Table 2. Characteristics of the mothers and their offspring according to maternal hypertensive disorders

	Normotensive 3524	Any hypertension in pregnancy n=1780*	Gestational hypertension n=1336	Preeclampsia, non-severe n=97	Preeclampsia, severe n=134	Missing
Men	1836 (52.1%)	899 (50.5%)	677 (50.7%)	54 (55.7%)	71 (53.0%)	0
Maternal						
Age at delivery	27.9 (5.3)	28.9 (5.7)	28.9 (5.8)	27.8 (4.9)	29.2 (6.1)	5
Height	159.5 (5.6)	159.7 (5.8)	159.6 (5.8)	160.0 (5.8)	160.2 (5.6)	266
Body mass index before delivery	26.0 (2.8)	26.8 (3.2)	26.8 (3.2)	27.0 (3.5)	26.8 (3.0)	339
Primiparous	1731 (49.1%)	1000 (56.2%)	731 (54.7%)	66 (68.0%)	101 (75.4%)	0
Birth						
Length of gestation (weeks)	40.0 (1.6)	39.9 (1.7)	40.0 (1.7)	39.7 (1.9)	39.3 (2.0)	285
Birth weight (g)	3430 (467)	3345 (518)	3379 (495)	3227 (514)	2881 (590)	0
Birth weight SD score	-0.3 (0.9)	-0.4 (1.1)	-0.4 (1.0)	-0.6 (1.0)	-1.3 (1.1)	285
Father's occupational status						0
..Unknown	211 (6.0%)	116 (6.5%)	88 (6.6%)	6 (6.2%)	9 (6.7%)	
Manual worker	2385 (67.7%)	1201 (67.5%)	903 (67.6%)	58 (59.8%)	81 (60.4%)	
Lower official	697 (19.8%)	339 (19.0%)	254 (19.0%)	21 (21.6%)	31 (23.1%)	
Higher official	231 (6.6%)	124 (7.0%)	91 (6.8%)	12 (12.4%)	13 (9.7%)	
Own adult occupational status						0
..Unknown	62 (1.8%)	32 (1.8%)	25 (1.9%)	1 (1.1%)	1 (0.7%)	
Manual worker	1416 (40.2%)	744 (41.8%)	563 (42.1%)	35 (36.1%)	56 (41.8%)	
Self-employed	330 (9.4%)	163 (9.2%)	121 (9.1%)	10 (10.3%)	12 (9.0%)	
Lower official	1327 (37.7%)	662 (37.2%)	500 (37.4%)	39 (40.2%)	46 (34.3%)	
Higher official	389 (11.0%)	179 (10.1%)	127 (9.5%)	12 (12.4%)	19 (14.2%)	
Adult						
Ever purchased medication for diabetes, n (%)	660 (18.7%)	363 (20.4%)	277 (20.7%)	17 (17.5%)	25 (18.7%)	0
Mean age at first purchase, years	62.5 (6.1)	61.7 (6.0)	61.8 (6.1)	62.6 (6.2)	61.4 (6.0)	0

Numbers are mean (SD) or n (%)

<sup>a</sup>The number includes in addition 213 mothers with chronic hypertension.

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Table 3. Hazard ratios for type 2 diabetes in the offspring according to maternal hypertension in pregnancy, adjusted for covariates

	Normotensive	Any hypertension	Gestational	Preeclampsia, non-	Preeclampsia, severe
	3524	in pregnancy	hypertension	severe	n=134
		n=1780 <sup>a</sup>	n=1336	n=97	
Model 1	Referent	1.13 (1.00, 1.29)	1.15 (1.00, 1.33)	0.92 (0.57, 1.50)	1.01 (0.68, 1.51)
Model 2	Referent	1.13 (0.99, 1.29)	1.16 (1.01, 1.35)	0.92 (0.57, 1.50)	0.95 (0.63, 1.44)
Model 3	Referent	1.13 (0.99, 1.30)	1.16 (1.00, 1.35)	0.90 (0.54, 1.51)	0.99 (0.65, 1.52)
Model 4	Referent	1.13 (0.99, 1.28)	1.14 (0.99, 1.32)	0.94 (0.58, 1.53)	1.02 (0.69, 1.53)

Analyses are stratified for offspring sex and year of birth

Model 1, unadjusted

Model 2, adjusted for length of gestation and birth weight SD score

Model 3, adjusted for 2 + maternal age, height, BMI and whether multiparous

Model 4, adjusted for childhood and adult socio-economic position.

<sup>a</sup>The number includes in addition 213 mothers with chronic hypertension.

Table 4. Hazard ratios for type 2 diabetes in the offspring of normotensive mothers and mothers with gestational hypertension, according to birth weight SD in relation to length of gestation

Birth weight SD score in thirds	Normotensive		Gestational hypertension	
	N diabetes/total (%)	Hazard ratio (95%) CI	N diabetes/total	Hazard ratio (95%) CI
Lowest	232/1043 (22.2%)	1.43 (1.18, 1.74)	112/450 (24.9%)	1.71 (1.35, 2.17)
Middle	207/1137 (18.2%)	1.16 (0.95, 1.41)	79/432 (18.3%)	1.19 (0.91, 1.55)
Highest	201/1222 (16.4%)	Referent	78/393 (19.9%)	1.30 (1.00, 1.69)
<i>Hazard ratio per one SD birth weight</i>				
		0.83 (0.76, 0.91)		
<i>p for linear trend</i>		<0.0001	0.1	
<i>p for quadratic trend</i>		0.05	0.2	
<i>p for interaction<sup>a</sup></i>			0.2	

Analyses are stratified for offspring sex and year of birth and adjusted for length of gestation.

<sup>a</sup>Interaction between gestational hypertension and birth weight SD score as a continuous variable

**Figure captions**

Figure 1. Hazard ratios and 95% confidence intervals for type 2 diabetes according to exposure to maternal hypertensive disorders in pregnancy. The percentages indicate proportion of cohort members with type 2 diabetes. "Any hypertension in pregnancy" includes also 213 mothers with chronic hypertension.

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**Background.** Women with hypertensive disorders in pregnancy are at an increased risk of cardiovascular disease and type 2 diabetes later in life. Offspring born from these hypertensive pregnancies have increased levels of cardiovascular risk factors; whether they are at an increased risk of type 2 diabetes is not known.

**Objective.** To study the risk of type 2 diabetes in the adult offspring exposed to maternal preeclampsia or gestational hypertension *in utero*.

**Study Design.** We studied 5335 members of the Helsinki Birth Cohort Study, who were born between 1934 and 1944 and who lived in Finland in 1995 when the National Medication Purchase Register was initiated. We ascertained gestational hypertension and preeclampsia according to modern criteria by using maternal and birth records. We defined type 2 diabetes through purchases of antidiabetic medication recorded in the comprehensive National Medication Purchase Register, excluding the 31 subjects who had purchased only insulin. We used Cox regression to assess hazard ratios for type 2 diabetes.

**Results.** 590 men (21.6%) and 433 women (16.9%) had purchased medication for diabetes. Hazard ratio for T2D for offspring exposed to any maternal hypertension in pregnancy was 1.13 (95% CI 1.00, 1.29; n=1780). For maternal gestational hypertension, it was 1.15 (95% CI 1.00, 1.33; n=1336) and for preeclampsia 0.98 (0.71, 1.34; n=231). For T2D with first medication purchase before 62 years, corresponding hazard ratios were 1.25 (1.04, 1.51); 1.28 (1.05, 1.58) and 1.18 (0.75, 1.84). The hazard ratios were similar when adjusted for birth weight SD score for gestation, length of gestation, maternal BMI in late pregnancy, height, age and parity and for childhood or adult socio-economic position. An increased risk of type 2 diabetes was also associated with low birth weight SD score, independent of the association with gestational hypertension.

**Conclusions.** Offspring exposed to maternal gestational hypertension *in utero* have an increased risk of type 2 diabetes in late adult life. This finding underlines the role of the whole spectrum of hypertensive disorders of pregnancy as risk factors of offspring disease throughout life. It also reinforces previous

suggestions that adult healthcare providers should incorporate birth histories when evaluating of an individual's risk to develop T2D.

Keywords: birth weight, cardiovascular disease, cerebrovascular disease, diabetes, gestational age, gestational hypertension, hypertension, ischemic heart disease, premature, preterm, preeclampsia

## Introduction

Hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension, are among the most common pregnancy disorders. Women with these conditions have higher levels of insulin resistance than women with normotensive pregnancy. This difference persists after pregnancy and contributes to a higher risk of type 2 diabetes (T2D) and cardiovascular disease in later life.<sup>1-3</sup> Offspring born to these women have also increased levels of cardiovascular risk factors such as higher blood pressure<sup>4-6</sup> and body mass index<sup>4,5</sup> and increased risk of manifest disease including stroke<sup>7</sup>. However, evidence on the offspring risk of diabetes is scanty. Studies on premorbid traits such as glucose metabolism remain inconclusive.<sup>4,8,9</sup> Two studies have assessed T2D as an outcome at mean ages of 47<sup>3</sup> and 45<sup>9</sup> years in offspring of mothers with preeclampsia. The association with T2D did not reach statistical significance in either study alone<sup>3,9</sup> or a combined analysis;<sup>5</sup> neither study assessed other hypertensive disorders of pregnancy.

We used the unique data of the Helsinki Birth Cohort Study (HBCS), with maternal hypertensive disorders confirmed from pregnancy and birth records using modern criteria,<sup>7</sup> to study their effect on the risk of T2D in offspring born between 1934 and 1944.

## Subjects and methods

We studied 6410 singleton members of the HBCS, born between 1934 and 1944, who had adequate antenatal clinic and birth hospital data to confirm diagnoses of maternal pregnancy disorders by modern criteria as described.<sup>7</sup> The specific criteria are shown in Table 1. Birth weight SD score, adjusted for gestational age and sex, was based on Finnish standards.<sup>10</sup>

Of the 6410 cohort members, 5335 lived in Finland in 1995, when the National Medication Reimbursement Database was initiated. Based on this database, we defined T2D as at least one purchase of medication for diabetes between 1995 to 2011. Because the early life origins of type 1 diabetes are likely to be distinct from those of T2D, we excluded the 31 subjects who had purchased only insulin, who are likely to have type 1 diabetes. This left us with 5304 subjects. Comparisons of these subjects with those who had died or

emigrated from Finland before 1995 are shown in Supplementary Table 1. Those who had died or emigrated were more likely to be men, they were born to younger mothers, and had lower and more frequently unknown adult socio-economic position. There was no difference in the frequency of hypertensive disorders of pregnancy or in childhood socio-economic position.

The study was approved by the Ethics Committee at Helsinki and Uusimaa Hospital District, and data were linked with permission from the Ministry of Social and Health Affairs, National Institute for Health and Welfare, and National Social Insurance Institution. We used Cox regression, stratified for offspring sex and year of birth, to calculate hazard ratios for offspring T2D. Other censoring events were death and migration from Finland, whichever occurred first. To allow for non-linear associations with covariates, values of categorical covariates with more than two categories (childhood and adulthood socio-economic position) were contrasted against an indicator category (lowest socio-economic position). Continuous covariates were first entered as first, second and third degree polynomials. As this had virtually no effect on the association between hypertensive pregnancy disorders and offspring T2D, we report the result adjusted for linear effects of the continuous covariates.

## Results

Clinical characteristics are shown in Table 2. 590 men (21.6%) and 433 women (16.9%) had purchased medication for diabetes. Mean age at first registered purchase was 61.7 years (SD 6.0) for men and 63.0 (SD 6.0) years for women. As there was no difference in the association between maternal hypertension in pregnancy and T2D between male and female offspring ( $p$  for interaction  $>0.3$ ), we report the results pooled for both sexes, stratified for sex and year of birth.

### Hypertension in pregnancy and T2D in adult offspring

Offspring of mothers with hypertension in pregnancy had a higher risk of developing T2D in adult life, compared with offspring of normotensive women (Figure 1). The risk was due to an increased risk in offspring of women with gestational hypertension. We then assessed these associations separately among

those whose first medication purchase for T2D occurred before and after 62 years, the approximate mean age of first purchase. We selected this cutoff because the medication purchase register started in 1995, when the subjects were aged 50 to 61 years. The increased risk of T2D was confined to those with first medication purchase before 62 years (Figure 1).

There was no association between the risk of T2D and maternal non-severe or severe preeclampsia (Figure 1). A post hoc analysis with any maternal preeclampsia combined showed hazard ratios of 0.98 (0.71, 1.34) for T2D; 1.18 (0.75, 1.84) for onset before and 0.83 (0.53, 1.29) after 62 years.

#### Prenatal factors and socio-economic status

A one SD higher birth weight SD score was associated with a hazard ratio of 0.87 for T2D (95% CI 0.81, 0.93). The risk of T2D was not associated with length of gestation or preterm birth (HR 1.18; 0.88, 1.58), although the association with preterm birth before 35 weeks of gestation, previously reported in the source cohort,<sup>11</sup> approached statistical significance (HR 1.60; 0.94, 2.72). The risk of T2D was also not associated with maternal age, height, BMI before delivery or parity or with childhood socio-economic position; offspring with lower adult socio-economic position had higher rates of T2D. Adjustment for these variables had a negligible effect on the association between maternal hypertensive disorders and offspring T2D (Table 3).

We then assessed the association between birth weight SD score and adult T2D separately among offspring from normotensive and hypertensive pregnancies (Table 4). The association appeared stronger among normotensive pregnancies, although the interaction was not formally statistically significant. Conversely, the association between maternal gestational hypertension and offspring adult T2D was strongest among offspring with the highest birth weight SD scores.

#### **Comment**

We found that offspring born to mothers with gestational hypertension have higher risk of T2D treated by medication than offspring of normotensive mothers. The association was limited to T2D with medication

initiated before 62 years of age. It was not confounded by maternal age or BMI in pregnancy or by childhood socio-economic status. We were unable to find any association between maternal preeclampsia and offspring T2D.

We have previously discussed the limitations of the maternal hypertension in pregnancy data in the Helsinki Birth Cohort Study.<sup>7</sup> A further limitation is that we have no information on maternal gestational diabetes or offspring adult BMI, key risk factors of offspring T2D. Adjustment for maternal BMI, however, did not change our findings. Moreover, while the use of medication purchase data enabled us to distinguish between type 1 and type 2 diabetes, we could not identify subjects with diabetes treated by diet only or subjects who died or emigrated before the register was started in 1995. However, comparisons between those who could not be included because of pre-1995 death or migration and those included raised little concern over bias. As described,<sup>7</sup> a number of mothers had no blood pressure recorded before 20 weeks of gestation. Thus the gestational hypertension group is likely also to include mothers that today would be classified as having chronic hypertension.

While gestational hypertension predicts subsequent T2D and other chronic diseases in the mother,<sup>1</sup> our study is to our knowledge the first to assess its effects on diabetes in adult offspring. The hazard ratios, 1.15 for any T2D and 1.34 for T2D before 62 years, are relatively modest. Yet, they compare with associations with established adult risk factors such as the risk ratio of 1.37 for T2D reported for current smoking.<sup>12</sup> For further comparison, previously reported hazard ratios of gestational hypertension in this same cohort include 1.4 for offspring stroke,<sup>7</sup> 1.19 for any severe mental disorder and 1.44 for severe mood disorder.<sup>13</sup>

The lack of association between maternal preeclampsia and offspring T2D should be interpreted with caution because of the smaller numbers. However, it is consistent with two previous studies that have focused on preeclampsia rather than gestational hypertension as an exposure.<sup>3, 5, 9</sup> One of these studies was based on the UK 1958 Birth Cohort and reported a hazard ratio of 1.19 (95% CI 0.48, 2.96), when the

outcome was self-reported T2D at 45 years.<sup>5, 9</sup> Another study assessed the offspring of mothers who had had pre-eclampsia in any of their pregnancies, identified T2D cases from medical records in a population followed up to 22 to 62 years and reported a hazard ratio of 1.38 (0.89, 2.14).<sup>3</sup> In the present study, the confidence interval of the 0.98 hazard ratio was (0.71, 1.34); it excludes any moderate or large effects with reasonable certainty.

Both low birth weight and gestational hypertension seemed to be independent, additive risk factors for offspring T2D. There was, however, some suggestion that the risk associated with gestational hypertension might be strongest among those born at high birth weight for gestation. This would be consistent with a role of maternal gestational diabetes or subthreshold hyperglycaemia, which are associated with gestational hypertension and high birth weight.

We conclude that intrauterine exposure maternal gestational hypertension is a novel risk factor of type 2 diabetes in adult life. This finding underlines the role of the whole spectrum of hypertensive disorders of pregnancy as risk factors of offspring disease throughout life. Further, it reinforces previous suggestions that adult healthcare providers should incorporate birth histories when evaluating of an individual's risk to develop T2D.

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Table 1. Definition of maternal hypertension in pregnancy according to the International Society for the Study of Hypertension in Pregnancy criteria, modified based on data available.<sup>7</sup>

	Blood pressure	Proteinuria
Normotension	All systolic measurements <140 mmHg and diastolic <90 mmHg	No
Gestational hypertension	At least one systolic measurement ≥140 mmHg or diastolic mmHg after 20 weeks of gestation, no chronic hypertension	No
Non-severe preeclampsia	At least one systolic measurement ≥140 mmHg or diastolic mmHg after 20 weeks of gestation, all systolic measurements <160 mmHg and diastolic <110 mmHg	Yes <sup>a</sup>
Severe preeclampsia	At least one systolic measurement ≥160 mmHg or diastolic mmHg after 20 weeks of gestation	Yes <sup>a</sup>
Chronic hypertension or superimposed preeclampsia	At least one systolic measurement ≥140 mmHg or diastolic mmHg before 20 weeks of gestation <sup>b</sup>	Yes/No
Any hypertension in pregnancy	Any of the above hypertensive conditions	

<sup>a</sup>Definition of proteinuria was based on a qualitative measurement, the cutoff of which approximates to 1 mg/mL of albumin

<sup>b</sup>816 of the 6410 mothers (12.7%) had blood pressure recordings before 20 weeks gestation and could be classified in relation to chronic hypertension / superimposed preeclampsia. Therefore we do not present chronic hypertension / superimposed preeclampsia as a separate exposure group but include the offspring of these mothers in the “any hypertension” category.

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Table 2. Characteristics of the mothers and their offspring according to maternal hypertensive disorders

	Normotensive 3524	Any hypertension in pregnancy n=1780*	Gestational hypertension n=1336	Preeclampsia, non-severe n=97	Preeclampsia, severe n=134	Missing
Men	1836 (52.1%)	899 (50.5%)	677 (50.7%)	54 (55.7%)	71 (53.0%)	0
Maternal						
Age at delivery	27.9 (5.3)	28.9 (5.7)	28.9 (5.8)	27.8 (4.9)	29.2 (6.1)	5
Height	159.5 (5.6)	159.7 (5.8)	159.6 (5.8)	160.0 (5.8)	160.2 (5.6)	266
Body mass index before delivery	26.0 (2.8)	26.8 (3.2)	26.8 (3.2)	27.0 (3.5)	26.8 (3.0)	339
Primiparous	1731 (49.1%)	1000 (56.2%)	731 (54.7%)	66 (68.0%)	101 (75.4%)	0
Birth						
Length of gestation (weeks)	40.0 (1.6)	39.9 (1.7)	40.0 (1.7)	39.7 (1.9)	39.3 (2.0)	285
Birth weight (g)	3430 (467)	3345 (518)	3379 (495)	3227 (514)	2881 (590)	0
Birth weight SD score	-0.3 (0.9)	-0.4 (1.1)	-0.4 (1.0)	-0.6 (1.0)	-1.3 (1.1)	285
Father's occupational status						0
..Unknown	211 (6.0%)	116 (6.5%)	88 (6.6%)	6 (6.2%)	9 (6.7%)	
Manual worker	2385 (67.7%)	1201 (67.5%)	903 (67.6%)	58 (59.8%)	81 (60.4%)	
Lower official	697 (19.8%)	339 (19.0%)	254 (19.0%)	21 (21.6%)	31 (23.1%)	
Higher official	231 (6.6%)	124 (7.0%)	91 (6.8%)	12 (12.4%)	13 (9.7%)	
Own adult occupational status						0
..Unknown	62 (1.8%)	32 (1.8%)	25 (1.9%)	1 (1.1%)	1 (0.7%)	
Manual worker	1416 (40.2%)	744 (41.8%)	563 (42.1%)	35 (36.1%)	56 (41.8%)	
Self-employed	330 (9.4%)	163 (9.2%)	121 (9.1%)	10 (10.3%)	12 (9.0%)	
Lower official	1327 (37.7%)	662 (37.2%)	500 (37.4%)	39 (40.2%)	46 (34.3%)	
Higher official	389 (11.0%)	179 (10.1%)	127 (9.5%)	12 (12.4%)	19 (14.2%)	
Adult						
Ever purchased medication for diabetes, n (%)	660 (18.7%)	363 (20.4%)	277 (20.7%)	17 (17.5%)	25 (18.7%)	0
Mean age at first purchase, years	62.5 (6.1)	61.7 (6.0)	61.8 (6.1)	62.6 (6.2)	61.4 (6.0)	0

Numbers are mean (SD) or n (%)

<sup>a</sup>The number includes in addition 213 mothers with chronic hypertension.

Table 3. Hazard ratios for type 2 diabetes in the offspring according to maternal hypertension in pregnancy, adjusted for covariates

	Normotensive	Any hypertension	Gestational	Preeclampsia, non-	Preeclampsia, severe
	3524	in pregnancy	hypertension	severe	n=134
		n=1780 <sup>a</sup>	n=1336	n=97	
Model 1	Referent	1.13 (1.00, 1.29)	1.15 (1.00, 1.33)	0.92 (0.57, 1.50)	1.01 (0.68, 1.51)
Model 2	Referent	1.13 (0.99, 1.29)	1.16 (1.01, 1.35)	0.92 (0.57, 1.50)	0.95 (0.63, 1.44)
Model 3	Referent	1.13 (0.99, 1.30)	1.16 (1.00, 1.35)	0.90 (0.54, 1.51)	0.99 (0.65, 1.52)
Model 4	Referent	1.13 (0.99, 1.28)	1.14 (0.99, 1.32)	0.94 (0.58, 1.53)	1.02 (0.69, 1.53)

Analyses are stratified for offspring sex and year of birth

Model 1, unadjusted

Model 2, adjusted for length of gestation and birth weight SD score

Model 3, adjusted for 2 + maternal age, height, BMI and whether multiparous

Model 4, adjusted for childhood and adult socio-economic position.

<sup>a</sup>The number includes in addition 213 mothers with chronic hypertension.

Table 4. Hazard ratios for type 2 diabetes in the offspring of normotensive mothers and mothers with gestational hypertension, according to birth weight SD in relation to length of gestation

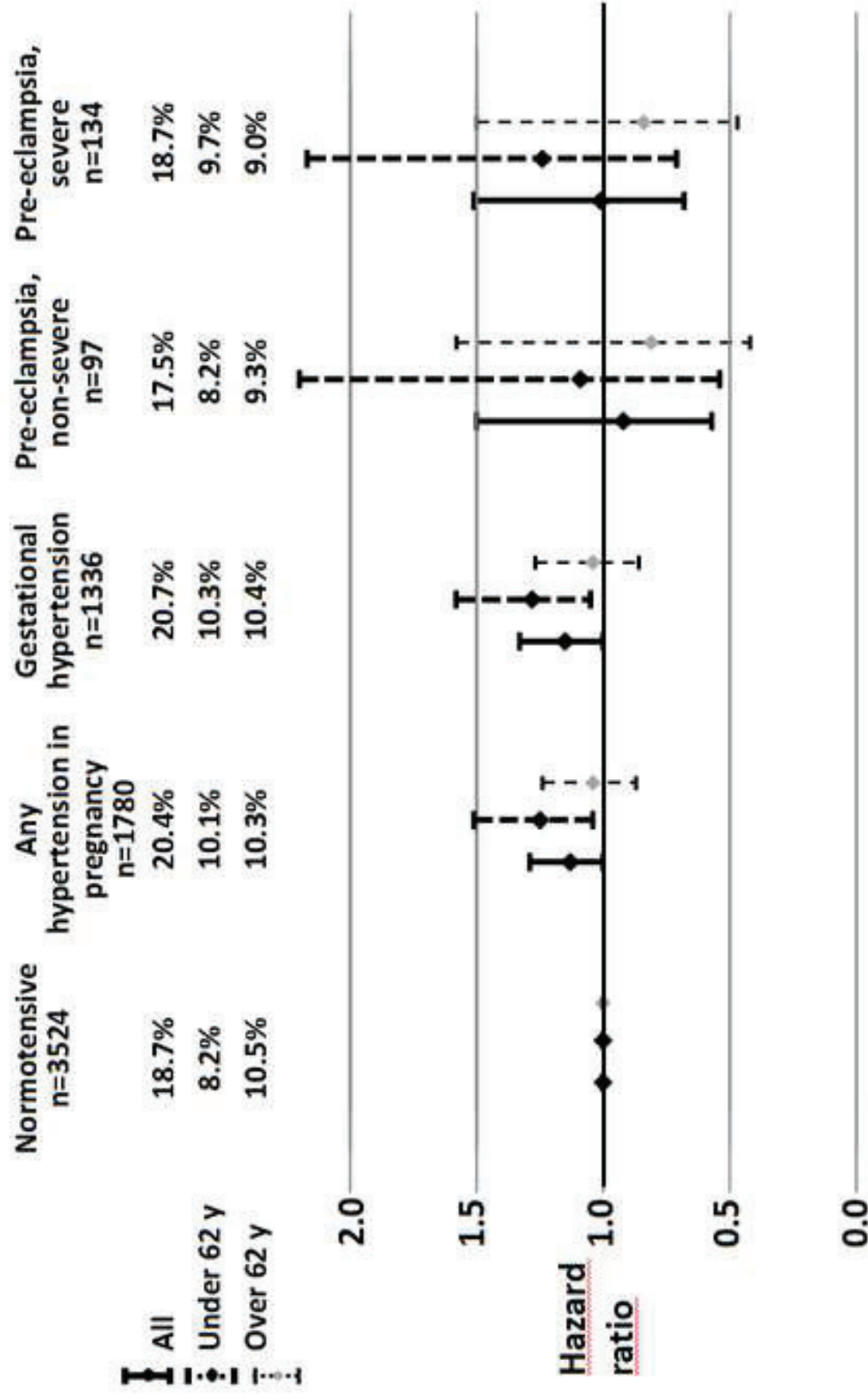
Birth weight SD score in thirds	Normotensive		Gestational hypertension	
	N diabetes/total (%)	Hazard ratio (95%) CI	N diabetes/total	Hazard ratio (95%) CI
Lowest	232/1043 (22.2%)	1.43 (1.18, 1.74)	112/450 (24.9%)	1.71 (1.35, 2.17)
Middle	207/1137 (18.2%)	1.16 (0.95, 1.41)	79/432 (18.3%)	1.19 (0.91, 1.55)
Highest	201/1222 (16.4%)	Referent	78/393 (19.9%)	1.30 (1.00, 1.69)
<i>Hazard ratio per one SD birth weight</i>				
		0.83 (0.76, 0.91)		
<i>p for linear trend</i>		<0.0001	0.1	
<i>p for quadratic trend</i>		0.05	0.2	
<i>p for interaction<sup>a</sup></i>			0.2	

Analyses are stratified for offspring sex and year of birth and adjusted for length of gestation.

<sup>a</sup>Interaction between gestational hypertension and birth weight SD score as a continuous variable

**Figure captions**

Figure 1. Hazard ratios and 95% confidence intervals for type 2 diabetes according to exposure to maternal hypertensive disorders in pregnancy. The percentages indicate proportion of cohort members with type 2 diabetes. "Any hypertension in pregnancy" includes also 213 mothers with chronic hypertension.



Kajantie et al. Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: The Helsinki Birth Cohort Study

Supplementary Table 1. Characteristics of subjects who were excluded because of having died or emigrated before the follow-up was started in 1995, as compared with study participants.

	Dead or emigrated before 1995 (n=1075)	Available for follow-up in 1995 (n=5304)	p value <sup>a</sup>
Men	599 (55.7%)	2735 (51.5%)	0.01
Maternal			
Age at delivery	27.8 (5.3)	28.2 (5.4)	0.01
Height	159.8 (5.8)	159.6 (5.7)	0.2
Body mass index before delivery	26.3 (3.0)	26.2 (2.9)	0.4
Primiparous	520 (48.5%)	2573 (51.5%)	0.07
Hypertension in pregnancy			0.6
Normotensive	727 (67.6%)	3524 (66.4%)	
Gestational hypertension	248 (23.1%)	1336 (25.2%)	
Pre-eclampsia, non-severe	23 (2.1%)	97 (1.8%)	
Pre-eclampsia, severe	30 (2.8%)	134 (2.5%)	
Birth			
Length of gestation (weeks)	40.0 (1.6)	39.9 (1.6)	0.6
Birth weight (g)	3428 (502)	3401 (486)	0.1
Birth weight SD score	-0.30 (1.02)	-0.33 (0.98)	0.4
Father's occupational status			0.2
..Unknown	80 (7.6%)	327 (6.2%)	
Manual worker	724 (67.3%)	3586 (67.6%)	
Lower official	207 (19.3%)	1036 (19.5%)	
Higher official	62 (5.8%)	355 (6.7%)	
Own adult occupational status			<0.0001
..Unknown	521 (48.5%)	94 (1.8%)	
Manual worker	253 (23.5%)	2160 (40.7%)	
Self-employed	48 (4.5%)	493 (9.3%)	
Lower official	179 (16.7%)	1989 (37.5%)	
Higher official	74 (6.5%)	568 (10.7%)	

<sup>a</sup>χ<sup>2</sup> test or t test





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### Short title

*MS Kajantie*

## Abstract

**Background.** Women with hypertensive disorders in pregnancy are at an increased risk of cardiovascular disease and type 2 diabetes later in life. Offspring born from these hypertensive pregnancies have increased levels of cardiovascular risk factors; whether they are at an increased risk of type 2 diabetes is not known.

**Objective.** To study the risk of type 2 diabetes in the adult offspring exposed to maternal preeclampsia or gestational hypertension *in utero*.

**Study Design.** We studied 5335 members of the Helsinki Birth Cohort Study, who were born between 1934 and 1944 and who lived in Finland in 1995 when the National Medication Purchase Register was initiated. We ascertained gestational hypertension and preeclampsia according to modern criteria by using maternal and birth records. We defined type 2 diabetes through purchases of antidiabetic medication recorded in the comprehensive National Medication Purchase Register, excluding the 31 subjects who had purchased only insulin. We used Cox regression to assess hazard ratios for type 2 diabetes.

**Results.** 590 men (21.6%) and 433 women (16.9%) had purchased medication for diabetes. Hazard ratio for T2D for offspring exposed to any maternal hypertension in pregnancy was 1.13 (95% CI 1.00, 1.29; n=1780). For maternal gestational hypertension, it was 1.15 (95% CI 1.00, 1.33; n=1336) and for preeclampsia 0.98 (0.71, 1.34; n=231). For T2D with first medication purchase before 62 years, corresponding hazard ratios were 1.25 (1.04, 1.51); 1.28 (1.05, 1.58) and 1.18 (0.75, 1.84). The hazard ratios were similar when adjusted for birth weight SD score for gestation, length of gestation, maternal BMI in late pregnancy, height, age and parity and for childhood or adult socio-economic position. An increased risk of type 2 diabetes was also associated with low birth weight SD score, independent of the association with gestational hypertension.

**Conclusions.** Offspring exposed to maternal gestational hypertension *in utero* have an increased risk of type 2 diabetes in late adult life. This finding underlines the role of the whole spectrum of hypertensive disorders of pregnancy as risk factors of offspring disease throughout life. It also reinforces previous

suggestions that adult healthcare providers should incorporate birth histories when evaluating of an individual's risk to develop T2D.

Keywords: birth weight, cardiovascular disease, cerebrovascular disease, diabetes, gestational age, gestational hypertension, hypertension, ischemic heart disease, premature, preterm, preeclampsia

## Introduction

Hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension, are among the most common pregnancy disorders. Women with these conditions have higher levels of insulin resistance than women with normotensive pregnancy. This difference persists after pregnancy and contributes to a higher risk of type 2 diabetes (T2D) and cardiovascular disease in later life.<sup>1-3</sup> Offspring born to these women have also increased levels of cardiovascular risk factors such as higher blood pressure<sup>4-6</sup> and body mass index<sup>4,5</sup> and increased risk of manifest disease including stroke<sup>7</sup>. However, evidence on the offspring risk of diabetes is scanty. Studies on premorbid traits such as glucose metabolism remain inconclusive.<sup>4,8,9</sup> Two studies have assessed T2D as an outcome at 47<sup>3</sup> and 45<sup>9</sup> years in offspring of mothers with preeclampsia. The association with T2D did not reach statistical significance in either study alone<sup>3,9</sup> or a combined analysis;<sup>5</sup> neither study assessed other hypertensive disorders of pregnancy.

We used the unique data of the Helsinki Birth Cohort Study (HBCS), with maternal hypertensive disorders confirmed from pregnancy and birth records using modern criteria,<sup>7</sup> to study their effect on the risk of T2D in offspring born between 1934 and 1944.

## Subjects and methods

We studied 6410 singleton members of the HBCS, born between 1934 and 1944, who had adequate antenatal clinic and birth hospital data to confirm diagnoses of maternal pregnancy disorders by modern criteria as described.<sup>7</sup> The specific criteria are shown in Table 1. Birth weight SD score, adjusted for gestational age and sex, was based on Finnish standards.<sup>10</sup>

Of the 6410 cohort members, 5335 lived in Finland in 1995, when the National Medication Reimbursement Database was initiated. Based on this database, we defined T2D as at least one purchase of medication for diabetes between 1995 to 2011. We excluded the 31 subjects who had purchased only insulin, who are likely to have type 1 diabetes. This left us with 5304 subjects.

The study was approved by the Ethics Committee at Helsinki and Uusimaa Hospital District, and data were linked with permission from the Ministry of Social and Health Affairs, National Institute for Health and Welfare, and National Social Insurance Institution. We used Cox regression, stratified for offspring sex and year of birth, to calculate hazard ratios for offspring T2D.

## Results

Clinical characteristics are shown in Table 2. 590 men (21.6%) and 433 women (16.9%) had purchased medication for diabetes. Mean age at first registered purchase was 61.7 years (SD 6.0) for men and 63.0 (SD 6.0) years for women. As there was no difference in the association between maternal hypertension in pregnancy and T2D between male and female offspring ( $p$  for interaction  $>0.3$ ), we report the results pooled for both sexes.

### Hypertension in pregnancy and T2D in adult offspring

Offspring of mothers with hypertension in pregnancy had a higher risk of developing T2D in adult life, compared with offspring of normotensive women (Figure 1). The risk was due to an increased risk in offspring of women with gestational hypertension. We then assessed these associations separately among those whose first medication purchase for T2D occurred before and after 62 years. We selected this cutoff because the medication purchase register started in 1995, when the subjects were aged 50 to 61 years. The increased risk of T2D was confined to those with first medication purchase before 62 years (Figure 1).

The risk of T2D was not associated with maternal non-severe or severe preeclampsia (Figure 1). A post hoc analysis with any maternal preeclampsia combined showed hazard ratios of 0.98 (0.71, 1.34) for T2D; 1.18 (0.75, 1.84) for onset before and 0.83 (0.53, 1.29) after 62 years.

### Prenatal factors and socio-economic status

A one SD higher birth weight SD score was associated with a hazard ratio of 0.87 for T2D (95% CI 0.81, 0.93). The risk of T2D was not associated with length of gestation or preterm birth (HR 1.18; 0.88, 1.58),

1 although the association with preterm birth before 35 weeks of gestation, previously reported in the source  
2 cohort.<sup>11</sup> approached statistical significance (HR 1.60; 0.94, 2.72). The risk of T2D was also not associated  
3 with maternal age, height, BMI before delivery or parity or with childhood socio-economic position;  
4 offspring with lower adult socio-economic position had higher rates of T2D. Adjustment for these variables  
5 had a negligible effect on the association between maternal hypertensive disorders and offspring T2D  
6 (Table 3).  
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14 We then assessed the association between birth weight SD score and adult T2D separately among offspring  
15 from normotensive and hypertensive pregnancies (Table 4). The association appeared stronger among  
16 normotensive pregnancies, although the interaction was not formally statistically significant. Conversely,  
17 the association between maternal gestational hypertension and offspring adult T2D was strongest among  
18 offspring with the highest birth weight SD scores.  
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## 26 27 **Comment**

28 We found that offspring born to mothers with gestational hypertension have higher risk of T2D treated by  
29 medication than offspring of normotensive mothers. The association was limited to T2D with medication  
30 initiated before 62 years of age. It was not confounded by maternal age or BMI in pregnancy or by  
31 childhood socio-economic status. We were unable to find any association between maternal preeclampsia  
32 and offspring T2D.  
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43 We have previously discussed the limitations of the maternal hypertension in pregnancy data in the  
44 Helsinki Birth Cohort Study.<sup>7</sup> A further limitation is that we have no information on maternal gestational  
45 diabetes or offspring adult BMI, key risks factors of offspring T2D. Adjustment for maternal BMI, however,  
46 did not change our findings. Moreover, while the use of medication purchase data enabled us to distinguish  
47 between type 1 and type 2 diabetes, we could not identify subjects with diabetes treated by diet only or  
48 subjects who died of emigrated before the register was started in 1995. As described,<sup>7</sup> a number of  
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1 mothers had no blood pressure recorded before 20 weeks of gestation. Thus the gestational hypertension  
2 group is likely also to include mothers that today would be classified as having chronic hypertension.  
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5 While gestational hypertension predicts subsequent T2D and other chronic diseases in the mother, <sup>1</sup> our  
6 study is to our knowledge the first to assess its effects on diabetes in adult offspring. The hazard ratios,  
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8 1.15 for any T2D and 1.34 for T2D before 62 years, are relatively modest. Yet, they compare with  
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10 associations with established adult risk factors such as the risk ratio of 1.37 for T2D reported for current  
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12 smoking.<sup>12</sup> For further comparison, previously reported hazard ratios of gestational hypertension in this  
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14 same cohort include 1.4 for offspring stroke,<sup>7</sup> 1.19 for any severe mental disorder and 1.44 for severe  
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16 mood disorder.<sup>13</sup>  
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22 The lack of association between maternal preeclampsia and offspring T2D should be interpreted with  
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24 caution because of the smaller numbers, although it is consistent with two previous studies that have  
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26 focused on preeclampsia rather than gestational hypertension as an exposure.<sup>3,5,9</sup> In the present study, the  
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28 confidence interval of the 0.98 hazard ratio (0.71, 1.34) excluded any moderate or large effects with  
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30 reasonable certainty.  
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35 Both low birth weight and gestational hypertension seemed to be independent, additive risk factors for  
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37 offspring T2D. There was, however, some suggestion that the risk associated with gestational hypertension  
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39 might be strongest among those born at high birth weight for gestation. This would be consistent with a  
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41 role of maternal gestational diabetes or subthreshold hyperglycaemia, which are associated with  
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43 gestational hypertension and high birth weight.  
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48 We conclude that intrauterine exposure maternal gestational hypertension is a novel risk factor of type 2  
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50 diabetes in adult life. This finding underlines the role of the whole spectrum of hypertensive disorders of  
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52 pregnancy as risk factors of offspring disease throughout life. Further, it reinforces previous suggestions  
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54 that adult healthcare providers should incorporate birth histories when evaluating of an individual's risk to  
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56 develop T2D.  
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Table 1. Definition of maternal hypertension in pregnancy according to the International Society for the Study of Hypertension in Pregnancy criteria, modified based on data available.<sup>7</sup>

	Blood pressure	Proteinuria
Normotension	All systolic measurements <140 mmHg and diastolic <90 mmHg	No
Gestational hypertension	At least one systolic measurement ≥140 mmHg or diastolic mmHg after 20 weeks of gestation, no chronic hypertension	No
Non-severe preeclampsia	At least one systolic measurement ≥140 mmHg or diastolic mmHg after 20 weeks of gestation, all systolic measurements <160 mmHg and diastolic <110 mmHg	Yes <sup>a</sup>
Severe preeclampsia	At least one systolic measurement ≥160 mmHg or diastolic mmHg after 20 weeks of gestation	Yes <sup>a</sup>
Chronic hypertension or superimposed preeclampsia	At least one systolic measurement ≥140 mmHg or diastolic mmHg before 20 weeks of gestation <sup>b</sup>	Yes/No
Any hypertension in pregnancy	Any of the above hypertensive conditions	

<sup>a</sup>Definition of proteinuria was based on a qualitative measurement, the cutoff of which approximates to 1 mg/mL of albumin

<sup>b</sup>816 of the 6410 mothers (12.7%) had blood pressure recordings before 20 weeks gestation and could be classified in relation to chronic hypertension / superimposed preeclampsia. Therefore we do not present chronic hypertension / superimposed preeclampsia as a separate exposure group but include the offspring of these mothers in the “any hypertension” category.

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Table 2. Characteristics of the mothers and their offspring according to maternal hypertensive disorders

	Normotensive 3524	Any hypertension in pregnancy n=1780*	Gestational hypertension n=1336	Preeclampsia, non-severe n=97	Preeclampsia, severe n=134	Missing
Men	1836 (52.1%)	899 (50.5%)	677 (50.7%)	54 (55.7%)	71 (53.0%)	0
Maternal						
Age at delivery	27.9 (5.3)	28.9 (5.7)	28.9 (5.8)	27.8 (4.9)	29.2 (6.1)	5
Height	159.5 (5.6)	159.7 (5.8)	159.6 (5.8)	160.0 (5.8)	160.2 (5.6)	266
Body mass index before delivery	26.0 (2.8)	26.8 (3.2)	26.8 (3.2)	27.0 (3.5)	26.8 (3.0)	339
Primiparous	1731 (49.1%)	1000 (56.2%)	731 (54.7%)	66 (68.0%)	101 (75.4%)	0
Birth						
Length of gestation (weeks)	40.0 (1.6)	39.9 (1.7)	40.0 (1.7)	39.7 (1.9)	39.3 (2.0)	285
Birth weight (g)	3430 (467)	3345 (518)	3379 (495)	3227 (514)	2881 (590)	0
Birth weight SD score	-0.3 (0.9)	-0.4 (1.1)	-0.4 (1.0)	-0.6 (1.0)	-1.3 (1.1)	285
Father's occupational status						0
..Unknown	211 (6.0%)	116 (6.5%)	88 (6.6%)	6 (6.2%)	9 (6.7%)	
Manual worker	2385 (67.7%)	1201 (67.5%)	903 (67.6%)	58 (59.8%)	81 (60.4%)	
Lower official	697 (19.8%)	339 (19.0%)	254 (19.0%)	21 (21.6%)	31 (23.1%)	
Higher official	231 (6.6%)	124 (7.0%)	91 (6.8%)	12 (12.4%)	13 (9.7%)	
Own adult occupational status						0
..Unknown	62 (1.8%)	32 (1.8%)	25 (1.9%)	1 (1.1%)	1 (0.7%)	
Manual worker	1416 (40.2%)	744 (41.8%)	563 (42.1%)	35 (36.1%)	56 (41.8%)	
Self-employed	330 (9.4%)	163 (9.2%)	121 (9.1%)	10 (10.3%)	12 (9.0%)	
Lower official	1327 (37.7%)	662 (37.2%)	500 (37.4%)	39 (40.2%)	46 (34.3%)	
Higher official	389 (11.0%)	179 (10.1%)	127 (9.5%)	12 (12.4%)	19 (14.2%)	
Adult						
Ever purchased medication for diabetes, n (%)	660 (18.7%)	363 (20.4%)	277 (20.7%)	17 (17.5%)	25 (18.7%)	0
Mean age at first purchase, years	62.5 (6.1)	61.7 (6.0)	61.8 (6.1)	62.6 (6.2)	61.4 (6.0)	0

Numbers are mean (SD) or n (%)

<sup>a</sup>The number includes in addition 213 mothers with chronic hypertension.

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Table 3. Hazard ratios for type 2 diabetes in the offspring according to maternal hypertension in pregnancy, adjusted for covariates

	Normotensive 3524	Any hypertension in pregnancy n=1780 <sup>a</sup>	Gestational hypertension n=1336	Preeclampsia, non- severe n=97	Preeclampsia, severe n=134
Model 1	Referent	1.13 (1.00, 1.29)	1.15 (1.00, 1.33)	0.92 (0.57, 1.50)	1.01 (0.68, 1.51)
Model 2	Referent	1.13 (0.99, 1.29)	1.16 (1.01, 1.35)	0.92 (0.57, 1.50)	0.95 (0.63, 1.44)
Model 3	Referent	1.13 (0.99, 1.30)	1.16 (1.00, 1.35)	0.90 (0.54, 1.51)	0.99 (0.65, 1.52)
Model 4	Referent	1.13 (0.99, 1.28)	1.14 (0.99, 1.32)	0.94 (0.58, 1.53)	1.02 (0.69, 1.53)

Analyses are stratified for offspring sex and year of birth

Model 1, unadjusted

Model 2, adjusted for length of gestation and birth weight SD score

Model 3, adjusted for 2 + maternal age, height, BMI and whether multiparous

Model 4, adjusted for childhood and adult socio-economic position.

<sup>a</sup>The number includes in addition 213 mothers with chronic hypertension.

Table 4. Hazard ratios for type 2 diabetes in the offspring of normotensive mothers and mothers with gestational hypertension, according to birth weight SD in relation to length of gestation

Birth weight SD score in thirds	Normotensive		Gestational hypertension	
	N diabetes/total (%)	Hazard ratio (95%) CI	N diabetes/total	Hazard ratio (95%) CI
Lowest	232/1043 (22.2%)	1.43 (1.18, 1.74)	112/450 (24.9%)	1.71 (1.35, 2.17)
Middle	207/1137 (18.2%)	1.16 (0.95, 1.41)	79/432 (18.3%)	1.19 (0.91, 1.55)
Highest	201/1222 (16.4%)	Referent	78/393 (19.9%)	1.30 (1.00, 1.69)
<i>Hazard ratio per one SD birth weight</i>				
		0.83 (0.76, 0.91)		
<i>p for linear trend</i>		<0.0001	0.1	
<i>p for quadratic trend</i>		0.05	0.2	
<i>p for interaction<sup>a</sup></i>			0.2	

Analyses are stratified for offspring sex and year of birth and adjusted for length of gestation.  
<sup>a</sup>Interaction between gestational hypertension and birth weight SD score as a continuous variable

**Figure captions**

Figure 1. Hazard ratios and 95% confidence intervals for type 2 diabetes according to exposure to maternal hypertensive disorders in pregnancy. The percentages indicate proportion of cohort members with type 2 diabetes. "Any hypertension in pregnancy" includes also 213 mothers with chronic hypertension.



American Journal of Obstetrics & Gynecology

Dear Editor,

Oulainen, 9th August 2016

Enclosed please find our manuscript by Kajantie et al., entitled "Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: The Helsinki Birth Cohort Study", which we submit for evaluation of possible publication in the *American Journal of Obstetrics & Gynecology*.

In the manuscript we show that offspring who were *in utero* exposed to maternal gestational hypertension have an increased risk of type 2 diabetes in adult life. Among working-age individuals, the hazard ratio for T2D is 1.37, which corresponds that of established adult risk factors such as tobacco smoking.

The risk is not explained by confounding factors such as maternal age or body mass index or childhood socio-economic position, and it is independent of the risk associated with low birth weight.

The data have neither been published nor are under consideration of publication elsewhere.

We believe this study is of interest to the wide readership of *AJOG* because:

- While there has been extensive research confirming the association between hypertension in pregnancy and subsequent T2D and insulin resistance in the mother, this study is to our knowledge the first to demonstrate an increased risk of T2D in the offspring of mothers with gestational hypertension.
- Our study is based on unique data. The Helsinki 1934-1944 Birth Cohort is the oldest cohort with diagnoses of hypertension in pregnancy confirmed from medical records according to modern criteria. We assess T2D through the Finnish National Medication Purchase Register with nearly universal coverage.
- Our findings emphasize the role of the whole spectrum of hypertensive disorders of pregnancy as risk factors of offspring disease throughout life.

We hope you agree and shall be looking forward to your reply.

Yours sincerely,

Eero Kajantie, MD, DrMedSc

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Each author is required to submit a signed Statement of Authorship upon submission. This applies to all submission types including Editorial, Letters to the Editor, etc.

Manuscript # (if available): \_\_\_\_\_

Date: Aug 9<sup>th</sup>, 2016

Manuscript title: *Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: The National Birth Cohort Study*

Corresponding author: *Erica Kajantie*

Authors may either sign the same form or submit individually

I am an author on this submission, have adhered to all editorial policies for submission as described in the information for Authors, attest to having met all authorship criteria, and all potential conflicts of interest / financial disclosures appears on the title page of the submission.

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Date: Aug 9<sup>th</sup>, 2016

Manuscript # (if available): \_\_\_\_\_

Manuscript title: *Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: The Helsinki Birth Cohort Study*

Corresponding author: Eero Kajantie

**Authors may either sign the same form or submit individually**

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Date: Aug 9<sup>th</sup>, 2016

Manuscript # (if available): \_\_\_\_\_

Manuscript title: *Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: The Helsinki Birth Cohort Study*

Corresponding author: Eero Kajantie

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A handwritten signature in black ink, appearing to be 'J. Eriksson', written over a horizontal line.

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