#### Lower daily carbohydrate consumption than recommended by the Institute of Medicine is common among women with type 2 diabetes in early pregnancy in Denmark

Ásbjörnsdóttir, Björg; Ronneby, Helle; Vestgaard, Marianne; Ringholm, Lene; Nichum, Vibeke Ladefoged; Jensen, Dorte M; Raben, Anne; Damm, Peter; Mathiesen, Elisabeth R

Published in: **Diabetes Research and Clinical Practice** 

DOI: 10.1016/j.diabres.2019.05.012

Publication date: 2019

Document version Peer reviewed version

Document license: CC BY-NC-ND

*Citation for published version (APA):* Ásbjörnsdóttir, B., Ronneby, H., Vestgaard, M., Ringholm, L., Nichum, V. L., Jensen, D. M., ... Mathiesen, E. R. (2019). Lower daily carbohydrate consumption than recommended by the Institute of Medicine is common among women with type 2 diabetes in early pregnancy in Denmark. Diabetes Research and Clinical Practice, 152, 88-95. https://doi.org/10.1016/j.diabres.2019.05.012

#### Accepted Manuscript

Lower daily carbohydrate consumption than recommended by the Institute of Medicine is common among women with type 2 diabetes in early pregnancy in Denmark

Björg Ásbjörnsdóttir, Helle Ronneby, Marianne Vestgaard, Lene Ringholm, Vibeke L. Nichum, Dorte M. Jensen, Anne Raben, Peter Damm, Elisabeth R. Mathiesen

PII:	S0168-8227(18)31890-4
DOI:	https://doi.org/10.1016/j.diabres.2019.05.012
Reference:	DIAB 7733

Diabetes Research and Clinical Practice

Received Date:20 December 2018Revised Date:9 May 2019Accepted Date:13 May 2019

To appear in:



Please cite this article as: B. Ásbjörnsdóttir, H. Ronneby, M. Vestgaard, L. Ringholm, V.L. Nichum, D.M. Jensen, A. Raben, P. Damm, E.R. Mathiesen, Lower daily carbohydrate consumption than recommended by the Institute of Medicine is common among women with type 2 diabetes in early pregnancy in Denmark, *Diabetes Research and Clinical Practice* (2019), doi: https://doi.org/10.1016/j.diabres.2019.05.012

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

#### 1 Original article

# Lower daily carbohydrate consumption than recommended by the Institute of Medicine is common among women with type 2 diabetes in early pregnancy in Denmark

- 4 Björg Ásbjörnsdóttir<sup>a,b,c</sup>, Helle Ronneby<sup>a,d</sup>, Marianne Vestgaard<sup>a,b,c</sup>, Lene Ringholm<sup>a,b,e</sup>, Vibeke L.
- 5 Nichum<sup>a,f</sup>, Dorte M. Jensen<sup>g,h</sup>, Anne Raben<sup>i</sup>, Peter Damm<sup>a,c,f</sup>, Elisabeth R. Mathiesen<sup>a,b,c</sup>.
- 6
- <sup>7</sup> <sup>a</sup>Center for Pregnant Women with Diabetes, Rigshospitalet, Blegdamsvej 9 4001, 2100
- 8 Copenhagen Ø, Denmark,
- <sup>b</sup>Department of Endocrinology, Rigshospitalet, Ole Måløes Vej 24 7551, 2100 Copenhagen Ø,
  Denmark,
- 11 <sup>c</sup>Institute of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen,
- 12 Blegdamsvej 3, 2200 Copenhagen N, Denmark,
- <sup>d</sup>The Nutrition Unit, Rigshospitalet, Henrik Harpestrengs Vej 4 5711, 2100 Copenhagen  $\emptyset$ ,
- 14 Denmark,
- <sup>15</sup> <sup>e</sup>Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, 2820 Gentofte, Denmark,
- <sup>16</sup> <sup>f</sup>Department of Obstetrics, Rigshospitalet, Blegdamsvej 9 4031, 2100 Copenhagen Ø, Denmark,
- <sup>17</sup> <sup>g</sup>Steno Diabetes Center Odense, Odense University Hospital, Kløvervænget 10, 5000 Odense C,
- 18 Denmark,
- <sup>19</sup> <sup>h</sup>Department of Gynaecology and Obstetrics, Odense University Hospital, Kløvervænget 23,
- 20 5000 Odense C, Denmark
- <sup>1</sup>Department of Nutrition, Exercise and Sports, University of Copenhagen, Rolighedsvej 26, 1958
- 22 Frederiksberg C, Denmark.
- 23

#### 24 Corresponding author:

- 25 Björg Ásbjörnsdóttir, MD
- 26 Center for Pregnant Women with Diabetes
- 27 Rigshospitalet
- 28 Blegdamsvej 9 4001
- 29 2100 Copenhagen Ø
- 30 Denmark
- 3132 Home address:
- 33 Sandkaj 21, st.tv
- 34 2150 Nordhavn
- 35 Denmark
- 36
- 37 Telephone-number: +45 2285 6797
- 38 Fax number: +45 3545 2240
- 39 E-mail address: bjoerg.asbjoernsdottir.01egionh.dk
- 40 E-mail addresses of the authors:
- 41 Helle Ronneby: <u>Helle.Ronneby@regionh.dk</u>
- 42 Marianne Vestgaard: <u>marianne.jenlev.vestgaard@regionh.dk</u>

- Lene Ringholm: <u>enel@dadlnet.dk</u>
- Vibeke L. Nichum: vibeke.ladefoged.nichum@regionh.dk
- Dorte M. Jensen: Dorte.Moeller.Jensen@rsyd.dk
- Anne Raben: ara@nexs.ku.dk
- Acctebilten

#### 53 <u>Aims:</u>

- 54 To secure adequate carbohydrate supply in pregnancy, the Institute of Medicine (IOM) recommends
- a minimum amount of carbohydrates of 175 g daily. Currently a low carbohydrate diet is a popular
- health trend in the general population and this might also be common among overweight and obese
- 57 pregnant women with type 2 diabetes (T2D). Thus, we explored carbohydrate consumption among
- pregnant women with T2D including women with type 1 diabetes (T1D) for comparison.
- 59
- 60 <u>Methods</u>:
- A retrospective cohort study of consecutive women with T2D (N=96) and T1D (N=108), where
- 62 dietary records were collected at the first antenatal visit.
- 63
- 64 <u>Results</u>:
- Among women with T2D and T1D, bodyweight at the first visit was 90.8±22 (mean±SD) and
- 66 75.5±15 kg (P<0.001) while HbA1c was 6.6±1.2% (49±13 mmol/mol) and 6.6±0.8% (48±8
- 67 mmol/mol), P=0.8, respectively. The average daily carbohydrate consumption from the major
- carbohydrate sources was similar in the two groups ( $159\pm56$  and  $167\pm48$  g, P=0.3), as was the level
- of total daily physical activity (median (interquartile range)): 215 (174-289) and 210 (178-267)
- 70 metabolic equivalent of task-hour/week (P=0.9). A high proportion of women with T2D and T1D
- 71 (52% and 40%, P=0.08) consumed fewer carbohydrates than recommended by the IOM. The
- 72 prevalence of ketonuria ( $\geq 4 \text{ mmol/L}$ ) was 1% in both groups.
- 73
- 74 <u>Conclusions:</u>

, CC

- 75 In early pregnancy, a lower daily carbohydrate consumption than recommended by the IOM was
- common among women with T2D. The results were quite similar to women with T1D, despite a
- markedly higher bodyweight in women with T2D. Reassuringly, ketonuria was rare in both groups.
- 78
- 79 Keywords: Carbohydrate, pregnancy, type 2 diabetes, type 1 diabetes.
- 80

81 1. Introduction

Pregnancies complicated by diabetes are associated with increased risk of adverse perinatal 82 outcomes including infants born large for gestational age (1,2). This is mostly attributed to the 83 maternal transfer of excessive glucose across the placenta leading to accelerated fetal growth (3). 84 The total amount of carbohydrates is the main dietary factor affecting postprandial blood glucose 85 (4). Therefore a restricted carbohydrate consumption in pregnant women with diabetes could be 86 sensible but as both the maternal and the fetal brain mainly use glucose as an energy source, the 87 88 Institute of Medicine (IOM) and the American Diabetes Association (ADA) recommend a minimum of 175 g of carbohydrates daily for pregnant women (5,6). The average daily 89 carbohydrate consumption in early pregnancy in healthy women is in general reported to be well 90 above the minimum amount recommended by the IOM (7,8) and excessive gestational weight gain 91 is common (9). 92

A low carbohydrate diet aiming at reducing plasma glucose levels and obtaining weight loss is a 93 popular health trend in the general population (10) and in patients with type 2 diabetes (T2D) (11) 94 but may be harmful during pregnancy. Insufficient carbohydrate consumption can lead to increased 95 96 lipolysis and ketone body production and pregnant women are in general more prone to ketosis than non-pregnant women (12-14). Previous observational studies in offspring of women with diabetes 97 suggests that elevated maternal ketone bodies may have a negative effect on the developing fetal 98 central nervous system (15,16). Thus, we speculate that, in pregnant women with diabetes, 99 sufficient daily carbohydrate consumption and avoidance of ketonemia are probably important for 100 normal fetal brain development. 101

The total amount of macronutrients required to maintain body weight is dependent on the body
 composition and the level of physical activity. Therefore, the recommendations on carbohydrate
 consumption are often given per kilo bodyweight which probably can lead to inappropriately high

carbohydrate consumption in obese women where the recommended gestational weight gain is
smaller than in normal weight women (14). High prevalence of excessive gestational weight gain
has been reported among pregnant women with diabetes (17-19). Recommendations on lower
energy percent (E%) of carbohydrates in obese pregnant women with diabetes has been suggested
(20).

Modern diabetes treatment respects a flexible lifestyle (21) and the daily amount of carbohydrates varies considerably from day to day in pregnant women with type 1 diabetes (T1D) (22). In a real world, daily dietary intake may therefore vary considerably from the dietary advises given. One small study including 19 women with T2D at 22 gestational weeks found an average carbohydrate consumption of 259 g daily (23). Sufficient intake of lipids and proteins as well as micronutrients during pregnancy is also important for fetal growth (24), but this study is restricted to carbohydrate consumption.

In a real-world setting, we aimed to explore carbohydrate consumption and prevalence of ketonuriain early pregnancy among women with T2D including women with T1D for comparison.

119 2. Subjects, Materials and Methods

120 2.1 Study population

As a part of routine care since January 2013, all pregnant women referred to Center for Pregnant Women with Diabetes at Rigshospitalet have been asked to fill out a 3-day dietary record focusing on carbohydrates before their first antenatal visit at the centre. Thus, a dietary record form was sent to the women along with a welcome letter by mail. The inclusion criteria in this retrospective cohort study from August 2013 to September 2017 were: women with T2D or T1D, Danish speaking, singleton pregnancy and first antenatal visit before 20 gestational weeks. Aiming for a comparable number of women in the two diabetes groups and since data on carbohydrate consumption in

pregnant women with T1D have already been published for the period January 2013 to December
2014 (22), we decided to include women with T1D from January 2015 to September 2017.
In the inclusion period the following women did not meet the inclusion criteria: not-Danish
speaking (n=47 with T2D and n=1 with T1D), multifetal pregnancy (n=10 and n=8), first antenatal
visit later than 20 gestational weeks (n=20 and n=2) and 5 (n=4 and n=1) with previous bariatric
surgery, resulting in 171 eligible women with T2D and 248 with T1D of which 96 (56%) and 108
(44%), respectively had completed the dietary records.

135 2.2 Dietary analysis

At the first antenatal visit, all women had a one-hour appointment with a specialized dietician who 136 used the information from the dietary records as a basis for individualized dietary advice. Based on 137 the dietary records, the dietician counted the recorded carbohydrates and used validated tables (25), 138 photos (26) and a carbohydrate counting app, recommended by the Danish Diabetes Association, 139 when needed. The quantity of the carbohydrates was calculated from the major carbohydrate 140 sources only, i.e. bread products, potatoes, rice, pasta, fruits, dairy products and sweets. The major 141 carbohydrate sources account for the majority of carbohydrates consumed e.g. a commonly 142 recommended Danish diabetes diet for women, regardless of pregnancy, contains 1612 kcal (6743 143 kJ) including 175 g of carbohydrates in total (46 E%). Of those the major carbohydrate sources 144 account for 86% (150 g) of the total amount of carbohydrates while 700 g of vegetables account for 145 the remaining 25 g of carbohydrates. A pragmatic evaluation of the *glycaemic index* (27) based on 146 an calculation of the total daily carbohydrate consumption was performed by the dietician in the 147 following way: The amount of carbohydrates from low glycaemic index sources was identified and 148 divided by the total amount of carbohydrates consumed. We stratified the glycaemic index score as 149 0-33%, 34-66% or 67-100% of carbohydrates deriving from low glycaemic index sources. 150 Furthermore, the number of meals and snacks consumed daily and whether the women used 151

- 152 carbohydrate counting in each meal and snack (yes/no) were registered, whereas total E%,
- 153 glycaemic load, lipid- and protein consumption were not assessed.

154 In Denmark, the recommended diet for women with diabetes, regardless of pregnancy, consists of approximately 55 E% of carbohydrates mainly from low glycaemic index sources with high amount 155 of fibres (28,29). In general, individualized dietary plans including 3 main meals and 2-3 snacks are 156 tailored with respect of the women's eating habits, cultural, ethnical and economic status and 157 presence of nausea (28,30). With the aim to prevent excessive gestational weight gain and by 158 assuming that eating more than recommended is frequent, a total daily energy intake of 159 approximately 1673 kcal (7000 kJ) regardless of pre-pregnancy BMI or trimester is recommended 160 for pregnant women with diabetes at our centre. The recommendation includes at least 175 g of 161 carbohydrates with 150 g deriving from the major carbohydrate sources. The initially recommended 162 total energy intake can be upregulated during pregnancy according to individual needs including 163 changes in the level of physical activity aiming for appropriate weekly gestational weight gain 164 without hunger or ketonuria. To secure sufficient intake of micro- and macronutrients, a reduction 165 in the total energy intake is not recommended and it is our experience that upregulating the 166 recommended energy intake is seldomly needed. 167

168 2.3 Questionnaire on physical activity and early pregnancy events

169 Since 2015, the women were asked to answer a questionnaire at first antenatal visit. The

170 questionnaire included a validated Pregnancy Physical Activity Questionnaire (PPAQ) (31)

171 consisting of 33 questions grouped into different types of activity (i.e. household/caregiving,

172 occupation, sports). The women could add two physical activities not listed in the questionnaire,

- where the intensities were individually estimated using the Compendium of Physical Activity (32).
- 174 In Denmark, bicycling is very common and therefore two questions were added into the
- 175 questionnaire, one on bicycling as transportation and one on bicycling as leisure activity (33). For

each of the 35 questions, the duration of time spent in each activity was multiplied by the intensity 176 to get the average weekly energy expenditure (metabolic equivalent of task per hour (METs-177 hr.)/wk.). The questionnaire also included non-validated questions about number of times where the 178 women had eaten extra snacks due to hypoglycaemia the previous week, number of times where the 179 women had eaten less or more due to nausea the previous week, number of episodes of vomiting in 180 the previous week, number of weekly blood glucose measurements before pregnancy as well as 181 during the previous week and average number of sleeping hours. Fifty-two percent of women with 182 T2D and 39% of women with T1D, answered this questionnaire at first antenatal visit. 183 184 2.4 Demographic and clinical data Demographic and clinical data were collected from two standardized forms in the original medical 185 records. 186 HbA1c was measured at the first antenatal visit in capillary blood and analysed immediately by a 187 DCA 2000 analyser by a latex immunoagglutination inhibition method (DCA 200; Bayer, 188 Mishawaka, IN). Early gestational weight gain was defined as the weight measured at the first 189 antenatal visit minus self-reported weight before pregnancy (kg). Spot urine samples were collected 190 at the clinic in the morning hours of the visits. The occurrence of ketonuria was noted if the 191 concentration of ketone bodies was  $\geq$ 4.0 mmol/L, detected on a dipstick of sterile urine (analysed 192 by Siemens CLINITEK Status<sup>®</sup> + Analyzer). If urine ketone bodies  $\geq$ 4.0 mmol/L were detected, 193 blood ketone bodies were routinely measured (FreeStyle Precision, Abbott). Urine ketone body 194 levels of 4.0-7.9 mmol/L corresponding to +3 on the dipstick was equivalent to a median (range) 195 blood ketone body level of 0.2 (0-0.8) mmol/L (N=18) (unpublished data from our department). 196 2.5 Routine diabetes care 197

198 In Denmark, most non-pregnant women T2D receive diabetes treatment in general practice, while

199 women with T1D are treated at local diabetes centres. The national recommendations for routine

diabetes care aim for HbA1c  $\leq$ 7.0 % (53 mmol/mol) before pregnancy and  $\leq$ 6.5 % (48 mmol/mol) in early pregnancy (34). The majority of women with T2D are treated with diet alone or in a combination with oral antidiabetic drugs and/or injections with Glucagon-like Peptide-1 analogue before pregnancy until pregnancy planning or at the latest up to the first antenatal visit where the treatment is changed to an insulin regimen.

205 2.6 Statistical analysis

206 Continuous data with normal distribution are reported as mean (± standard deviation (SD)),

continuous data with skewed distribution as median (interquartile range (IQR)) and categorical data
as number (%). Descriptive results are given for T2D and T1D separately. Comparisons of the
groups were performed by student's t-test, Mann-Whitney U-test, Chi square test or Fisher's exact
tests when appropriate.

211 Since the carbohydrate recommendations and carbohydrate consumption during pregnancy were

similar for women with T2D and T1D, univariate regression analysis was performed in the
combined cohort (T2D and T1D) as well as in the individual diabetes groups. In the univariate
linear regression analyses the carbohydrate consumption per 100 g was used as an independent
variable and HbA1c (%) as an outcome variable.

The multivariate regression analysis was performed in the combined cohort only, using carbohydrate consumption per 100 g as independent variable and HbA1c (%) as an outcome variable with the following potential confounders; maternal age, pre-gestational BMI, daily insulin dose/bodyweight (IU/kg/24h), treatment with insulin pump (yes/no) and type of diabetes (T2D and T1D). The results of the linear regression analyses are given as the regression coefficient beta ( $\beta$ ) with a 95% confidence interval (CI), expressing the change in the outcome variable for a unit change in the independent variable.

Statistical analyses were performed with IBM statistics SPSS version 22. Statistically significant
 differences were defined as a two-sided p <0.05.</li>

225 2.7 Ethics

Approvals from the local Ethic committee (H-15009413) and the Danish Data Protection Agency

227 (2007-58-0015 and 2012-58-0004) were obtained and all patients gave informed consent as

appropriate according to Danish laws. The principles of The Helsinki Declaration were observed.

229 3. Results

230 Clinical characteristics at first antenatal visit are given in Table 1. The mean HbA1c was

comparable in early pregnancy, while the women with T2D had higher prepregnancy BMI and

lower weekly gestational weight gain prior to first antenatal visit than the women with T1D.

Daily carbohydrate consumption was similar in the women with T2D vs. T1D ( $159 \pm 56$  vs.  $167 \pm 48$ 

g, P=0.3) with a carbohydrate consumption per bodyweight of  $1.9 \pm 0.9$  vs.  $2.3 \pm 0.8$  g/kg, P<0.001,

respectively (Table 2). Fifty-two percent of the women with T2D and 40% of the women with T1D

consumed fewer carbohydrates than recommended by the IOM (P=0.08) (Table 2). In the combined

237 group of women with diabetes, the women who consumed fewer carbohydrates than recommended

238 by the IOM had comparable HbA1c ( $6.5 \pm 1.0\%$  ( $48 \pm 11 \text{ mmol/mol}$ ) vs.  $6.6 \pm 1.0\%$  ( $49 \pm 11$ 

239 mmol/mol), P=0.5) but lower weekly gestational weight gain (126 (13-260) vs. 200 (67-377) g,

P=0.02) than the women following the IOM recommendations. Ten (10%) women with T2D and 8

241 (7%) women with T1D reported consuming <100 g of carbohydrates daily (Table 2) with a mean

daily consumption of 83 and 78 g, respectively. None of these 18 women had ketonuria at first

antenatal visit. Daily carbohydrate consumption >200 g was reported by 16 (17%) women with

244 T2D and 20 (19%) women with T1D.

Among women with T2D the glycaemic index score of the carbohydrates was less favourable compared with women with T1D (P=0.04) and carbohydrate counting was less frequently used (Table 2).

In an univariate linear regression analysis, a significant association between daily carbohydrate consumption and HbA1c could not be detected in neither the combined cohort ( $\beta$ :0.13 (95% CI: -0.1-0.4) %, P=0.3) or when calculated separately for the women with T2D ( $\beta$ :0.2 (95% CI: -0.2-0.6) %, P=0.4) and T1D ( $\beta$ :0.04 (95% CI: -0.3-0.4) %, P=0.8). Similar no association was found in the multiple regression analysis.

One woman with T2D and one woman with T1D had ketonuria with urine ketone concentration of 4.0-7.9 mmol/L at first antenatal visit (Table 1). The mean carbohydrate consumption was reported to be 160 g/day and 121 g/day, respectively, and only the woman with T2D had a bedtime snack.

Data on physical activity was available in a subgroup of 56% vs. 38% patients, respectively. The
total physical activity level was comparable in women with T2D and T1D (Table 3). The women
with T2D spent significantly more energy on household/caregiving than the women with T1D while
no difference between the groups was found in energy expenditure during occupation and sports
(Table 3). A higher energy expenditure during household/caregiving was found among multipara
compared to nullipara (100 (66-140) vs. 49 (30-70) METs-hr./wk., P<0.001).</li>

Insulin treated women with T2D reported consuming extra carbohydrates due to episodes of
hypoglycaemia twice weekly while women with T1D consumed extra carbohydrates 5.5 times/week
(Table 3).

Nausea leading to eating less or more food during the previous week was reported by 54% of the women with T2D and 64% of the women with T1D (Table 3). Nauseous women consumed  $165 \pm 50$ g of carbohydrates daily, while women without nausea consumed  $148 \pm 56$  g daily (P=0.1).

11

Among the women with T2D, a high number were of non-North-European Origin. The

carbohydrate consumption in the women with T2D of North-European origin was comparable with

women of non-North-European origin ( $165 \pm 60$  vs.  $154 \pm 53$  g, P=0.4) as was the number of women

271 consuming  $\leq 150$  g carbohydrates daily (46% vs. 58%, P=0.3). HbA1c was 6.8  $\pm 1.3\%$  (51  $\pm 14$ 

272 mmol/mol) vs.  $6.4 \pm 1\%$  (47 ±11 mmol/mol) P=0.2, in women of North-European origin vs. non-

273 North-European origin.

274 4. Discussion

This cohort study from Denmark, in a real-world setting, demonstrates that the women with T2D often consumed fewer carbohydrates than recommended by the IOM in early pregnancy. The average carbohydrate consumption from the major carbohydrate sources was similar in women with T2D and T1D. Women with T2D weighted on average 15.3 kg more than women with T1D and ketonuria in early pregnancy was rare in both groups.

The average carbohydrate consumption in this study was lower than previously described for 280 women with T2D (23), T1D (22) and healthy pregnant women where 286 and 393 g daily has been 281 reported (7,8), even if the expected 25 g from the minor sources is added. In healthy women, 282 carbohydrate consumption throughout pregnancy has been reported rather stable with an average 283 4% higher consumption in late pregnancy (7,8,35). In both our and the Canadian study (23), the 284 average carbohydrate consumption was similar in women with T2D and T1D while the bodyweight 285 was approximately 15 kg higher in women with T2D. This may reflect similar intake of the total 286 energy or a different distribution in the macronutrient consumption with higher fat and/or protein 287 intake in obese women compared with normal weight women. 288

The minimum amount of carbohydrates required to prevent ketosis is 50 to 100 g daily outside of pregnancy (36). During third trimester, the fetal brain is estimated to use approximately 35 g of

carbohydrates per day as an energy source (6) and additional carbohydrates are used for fetalgrowth.

A high proportion of women in our study reported an intake of fewer carbohydrates than 293 recommended by the IOM. Older studies have raised concern about the adverse effect of ketone 294 bodies on the developing fetal brain in pregnancies complicated with diabetes (15,16). An inverse 295 correlation between the mothers' third trimester plasma β-hydroxybutyrate and children's 296 intelligence both at the age of 2 and 3-5 years has been reported (15). A recent study from our own 297 group reported lower intelligence in teenage offspring of mothers suffering from ketoacidosis 298 during pregnancy, but numbers were small (37). Therefore, it is reassuring that the occurrence of 299 ketonuria in early pregnancy was low in the present study. 300

In contrast to our previous findings (22), we did not observe an association between carbohydrate consumption and HbA1c in this cohort. This may be due to a lower number of women with a carbohydrate consumption exceeding 200 g daily and less variation in HbA1c in the present cohort. Carbohydrate counting is important to obtain tight glycaemic control with a flexible lifestyle in patients with T1D who do not have an endogenous insulin production (22,38) and was frequently used in the investigated women. Carbohydrate counting in women with T2D was rare and whether pregnant women with T2D also benefit from carbohydrate counting needs to be investigated.

To our knowledge, this is the largest study to date, evaluating the carbohydrate consumption in early pregnancy as part of routine care in a cohort of women with T2D in a real-world setting, including data on ketonuria, nausea and vomiting. The evaluation of the carbohydrate consumption is meaningful for insulin treated patients and diabetes caregivers. The same dietician (HR) evaluated the amount of carbohydrates consumed and the glycaemic index score which gives consistency of the method.

It is a limitation that the women's carbohydrate consumption was self-reported and the total E%, 314 glycaemic load, lipid- and protein consumption were not recorded. To minimize the recall bias, the 315 women were asked to complete the dietary records prospectively over 3 days before the first 316 antenatal visit. The women may have chosen a healthier diet during the dietary registration and/or 317 omitted to register all carbohydrates from the major carbohydrates consumed. It is known that less 318 healthy eaters are more likely to underreport food intake (39). Despite these limitations, this is one 319 of the best options for evaluation of carbohydrate consumption in a large population. All eligible 320 women reporting at least one day of dietary records were included in the study to improve the 321 external validity of the study, but this might have biased the estimation of the daily carbohydrate 322 consumption. It would have added value to our study, if the women had tested for ketonuria at 323 home the same days as the dietary registration. There is a risk of selection bias as the less compliant 324 women with unhealthy eating habits may not have filled out the dietary records. Data from the 325 PPAQ was only available in 52% and 39% of included women with T2D and T1D, respectively. 326

327 4.1 Conclusions

In early pregnancy, a lower daily carbohydrate consumption than recommended by the IOM was common among women with T2D. The results were quite similar to women with T1D, despite a markedly higher bodyweight in women with T2D. Reassuringly, ketonuria was rare in both groups. Future studies should focus on the safety of consuming a low amount of carbohydrates during pregnancy in women with diabetes.

333 5. Acknowledgements

Author Contributions. E.R.M. and B.Á. contributed to the idea. H.R. conducted the diet analyses in the women. B.Á and M.V. collected the data. B.Á. analysed data and wrote the manuscript. All authors were involved in the interpretation of data, contributed to the discussion, reviewed and edited the manuscript and approved the final version. E.R.M. is the guarantor of this work and, as

such, has full access to all the data in the study and takes responsibility for the integrity of the data

338

339	and the accuracy of the data analysis.
340	Statements of assistance. We kindly thank midwife at Rigshospitalet, Maria Anna Mikkelsen for
341	helping with the data collection.
342	Funding. This study was supported by The Novo Nordisk Foundation. The sponsor of the study was
343	not involved in design, conduct, or interpretation of the study.
344	Conflicts of interest. No potential conflicts of interest relevant to this article were reported.
345	
346	
347	
348	
349	

350		
351		Reference List
352		
353 354	1.	Persson M, Norman M, Hanson U: Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. <i>Diabetes Care</i> 32:2005-2009, 2009
355 356	2.	Sugrue R, Zera C: Pregestational Diabetes in Pregnancy. <i>Obstet Gynecol Clin North Am</i> 45:315-331, 2018
357 358	3.	PEDERSEN J: Weight and length at birth of infants of diabetic mothers. <i>Acta Endocrinol (Copenh)</i> 16:330-342, 1954
359 360 361	4.	Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer FX, Mayer-Davis E, Kulkarni K, Geil P: Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the american diabetes association. <i>Diabetes Care</i> 27:2266-2271, 2004
362 363	5.	13. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. <i>Diabetes Care</i> 41:S137-S143, 2018
364 365 366	6.	Institute of Medicine of the National Academies. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (Macronutrients). 2005. Washington DC, National Academy Press.
367 368 369	7.	Diemert A, Lezius S, Pagenkemper M, Hansen G, Drozdowska A, Hecher K, Arck P, Zyriax BC: Maternal nutrition, inadequate gestational weight gain and birth weight: results from a prospective birth cohort. <i>BMC Pregnancy Childbirth</i> 16:224, 2016
370 371 372	8.	Okubo H, Crozier SR, Harvey NC, Godfrey KM, Inskip HM, Cooper C, Robinson SM: Maternal dietary glycemic index and glycemic load in early pregnancy are associated with offspring adiposity in childhood: the Southampton Women's Survey. <i>Am J Clin Nutr</i> 100:676-683, 2014
373 374 375 376	9.	Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, Li N, Hu G, Corrado F, Rode L, Kim YJ, Haugen M, Song WO, Kim MH, Bogaerts A, Devlieger R, Chung JH, Teede HJ: Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta- analysis. <i>JAMA</i> 317:2207-2225, 2017
377	10.	Freedman MR, King J, Kennedy E: Popular diets: a scientific review. Obes Res 9 Suppl 1:1S-40S, 2001
378 379	11.	Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL: Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. <i>J Am Diet Assoc</i> 108:91-100, 2008
380 381	12.	Felig P, Lynch V: Starvation in human pregnancy: hypoglycemia, hypoinsulinemia, and hyperketonemia. <i>Science</i> 170:990-992, 1970
382 383	13.	Knopp RH, Magee MS, Raisys V, Benedetti T, Bonet B: Hypocaloric diets and ketogenesis in the management of obese gestational diabetic women. <i>J Am Coll Nutr</i> 10:649-667, 1991

- Rasmussen KM, Yaktine AL: Weight Gain During Pregnancy: Reexamining the Guidelines. [article
   online], 2009. Available from <u>http://www.nap.edu/catalog.php?record\_id=12584</u>. Accessed 29 April
   2012
- Rizzo T, Metzger BE, Burns WJ, Burns K: Correlations between antepartum maternal metabolism and child intelligence. *N Engl J Med* 325:911-916, 1991
- Stehbens JA, Baker GL, Kitchell M: Outcome at ages 1, 3, and 5 years of children born to diabetic
   women. *Am J Obstet Gynecol* 127:408-413, 1977
- Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F: ATLANTIC-DIP: excessive
   gestational weight gain and pregnancy outcomes in women with gestational or pregestational
   diabetes mellitus. J Clin Endocrinol Metab 99:212-219, 2014
- Parellada CB, Asbjornsdottir B, Ringholm L, Damm P, Mathiesen ER: Fetal growth in relation to
   gestational weight gain in women with type 2 diabetes: an observational study. *Diabet Med* 31:1681 1689, 2014
- Secher AL, Parellada CB, Ringholm L, Asbjornsdottir B, Damm P, Mathiesen ER: Higher gestational
   weight gain is associated with increasing offspring birth weight independent of maternal glycemic
   control in women with type 1 diabetes. *Diabetes Care* 37:2677-2684, 2014
- 400 20. Jovanovic L: Role of diet and insulin treatment of diabetes in pregnancy. *Clin Obstet Gynecol* 43:46401 55, 2000
- 402 21. 4. Lifestyle Management: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 41:S38-S50, 2018
- Asbjornsdottir B, Akueson CE, Ronneby H, Rytter A, Andersen JR, Damm P, Mathiesen ER: The
   influence of carbohydrate consumption on glycemic control in pregnant women with type 1 diabetes.
   *Diabetes Res Clin Pract* 127:97-104, 2017
- McManus RM, Bouwmeester A, Hinz L, Caraiscos VB, Nairn J, Giroux I: Costs of recalled and
   recommended diets for pregnant women with type 1, type 2 and gestational diabetes. *Can J Diabetes* 37:301-304, 2013
- 410 24. Abu-Saad K, Fraser D: Maternal nutrition and birth outcomes. *Epidemiol Rev* 32:5-25, 2010
- Ygil KH. Mål, vægt og portionsstørrelser på fødevarer. [article online], 2013. Available from
   <u>http://orbit.dtu.dk/files/54035130/maal\_vaegt\_portionsstoerrelser\_marts\_13.pdf</u>. Accessed 12 April
   2018. Danmarks Tekniske Universitet, Fødevareinstituttet.
- Alta
  26. Nielsen TH, Biltoft-Jensen AP, and Ygil KH. Udvikling af billedserier til Den nationale undersøgelse af danskernes kostvaner og fysiske aktivitet 2011. [article online], Nov 2011. Available from
  Attp://www.food.dtu.dk/Publikationer/Ernaering-og-kostvaner/De\_nationale\_kostundersoegelser.
  Accessed 12 April 2018. Danmarks Tekniske Universitet, Fødevareinstituttet.
- 418 27. Atkinson FS, Foster-Powell K, Brand-Miller JC: International tables of glycemic index and glycemic
  419 load values: 2008. *Diabetes Care* 31:2281-2283, 2008

- 420 28. Knold B, Wolff C, Jensen B, and Brown P. Diætbehandling ved prægestationel diabetes mellitus.
  421 [article online], 2006. Available from
- 422 https://www.diaetist.dk/media/1904/03FaKD\_Rammeplan\_pregestationel%20diabetes%20mellitus%
   423 202006.pdf Accessed 3 April 2019. Foreningen af kliniske diætister.
- Schelde B, Pallesen B, and Sode V. Diætbehandling ved type 1 diabetes mellitus. [article online], 2011.
  Available from https://www.diaetist.dk/media/1928/FaKD\_diaetbeh\_type1\_voksne2011.pdf
  Accessed 7 May 2019. Foreningen af kliniske diætister.
- 30. Roskjaer AB, Andersen JR, Ronneby H, Damm P, Mathiesen ER: Dietary advices on carbohydrate
  intake for pregnant women with type 1 diabetes. *J Matern Fetal Neonatal Med* 28:229-233, 2015
- 429 31. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS: Development and
   430 validation of a Pregnancy Physical Activity Questionnaire. *Med Sci Sports Exerc* 36:1750-1760, 2004
- 431 32. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, Greer JL, Vezina J,
  432 Whitt-Glover MC, Leon AS: 2011 Compendium of Physical Activities: a second update of codes and
  433 MET values. *Med Sci Sports Exerc* 43:1575-1581, 2011
- 33. Simmons D, Devlieger R, van AA, Jans G, Galjaard S, Corcoy R, Adelantado JM, Dunne F, Desoye G,
  Harreiter J, Kautzky-Willer A, Damm P, Mathiesen ER, Jensen DM, Andersen L, Lapolla A, Dalfra MG,
  Bertolotto A, Wender-Ozegowska E, Zawiejska A, Hill D, Snoek FJ, Jelsma JG, van Poppel MN: Effect of
  Physical Activity and/or Healthy Eating on GDM Risk: The DALI Lifestyle Study. *J Clin Endocrinol Metab*102:903-913, 2017
- 34. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER: The Effect of Real-Time Continuous
  Glucose Monitoring in Pregnant Women With Diabetes: A randomized controlled trial. *Diabetes Care*36:1877-1883, 2013
- Kubota K, Itoh H, Tasaka M, Naito H, Fukuoka Y, Muramatsu KK, Kohmura YK, Sugihara K, Kanayama
  N: Changes of maternal dietary intake, bodyweight and fetal growth throughout pregnancy in
  pregnant Japanese women. J Obstet Gynaecol Res 39:1383-1390, 2013
- 445 36. Calloway DH: Dietary components that yield energy. *Environ Biol Med* 1:175-186, 1972
- 37. Bytoft B, Knorr S, Vlachova Z, Jensen RB, Mathiesen ER, Beck-Nielsen H, Gravholt CH, Jensen DM,
  Clausen TD, Mortensen EL, Damm P: Long-term Cognitive Implications of Intrauterine Hyperglycemia
  in Adolescent Offspring of Women With Type 1 Diabetes (the EPICOM Study). *Diabetes Care* 39:13561363, 2016
- 450 38. Hommel E, Schmidt S, Vistisen D, Neergaard K, Gribhild M, Almdal T, Norgaard K: Effects of advanced
  451 carbohydrate counting guided by an automated bolus calculator in Type 1 diabetes mellitus
  452 (StenoABC): a 12-month, randomized clinical trial. *Diabet Med* 34:708-715, 2017
- 453 39. Muhlheim LS, Allison DB, Heshka S, Heymsfield SB: Do unsuccessful dieters intentionally underreport
  454 food intake? *Int J Eat Disord* 24:259-266, 1998
- 455 456
- 457

Table 1. Clinical characteristics of pregnant women with type 2 diabetes compared with pregnantwomen with type 1 diabetes at first antenatal visit.

	Type 2 diabetes	Type 1 diabetes	P-value
Number	96	108	
Age (years)	34 ±5	31 ±5	0.001
Duration of diabetes (years)	3 (1-6)	16 (9-22)	< 0.001
Prepregnancy weight (kg)	89.5 ±23	73.4 ±15	< 0.001
Prepregnancy diet treatment only	23 (24%)		
Prepregnancy oral antidiabetic medication <sup>†</sup>	60 (63%)		
Prepregnancy treatment with Glucagon-Like-	9 (9%)		
Peptide-1-antagonist <sup>‡</sup>			
Height (cm)	165 ±7	168 ±6	0.001
Prepregnancy BMI (kg/m <sup>2</sup> )	32.8 ±7	$26.0 \pm 5$	< 0.001
North-European Origin	52 (55%)	98 (93%)	< 0.001
Nulliparous	36 (38%)	55 (51%)	0.06
Smoking	2/49 (4%)	1/43 (2%)	0.6
Gestational age (days)	71 (60-87)	63 (56-76)	0.003
HbA1c (%)	6.6 ±1.2	$6.6 \pm 0.8$	0.8
(mmol/mol)	49 ±13	48 ±8	
Insulin treatment	18 (19%)	108 (100%)	-
Insulin pump treatment	0%	36 (33%)	-
Insulin dose (IU/kg/24h)§	$0.67 \pm 0.40$	$0.61 \pm 0.28$	0.6
Weight (kg)	90.8 ±22	75.5 ±15	< 0.001
Early gestational weight gain (kg)	1.5 ±2.7	2.1 ±2.1	0.07
Early weekly gestational weight gain (g)	145 ±247	$233 \pm 230$	0.01
Ketonuria (≥4.0 mmol/L)	1 (1%)	1 (1%)	1.0

460 Data are given as mean ±standard deviation, median (interquartile range) or n (%). †Monotherapy with Biguanide

461 (N=39). Combination therapy with Biguanide and Glucagon-Like-Peptide-1-antagonist (GLP-1-antagonist) (N=6),

462 Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors (N=6), Sodium-Glucose co-Transporter-2 (SGLT2) Inhibitors (N=1)

463 Sulphonylureas (N=1) and insulin (N=6) respectively. Combination therapy with Biguanide, DPP-IV-Inhibitor and

464 SGLT-2-Inhibitor (N=1). ‡Monotherapy with GLP-1-antagonist (N=1). Combination therapy with GLP-1-antagonist

465 and Biguanide (N=6) and insulin (N=2), respectively. §Numbers are given for those on insulin treatment.

466

467	Table 2. Dietary analysis based on dietary records in early pregnancy by women with type 2
468	diabetes and women with type 1 diabetes.

	Type 2 diabetes	Type 1 diabetes	P-value
Number	96	108	
Dietary records			
• 1 day	12 (12%)	32 (30%)	0.002
• 2 days	15 (16%)	23 (21%)	
• 3 days	69 (72%)	53 (49%)	
Carbohydrate consumption (g/day)	159 ±56	167 ±48	0.3
Carbohydrate consumption/kg bodyweight	1.9 ±0.9	$2.3 \pm 0.8$	< 0.001
(g/kg/day)			
Consuming fewer carbohydrates than	50 (52%)	43 (40%)	0.08
recommended by the Institute of Medicine <sup>†</sup>			
Consuming <100 g of carbohydrates	10 (10%)	8 (7%)	0.5
The glycaemic index score <sup>‡§</sup>			
• 0-33%	13 (18%)	6 (6%)	0.04
• 34-66%	21 (30%)	36 (36%)	
• 67-100%	37 (52%)	57 (58%)	
Use of carbohydrate counting	6 (6%)	83 (77%)	< 0.001
Number of daily meals and snacks <sup>§</sup>			
• $\geq$ 3 main meals	74 (96%)	75 (94%)	0.7
Snacks			
o 3-4	29 (38%)	46 (58%)	0.002
o 2	17 (22%)	22 (27%)	
o 0-1	30 (40%)	12 (15%)	

469 Data are given as n (%) or mean ±standard deviation. Carbohydrates calculated from the major carbohydrate sources.

470 †≤150 g daily. ‡A score of 67-100% means that the majority of recorded carbohydrates derived from low glycaemic
 471 index sources. §Data available from 74-92%.

472

**C**CCC

#### Table 3. Eating behaviour and lifestyle in pregnant women with type 2 or type 1 diabetes in early 473 pregnancy. 474

	Type 2 diabetes	Type 1 diabetes	P-value
Number	54	42	
Total physical activity (METs-h/wk.) <sup>†</sup>	215 (174-289)	210 (178-267)	0.9
Household/caregiving	85 (50-136)	57 (36-82)	0.002
Occupation	71 (0-106)	81 (71-108)	0.06
Sports	11 (3-19)	10 (4-16)	0.9
• Other	49 (34-67)	63 (44-77)	0.02
Number of extra snacks eaten due to	2 (0-6)	5.5 (3-8)	0.005
hypoglycaemia in the previous week			
Changed eating behaviour due to nausea in the		2	
previous week			
• Eating less due to nausea $\geq 1/wk$ .	24 (44%)	19 (49%)	0.7
• Number of times eating less due to	3 (1.5-6)	2 (1-5)	0.4
nausea/wk.			
• Eating more due to nausea $\geq 1/wk$ .	15 (29%)	17 (41%)	0.2
Number of times eating more due to	3 (2-7)	6 (2-7)	0.3
nausea/wk.			
• Eating less or more due to nausea $\geq 1/wk$ .	29 (54%)	27 (64%)	0.3
Vomiting in the previous week	12 (23%)	14 (34%)	0.2
• Number of vomiting/wk.	2 (1-3)	1.5 (1-5)	0.5
Number of blood glucose measurements/wk.	0.5 (0-5)	30 (7-50)	< 0.001
before pregnancy			
Number of blood glucose measurements in the	48 (24-49)	60 (30-70)	0.001
previous week			
Sleeping hours/24h in the previous week	7.7 ±1.3	$7.9 \pm 1.0$	0.5

475

Data are given as median (interquartile range), n (%) or mean ±standard deviation. Data available from 93-100%. †METs-h/wk.=metabolic equivalent of task per hour/week.

476

477