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No evidence of seasonality of birth in adult type 2 diabetes in Denmark

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Abstract

Aims/hypothesis The season of birth might influence prenatal circumstances, which may influence the risk of developing type 2 diabetes. The aim of this study was to determine whether the diagnosis of type 2 diabetes in Denmark changed with the season of birth.

Methods This study used data from the population-based Copenhagen School Health Records Register (CSHRR) that includes schoolchildren born between 1930 and 1989. Via a personal identification number, the CSHRR was linked to the National Patient Register containing hospital discharge diagnoses since 1977. The effect of seasonal variation in birth on the risk of type 2 diabetes was assessed using Cox regression, with month or season of birth as the predictor. The underlying time variable was age, and follow-up started in 1977 or at age 30 years.

Results The study population consisted of 223,099 people, of whom 12,486 developed adult type 2 diabetes. Using January as the reference month, the risk of type 2 diabetes by month of birth was not statistically different for any of the 11 comparative birth months. Grouping month of birth into seasons (spring was the reference) gave essentially similar results, showing no difference in the risk of type 2 diabetes for any season. Repeating the analysis by sex, birth cohort and birthweight categories revealed no associations.

Conclusions/interpretation The risk of adult type 2 diabetes was not associated with month of birth in a large Danish population-based study. The results suggest that the causes of seasonality in birthweight are not causes of type 2 diabetes.

Keywords Birthweight · Denmark · Diabetes mellitus · Fetal development · Pregnancy · Registries · Seasons · Type 2 · Vitamin D

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Abbreviations
CSHRR   The Copenhagen School Health Records Register
NPR   National Patient Register

Introduction

Studies have shown that suboptimal prenatal circumstances may lead to an increased risk of disease later in life, with type 2 diabetes being perhaps the most well-documented example of this association [1–4]. The mechanisms underlying prenatal programming of type 2 diabetes are not well understood, but it

is possible that environmental influences during critical periods of prenatal life can programme the structure and function of organs and tissues that are essential for glucose homeostasis later in life [5].

Birthweight has been found to vary according to the season of birth, with peaks in birthweight in both autumn and summer [6, 7], and it has been suggested that risk of type 2 diabetes displays a similar seasonal variation depending on the month of birth [8–10]. Indeed, studies in American children [10] and in adult populations in the Netherlands [8] and Ukraine [9] have reported seasonal variations in type 2 diabetes development according to month of birth. The lowest type 2 diabetes prevalence in these studies was observed in people born in October to December, and the highest prevalence was in people born in January to April. These findings suggest that there may be shared aetiology and mechanisms behind the seasonality of birthweight and type 2 diabetes risk, in which fetal growth and eventual birthweight may or may not mediate the effects on type 2 diabetes risk.

Many factors vary with the season, including the availability and nutritional quality of foods, temperature, hours of sunshine, number of wet days, vitamin D synthesis (as a consequence of varying ultraviolet B radiation) and infection load. From historical famine studies in China, the Netherlands and Ukraine, we know that reduced energy intake during pregnancy is associated with a higher risk of type 2 diabetes in the offspring [11–13], and it is possible that the nutritional value of food is lower in winter than in summer. The winter hypothesis suggests that a cold temperature and fewer hours of sunshine during pregnancy signals a need for energy accrual and storage in the fetus, which will become programmed and last for life [14]. A study into vitamin D status during pregnancy and offspring risk of type 2 diabetes suggested a protective effect of vitamin D, which might be reflected in the seasonal analysis [15]. Infections during pregnancy are suspected to alter metabolic programming and might therefore influence the risk of type 2 diabetes [16]. Another hypothesis involves postnatal factors including breast feeding [17]. It has been reported that children born in summer are breastfed for shorter periods than children born in winter [18], and the duration of breastfeeding has been reported to be inversely associated with the risk of type 2 diabetes later in life [17, 19].

The aim of the present study was to investigate whether the incidence of type 2 diabetes varied according to season of birth in a Danish cohort of men and women born between 1936 and 1983.

Methods

Study population The present study is based on a cohort from the Copenhagen School Health Records Register (CSHRR), a population-based register that includes virtually every schoolchild in Copenhagen municipality born between 1930 and 1989. The register includes 372,636 records and contains computerised information about 329,968 of these children (name, sex, date of birth, personal identification number), along with measures of height and weight. Information on birthweight was obtained from the birth year of 1936 onwards at the school entry examination when children were approximately 5–7 years of age. In general, mothers have been found to recall offspring birthweight very well [20, 21]. The CSHRR is described in greater detail elsewhere [22].

Via the personal identification number, which was established on 2 April 1968, records in the CSHRR were linked to data from the National Patient Register (NPR) [23]. The NPR contains up to 20 hospital discharge diagnoses since 1 January 1977.

Type 2 diabetes was identified from hospital discharge diagnoses (i.e. action diagnoses, supplementary diagnoses or underlying diagnoses) in the NPR using ICD-8 (www. wolfbane.com/icd/icd8.htm) code 250 (diabetes mellitus) and ICD-10 (www.who.int/classifications/icd/en/) codes E11 (non-insulin-dependent diabetes mellitus), E12 (malnutrition-related diabetes mellitus), E13 (other specified diabetes mellitus), E14 (unspecified diabetes mellitus). The ICD-9 system was never introduced in Denmark; therefore, these codes were not included. Individuals registered in the NPR were included as cases at the first diagnosis of diabetes.

Type 1 and type 2 diabetes patients were indistinguishable until 1987 in the NPR, when ICD-8 code 249 (insulin-dependent diabetes mellitus) was introduced in Denmark. This means that ICD-8 code 250 also includes type 1 diabetes until 1987. To reduce the number of type 1 diabetes patients included as cases, we applied an age cut-off of 30 years because the majority of individuals with type 1 diabetes are diagnosed before this age. The incidence of diabetes diagnosed after 30 years of age was used as an indicator of type 2 diabetes. Due to this age-cut-off, children born after 1983 were excluded.

Statistical analysis The effect of seasonal variation in birth on the risk of type 2 diabetes was assessed using Cox regression analysis, with month of birth as the predictor. Risk time was calculated from 1 January 1977 or 30 years of age, whichever was later. Risk time ended on the date of a diabetes diagnosis as registered in the NPR, death, emigration or loss to follow-up, or on 31 December 2013, whichever came first.

The exposure variable was modelled in various ways. First, the date of birth was modelled categorically as month of birth (January–December) and as season of birth (winter, December–February; spring, March–May; summer, June–August; autumn, September–November).

The reference group was set to January in models that included the exposure variable in months, and spring in models that included the exposure variable in seasons. As a

sensitivity analysis, we performed analyses using different reference months to ensure this would not influence the outcome of our analyses.

When appropriate, analyses were stratified by sex and birth cohort (birth years 1936–1939, 1940–1944, 1945–1949, 1950–1954, 1955–1959, 1960–1964, 1965–1969, 1970–1974, 1975–1979 and 1980–1983). To investigate potential effect modification, the analyses were repeated by time periods defined according to the patterns of seasonal variation in birthweight that we observed in a previous study [7].

To evaluate whether a potential association between season of birth and risk of type 2 diabetes was independent of birthweight, we adjusted the analysis by birthweight (continuous and by the categories <2.75, 2.75–3.25, 3.25–3.75, 3.75–4.25 and ≥4.25). We also repeated the analysis by groups of birthweight (<3.25, 3.25–3.75 and >3.75 kg) to check for effect modification.

The assumption of proportional hazards was checked by stratifying the analysis by age at diagnosis in groups (30–39, 40–49, 50–59, 60–69 and 70–80 years).

Sensitivity analyses were performed using other type 2 diabetes definitions: patients >40 years of age, exclusion of E12–14 ICD10 codes (E12, malnutrition-related diabetes mellitus; E13, other specified diabetes mellitus; E14, unspecified diabetes mellitus), exclusion of patients ever diagnosed with type 1 diabetes, and diagnosis based on the National Diabetes Register (incident cases available from 1 January 1995) that in addition to information from the NPR includes information from the National Health Service Register (registration of chiropody and blood glucose measurements) and the Danish National Prescription Registry (purchase of oral glucose-lowering drugs) [24].

Results

Among those who had a personal identification number within the total population of 372,636 persons in the CSHRR, 262,743 were alive and living in Denmark on 1 January 1977 or when they turned 30 years of age. After excluding subjects who had missing information on birthweight or had a birthweight outside the range of 2.0–5.5 kg, the final study population consisted of 223,099 children (Fig. 1). Within the final study population, 12,486 developed type 2 diabetes (Table 1); of the participants who never received a diagnosis of type 2 diabetes, 30,360 died, 4,745 emigrated, 148 were lost to follow-up and 175,360 were alive on 31 December 2013. Mean age at the first type 2 diabetes diagnosis was 56.3 years (SD 10.2 years). The proportion (%) of individuals with type 2 diabetes was higher in males than in females for all birth months (Fig. 2).

Investigating the risk of type 2 diabetes by month of birth revealed no statistically significant difference in any of the
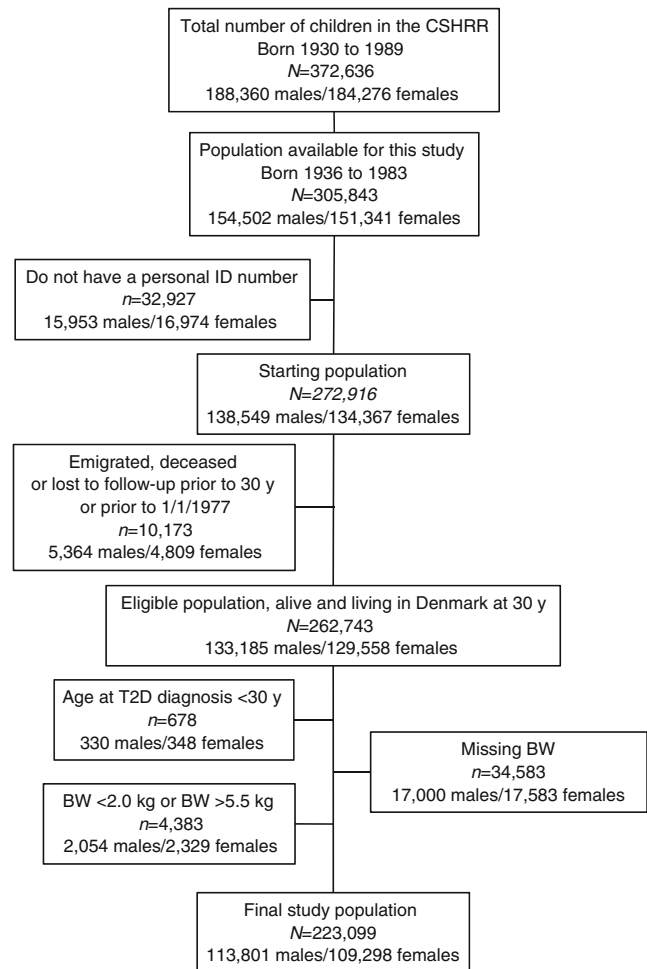

Fig. 1 Flow chart of eligible subjects and those included in the study. The study population includes children born between 1936 (when birth weight was first reported) and 1983 (due to the lower age limit for age at diagnosis of 30 years), who were alive in 1977 or at 30 years of age, and with available birthweight data. BW, birth weight; T2D, type 2 diabetes; y, years

birth months compared with the reference month of January (Fig. 3). Changing the reference month to any other month did not change the results (data not shown). There was no notable difference in the seasonal pattern in type 2 diabetes risk between males and females (Fig. 3).

Grouping month of birth into seasons before calculating the HR of type 2 diabetes showed no association between the season of birth and risk of type 2 diabetes when comparing any other season with spring (results not shown). Changing the reference group did not influence the results (data not shown).

We wanted to see whether the hypothesised association between month of birth and later risk of type 2 diabetes was independent of birthweight. Repeating the analysis of month of birth and type 2 diabetes by birthweight categories (<3.25, 3.25–3.75, >3.75 kg) revealed no effect modification (results not shown). When adjusting the analysis for birthweight

Table 1 Description of type 2 diabetes cases by ICD codes

Classification	Code	Description	Patients (n)		
			Men	Women	Total
ICD-8	250	Diabetes mellitus	962	551	1,513
ICD-10	E11	Non-insulin-dependent diabetes mellitus	6,204	3,852	10,056
	E12	Malnutrition-related diabetes mellitus	14	9	23
	E13	Other specified diabetes mellitus	66	36	102
	E14	Unspecified diabetes mellitus	504	288	792
Total			7,750	4,736	12,486

(continuous and in categories), we saw that the risk of type 2 diabetes was significantly associated with birthweight, but the association between month of birth and risk of type 2 diabetes was unchanged (results not shown). Adjusting for birthweight in models of season of birth and risk of type 2 diabetes also showed no associations (results not shown).

We stratified the analysis by age at diagnosis and used alternative type 2 diabetes definitions, but none of the sensitivity analyses revealed an association between birth month and risk of type 2 diabetes (results not shown). Further, we found no effect modification of time periods defined according to the patterns of seasonal variation in birthweight.

Discussion

In the present study, we investigated whether the risk of type 2 diabetes was associated with the month of birth. Our hypothesis was that pregnancy during different parts of the year, and the obvious seasonal variation in various environmental exposures that follow, would influence the later risk of type 2 diabetes. However, we found no evidence to support this hypothesis in our study of Danish register-based information.

A few other studies have investigated the potential association between month of birth and risk of type 2 diabetes: in contrast to our results, these studies did find significant seasonal variation in the risk of type 2 diabetes by month of birth [8–10]. We speculate that to some extent this could reflect publication bias.

In a large register-based study from the Ukraine, 52,214 type 2 diabetes patients born during the period 1920–1959, including the severe famine in Ukraine in 1933, were compared with a reference population of 1,567,917 people born during the same period and the same region [9]. Their results showed a peak in type 2 diabetes prevalence in people born in April and a nadir in type 2 diabetes prevalence in individuals born in November–December ($p<0.0001$). They investigated the risk in middle- to old-aged patients; the youngest patient included was 48 years at the first diagnosis. Both the time period and age group under study were similar in the Ukraine and in our study, but information on how they identified type 2 diabetes was very limited (onset after 39 years of age irrespective of type of treatment registered in the Ukrainian diabetes mellitus register). Therefore, we were unable to compare the different definitions used.

The different results observed in Ukraine and Denmark could theoretically be due to methodological differences. However, they might also be related to differences in latitude or in the standard of living between Denmark and Ukraine. Indeed, seasonal variation in both nutrition and weather was
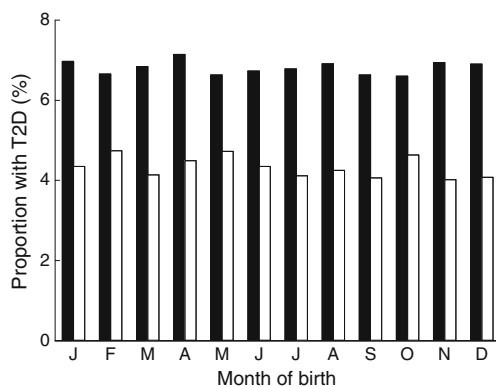

Fig. 2 The proportion of individuals with type 2 diabetes (%) per month of birth for males (black bars) and females (white bars). T2D, type 2 diabetes
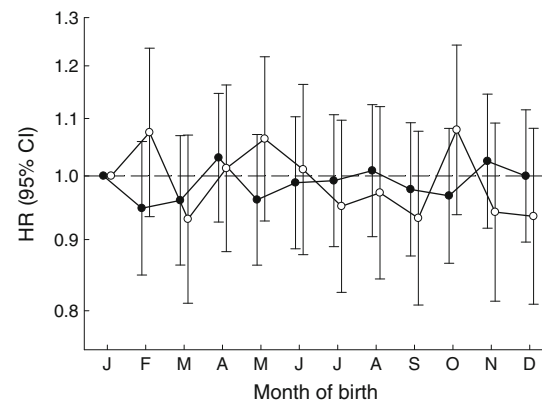

Fig. 3 HR and 95% CIs for adult type 2 diabetes according to the month of birth in males (black circles) and females (white circles). January is the reference month

much more extreme in Ukraine than in Denmark during the study periods; since Ukraine is a low-income country, the population might have experienced more pronounced extremes than in a more affluent country such as Denmark. Given that access to food during a famine period is likely to be most severe during spring, when food stocks are depleted, it could be speculated that the extreme famine affecting certain parts of Ukraine in 1933 may provide a partial explanation. However, the short duration of this famine period may not be sufficient to explain the seasonality of type 2 diabetes according to birth month that was seen across decades in Ukraine.

Another study that reported a seasonal variation in type 2 diabetes prevalence according to month of birth was performed in the Netherlands. It included a group of 282 type 2 diabetes patients selected from 30–90 year old individuals born during 1896–1959 in a hospital in Amsterdam, and a reference population of all births in the Netherlands during the years 1938–1970 ($n=7,591,902$) [8]. The results showed that the risk of developing type 2 diabetes was higher in persons born during January–March compared with October–December ($p<0.005$). Compared with the Ukraine, Denmark and the Netherlands are more similar with respect to latitude, climate and living conditions, and the study period covers some of the same years. However, one major difference is that the Dutch Hunger Winter in 1944 might have influenced the results in the Dutch study. Denmark did not experience famine during the Second World War. However, as with the Ukraine famine study, the short duration of the famine argues against this possibility.

Another study reporting that seasonal variation of birth affects type 2 diabetes risk (lowest risk of type 2 diabetes was observed in children born in October) was performed in Chicago, USA. It investigated the risk of childhood type 2 diabetes (age at diagnosis <18 years) according to month of birth [10]. Although type 2 diabetes was relatively prevalent among these US children, numbers were much lower than during adulthood. The childhood cases probably represent a group of more severely diseased patients with very different disease aetiologies than in adults. Also, one of the criteria they used to identify type 2 diabetes was obesity, and we did not apply this restriction to our patients. As a result, direct comparisons with our study are difficult because we did not examine the presumably severe form of type 2 diabetes that was investigated in this study. The study population was also ethnically different from ours since all participants were African-American, and nearly all children in the CSHRR were white [22].

A common limitation of the three previous studies was the lack of information on how they identified type 2 diabetes [8–10], which is important for comparing results. Varying definitions could give groups of patients with different subtypes of the disease, which might influence the results. We identified type 2 diabetes patients in various ways, and found no differences in our results whatever definition was used. Our data were based on hospitalisation discharge diagnoses, which to an unknown extent are likely to include patients with relatively more severe type 2 diabetes. By taking this approach, and with the much higher awareness of type 2 diabetes over the last decades and the lower, more inclusive glycaemic diagnostic criteria, we probably missed an equally large number of Danish citizens with the mildest type 2 diabetes cases.

The major strengths of the present study include the large sample size, the representativeness of the cohort, and the long study period and follow-up time. Another strength is that we identified type 2 diabetes cases using the NPR, which has complete coverage of all somatic in-patients diagnosed at Danish hospitals from 1 January 1977 onwards [23]. Limitations include the late start of the NPR, which means that for the oldest participants the earliest possible diagnosis was at age 41. As mentioned above, the identification of type 2 diabetes patients at hospital admission in our study may have selected for the most severe cases. However, the sensitivity analysis identified patients based on the National Diabetes Register, which includes information from the NPR, the National Health Service Register (registration of chiropody and blood glucose measurements) and the Danish National Prescription Registry (purchase of oral glucose-lowering drugs) [24]; changing the case definition had no impact on our results. The National Diabetes Register contains information on incident cases from the 1 January 1995, which means that the size of the eligible population was reduced in sensitivity analyses.

We were able to detect significant seasonal variations in birthweight in a previous study of the current Danish population [7], which support the validity of the birthweight data. This subsequently begs the question of which factors that are not fluctuating with the seasons may explain the association between low birthweight and the risk of developing type 2 diabetes. One possibility could be that genetic factors influencing both birthweight and the risk of type 2 diabetes explain the link; indeed, the *MODY2* diabetes gene (also known as *GCK*) as well as two or three of the more than 70 known type 2 diabetes susceptibility risk genotypes are also associated with low birthweight [25, 26]. However, these genetic associations are unlikely to explain the magnitude of the link between low birthweight and risk of type 2 diabetes, and other explanations including non-genetic factors should be looked for.

Conclusion We expected to see an association between season of birth and type 2 diabetes risk, but did not find it. The proposed pathways of association included mechanisms operating wholly or partly through birthweight, but also mechanisms that may be independent of birthweight. We found no evidence to support these hypotheses. On the other hand, we cannot exclude the possibility of mechanisms operating

through birthweight because the amplitude of the seasonal variation in birthweight was approximately 40 g, which may be too small to allow detection of an effect on type 2 diabetes risk. Although, in the current setting, seasonal variation in birthweight did not appear to affect the later risk of type 2 diabetes, further research in other settings with more severe seasonal variation might reveal such an association.

Duality of interest statement The supporting bodies for this project had no role in the design, implementation, analysis or interpretation of the data presented. The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement AV and TIAS conceived the research idea; CBJ, AV and TIAS designed the study; and CBJ performed the statistical analysis. All authors analysed and interpreted the data; CBJ drafted the manuscript; MG, BLH, TIAS, EZ, JLB and AV revised the manuscript critically for important intellectual content; and CBJ assumes primary responsibility for the final content. All authors read and approved the final version of the manuscript to be published. CBJ is the guarantor of this work.

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