Variability of Total Daily Dose of Insulin in Type 1 Diabetic Pre-Menarchal vs Post-Menarchal Females

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Research article

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Posted Date: September 22nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-70132/v1

Title Page

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Presented: Pediatric Academic Societies Meeting;Baltimore, Maryland; April, 28th 2019

Abstract Word Count: 244

Main Text Word Count: 1050

Declarations

Ethics approval and consent to to participate

- Not applicable

Consent for Publication

- Not applicable

Availability of Data and Materials

- The datasets generated during and/or analysed during the current study are not publicly available due the fact it is de identified HPI which is stored on our RedCap server through Loyola University Medical Center. However, it is available from the corresponding author on reasonable request.

Competing Interests

- The authors declare that they have no competing interests

Funding

- No funding was required for this study.

Structured Abstract

Study Objective

Quantify the change of insulin requirements in pre- vs post-menarchal adolescent females with type 1 diabetes (T1DM) by measuring the total daily dose (TDD; units/kg/day) of insulin administered before vs after menarche in order to provide anticipatory guidance of insulin requirements in adolescent females as they progress through puberty to help reduce the long-term complications of poorly controlled T1DM.

Design/Setting/Participants

A retrospective chart review study was conducted which included 52 adolescent females with T1DM, after subjects who were diagnosed with T1DM after menarche, those on hormonal contraceptives, or those that had hypothyroidism, major medical comorbidities, or incomplete records were excluded. Subject demographics along with body mass index (BMI) percentile, HgbA1c (hemoglobin A1c), and TDD of insulin were collected 0-2 years pre-, 0-2 years post-, and 2-4 years post-menarche to assess differences in TDD of insulin in pre- and post-menarchal adolescent females with T1DM.

Interventions

None

Main Outcome Measures

TDD of insulin at 0-2 years pre-, 0-2 years post-, and 2-4 years post-menarche in adolescent females with T1DM.

Results

There was a statistically significant difference of TDD of insulin in pre- vs. post-menarchal adolescent females with T1DM after controlling for HgbA1c and BMI.

Conclusions

While poor glycemic control is often attributed to adolescent non-compliance of insulin administration, a physiologic process similar to polycystic ovarian syndrome may induce insulin resistance in post-pubertal

adolescent females with T1DM.

Keywords

Type 1 diabetes, preburtal, postpubertal, premenarche, postmenarche, total daily dose of insulin, HgbA1c

Main Manuscript

Introduction

Achieving good diabetic control is multifactorial, and in women, it can be significantly impacted by their menses[7]. It has been shown that the age of menarche occurs later in adolescent females with type 1 diabetes (T1DM) as compared to adolescents without diabetes[4,8], or as compared to those who are diagnosed with T1DM after menarche.[1,3] Once menarche is achieved, menstrual irregularity is highly prevalent and may cause higher rates of premature ovarian failure (menopause) in females with T1DM.[2] Such menstrual irregularity is correlated with poorer glycemic control, and is specifically associated with hyperglycemia during the luteal phase of the menstrual cycle.[5,6] Although previous studies have shown

that hyperglycemic episodes are more prevalent with irregular menses and during a specific portion of the menstrual cycle, it is unclear whether poorer diabetic control is more prevalent post-menarche as compared to pre-menarche in adolescent females with T1DM. No previous study has quantified insulin resistance, as measured by the total daily dose (TDD; units/kg/day) of insulin, in premenarchal vs postmenarchal adolescents with T1DM.

Materials and Methods

IRB approval was obtained to conduct a retrospective chart review study of female adolescents with T1DM seen by the Loyola University Medical Center Pediatric Endocrinology team from 2007-2018. A patient consensus generated via EPIC obtained a total of 255 subjects, of which 52 were included in the study after subjects who were diagnosed with T1DM after menarche, those on hormonal contraceptives, or those with hypothyroidism, major medical comorbidities, or incomplete records were excluded. Subject demographics along with body mass index (BMI) percentile, HgbA1c (hemoglobin A1c), and TDD of insulin were collected 0-2 years pre-, 0-2 years post-, and 2-4 years post-menarche to assess differences in TDD of insulin in pre- and post-menarchal females with T1DM using RedCap (Figure 1). Descriptive statistics were calculated including means and standard deviations for continuous variables and counts and percentages for nominal variables. Boxplots were constructed to visualize the distribution of TDD at each time period. A linear mixed effect regression model was used to estimate mean TDD by time adjusted for age, BMI percentile, and HgbA1c. Pearson's correlation coefficient for HgbA1c and BMI percentile with TDD were estimated for each time period. Analyses were performed using R version 3.5.3 in RStudio.

Results

Overall there was no statistically significant difference of TDD of insulin in pre- vs. post-menarchal adolescent females with T1DM (Figure 2). However, there was a statistically significant increase of TDD of insulin in pre- vs. post-menarchal females with T1DM after controlling for HgbA1c and BMI (Figure 3). It is possible that post-menarchal females with T1DM experience insulin resistance similar to those with

polycystic ovary syndrome (PCOS)[9], requiring increased insulin requirements post-menarche. PCOS is associated with inherent abnormalities of ovarian and adrenal steroidogenesis: ovarian theca cells in this population secrete excess androgens and have exaggerated ovarian steroidogenic responses to gonadotropin stimulation.[9] In addition, many women with PCOS have insulin resistance, in which hyperinsulinemia can lead to increase in adrenal and ovarian hyperandrogenemia and bioavailability through reduced sex hormone binding protein (SHBG)[9]. Thus, PCOS is correlated with insulin resistance, which is at least partly independent of obesity, similar to the insulin resistance demonstrated in post-menarchal adolescents in this study, possibly due to an abnormal ovarian steroidogenic response to gonadotropin stimulation.

In addition, it may be expected that as the TDD of insulin increases, the HgbA1c should decrease because increased TDD of insulin would presumably provide better glycemic control and lower the HgbA1c. However, it can be noted that HgbA1c trended up despite increased TDD of insulin, with a statistically significant direct linear relationship 2-4 years post-menarche (Figure 5). This may demonstrate 1) adolescent non-compliance, 2) TDD of insulin is a reaction to the HgbA1c (i.e. elevated HgbA1c causes increased TDD of insulin to achieve better control), or 3) there is a degree of insulin resistance contributing to poor glycemic control despite increasing TDD of insulin, especially once menses have stabilized 2-4 years post-menarche.

Similar to the insulin resistance seen in PCOS that is partly independent of obesity[9], this study further demonstrated that BMI does not have a statistically significant relationship between HgbA1c or TDD of insulin (Figures 3, 4). Given that TDD of insulin is measured in units/kg/day, it is expected that there would be a consistent TDD of insulin regardless of the patient's BMI, as it is measured in kg/m^2. This demonstrates that our adolescent females received an appropriate insulin dose based on their weight. Further, it may be expected that as BMI increases, the HgbA1c (marker of insulin resistance) would also increase; however, this was not shown in our study, likely because T1DM is an autoimmune disorder that is independent of BMI (unlike patients with type 2 diabetes). In contrast, it may be expected that insulin

omission would cause increased HgbA1c and decreased BMI due to cell starvation; however, this was not observed in the study either because this study did not have sufficient power to find statistical significance, or the overall association between BMI and HgbA1c is multifactorial.

Lastly, it should be noted that any non-statistically significant result found in this study may be due to the low power of the study. Repeat investigation with a larger sample size is warranted to establish a more clear relationship between menses and glycemic control in adolescent females with T1DM.

Conclusions

While poor diabetes control in teens with T1DM and increases in HgbA1c are often attributed to adolescent insulin non-compliance, a physiologic process similar to polycystic ovarian syndrome (PCOS) may induce insulin resistance in post-pubertal adolescent females with T1DM. It is known that adolescents often require a higher TDD of insulin during puberty due to multiple factors. This study also suggests that higher doses of TDD of insulin are needed for female adolescents with T1DM beyond the pubertal period, especially 2-4 years (and likely beyond) post-menarche. Further investigation regarding the physiology of menses in girls with diabetes is needed to further understand the relationship of insulin resistance in adolescent females with T1DM.

Acknowledgements

We would like to thank Cara Joyce, PhD and the Department of Biostatistics for their statistical analysis for this study. We would also like to thank the Department of Pediatrics Research Committee (Loyola University Medical Center) for reviewing our study.

Disclosure/Conflict of Interest Statement

We have no disclosures or conflict of interests.

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Figures

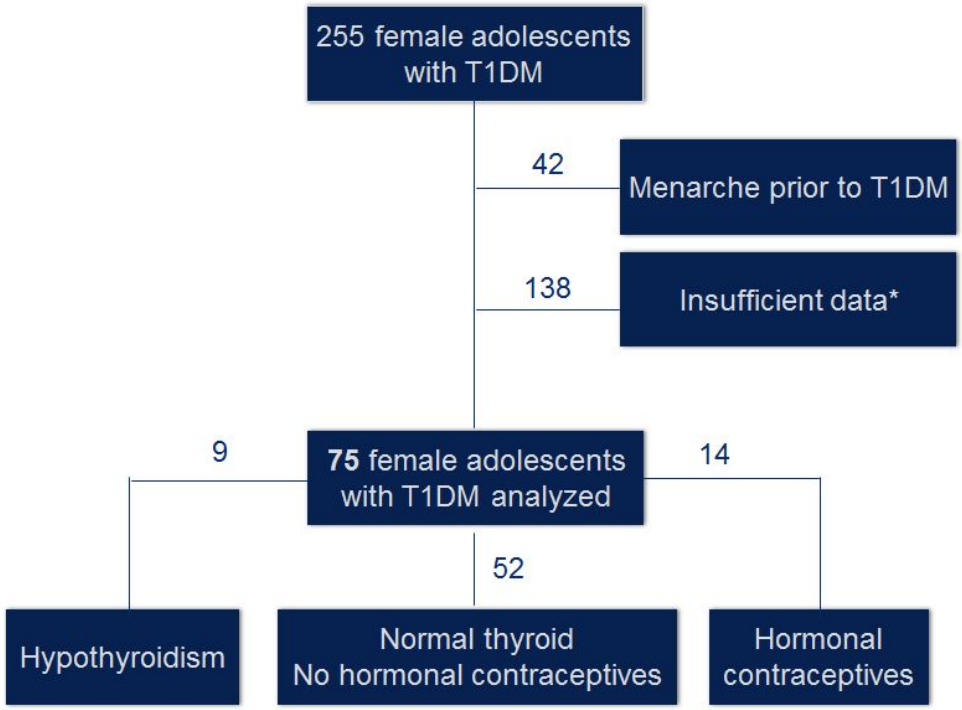


Figure 1: A patient consensus generated via EPIC obtained a total of 255 subjects aged 8-20 years old, of which 52 were included in the study after subjects who were diagnosed with T1DM after menarche, those on hormonal contraceptives, or those with hypothyroidism, major medical comorbidities, or incomplete records were excluded.

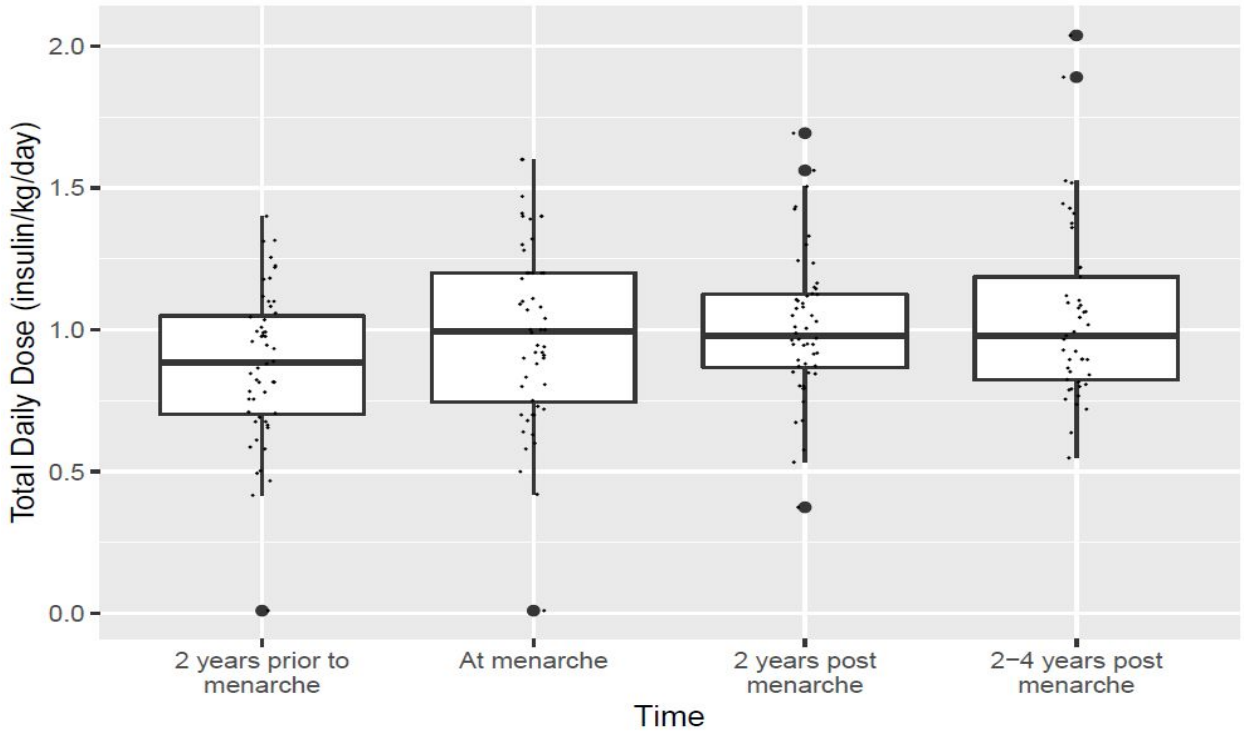


Figure 2 is a scatter plot showing the absolute distribution of TDD of insulin in pre- vs post-menarchal females. It shows that there is no statistical significance of TDD of insulin pre- vs. post-menarche. However, the mean TDD of insulin appears to be higher post-menarche (at menarche, 0-2 years post-menarche, and 2-4 years post-menarche) compared to pre-menarche (0-2 years prior to menarche); however, it is not statistically significant.

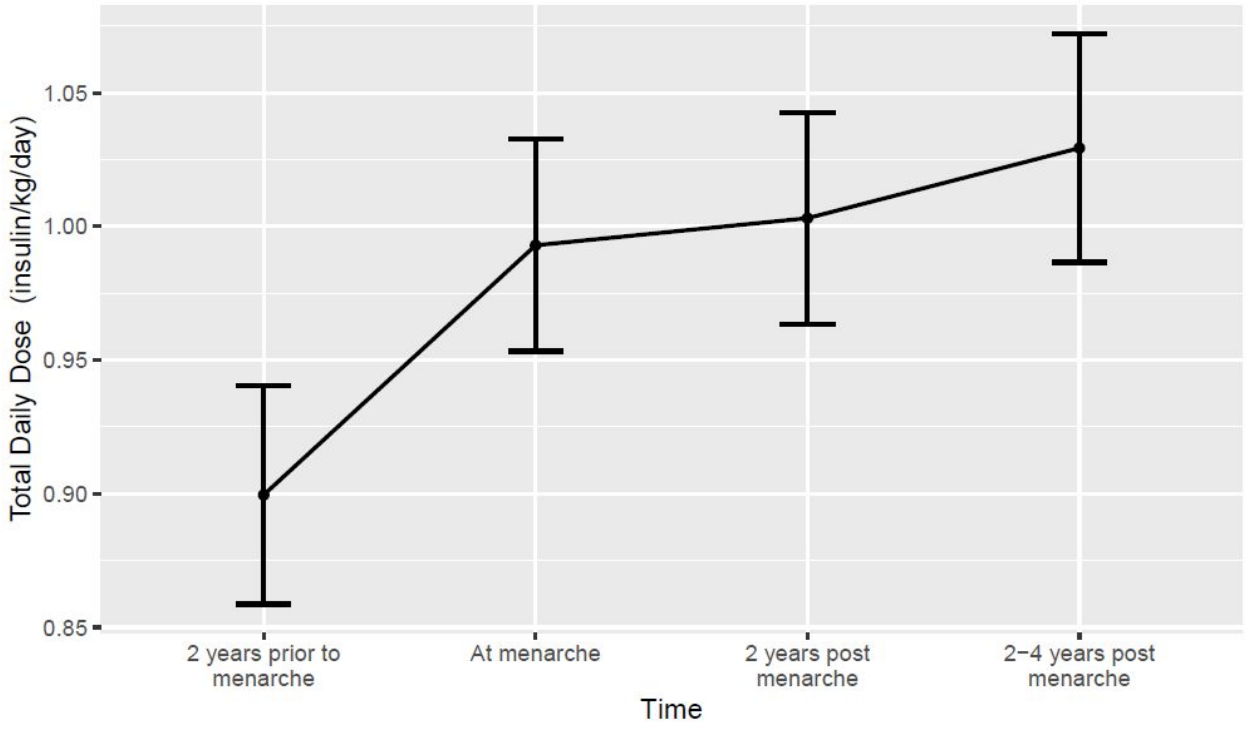


Figure 3 shows the mean TDD of insulin after adjusting for age, BMI, and HgbA1c in pre- vs post-menarchal females. This demonstrates that there is a statistical difference of TDD of insulin pre-menarche (0-2 years prior to menarche) versus post-menarche (at menarche, 0-2 years after menarche, and 2-4 years after menarche). Although not statistically significant, there is an upward trend in TDD of insulin after stabilization of menses (2-4 years after menarche) compared to onset of menses (at menarche and 0-2 years after menarche).

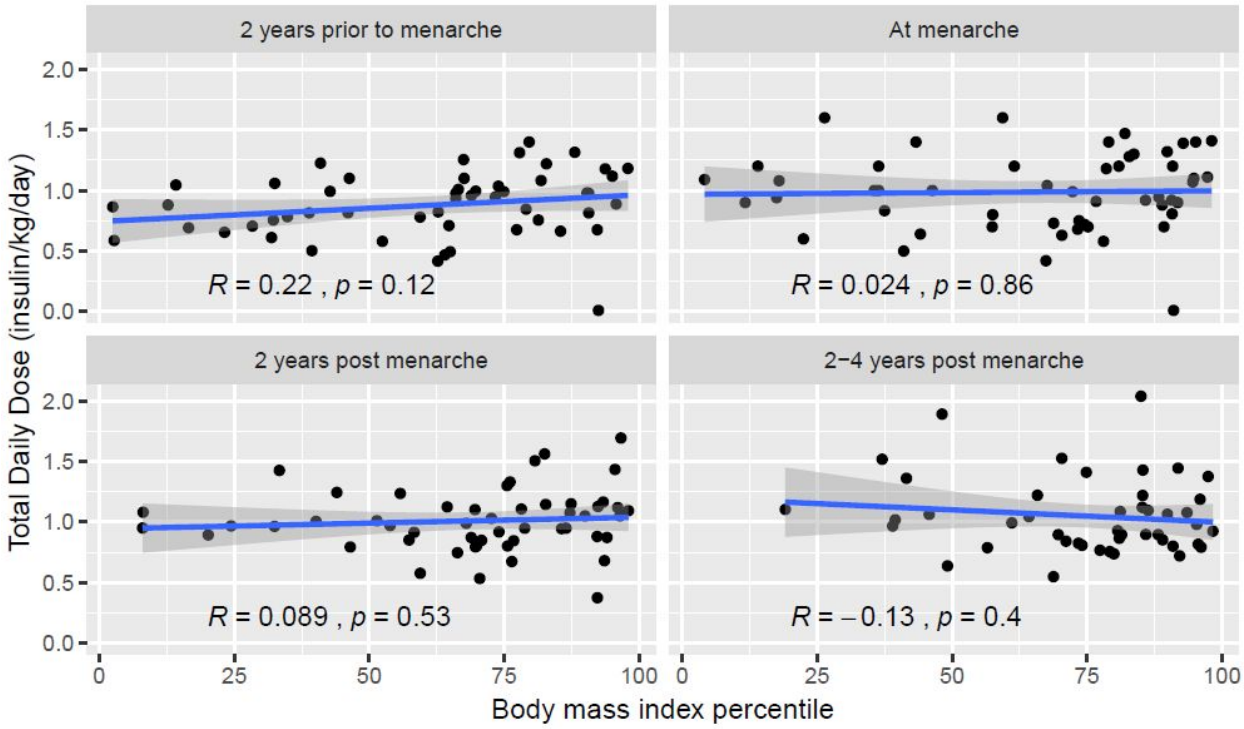


Figure 4 shows the association between BMI and TDD of insulin. There is no statistically significant association between TDD and BMI (p-value 0.12 to 0.86). There is also no consistent trend in the linear relationship between TDD and BMI (R-value -0.13 to 0.22).

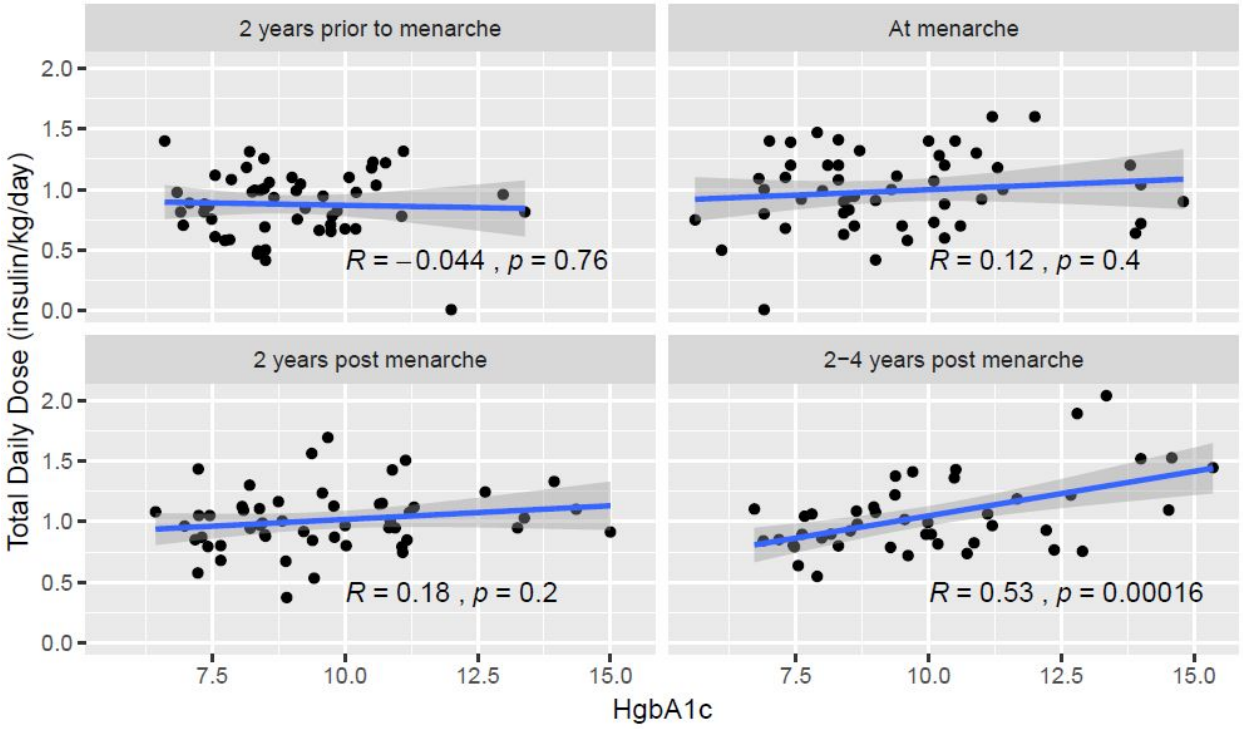


Figure 5 shows that the association of TDD of insulin and HgbA1c is significant (p=0.00016) after stabilization of menses (2-4 years post-menarche); however it is not significant pre- (0-2 years prior to menarche) and peri-menarche (at menarche, and 0-2 years after menarche). Although it is not statistically significant, there appears to be an upward trend between TDD and HgbA1c post-menarche as R value consistently increases from -0.044 to 0.53 with decreasing p-value.

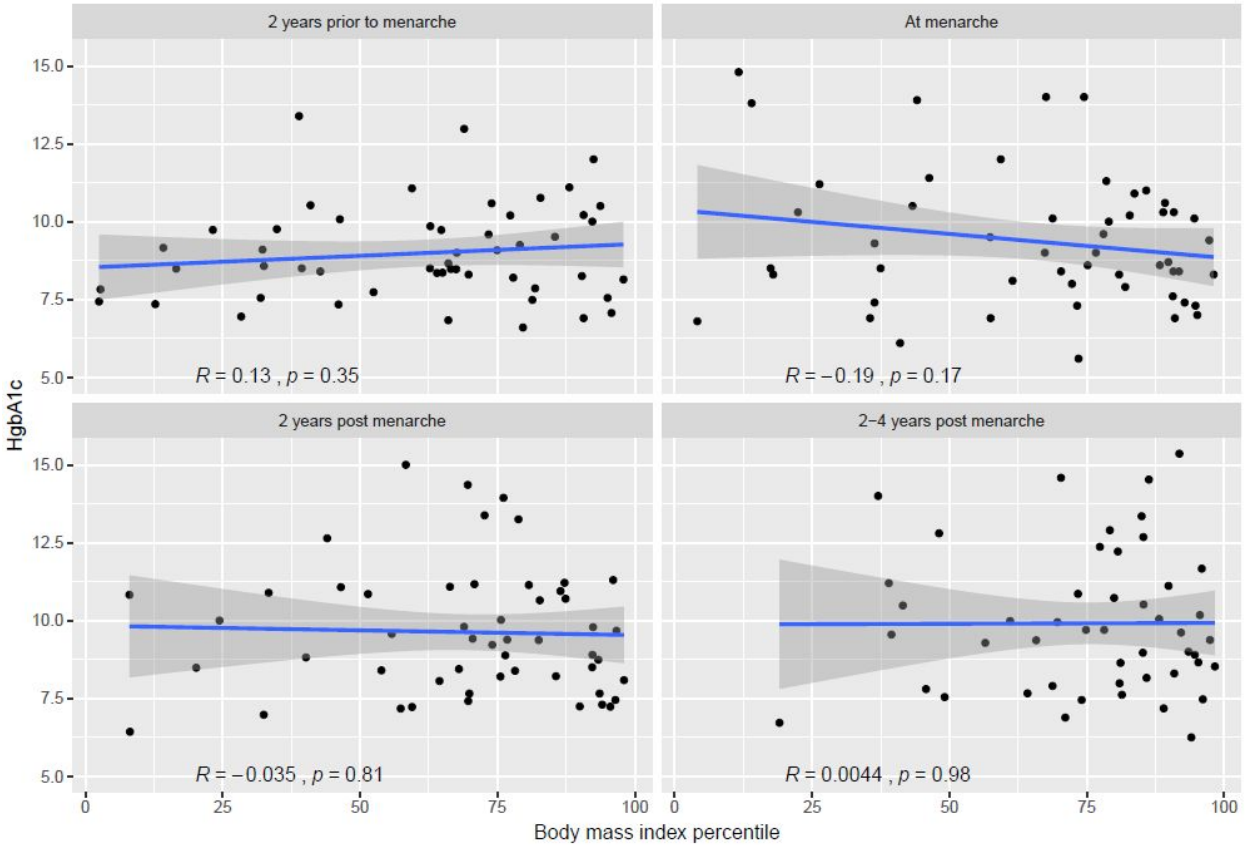


Figure 6 shows that there is no statistically significant association between HgbA1c and BMI (p-value 0.17 to 0.98). There is also no consistent trend in the linear relationship between HgbA1c and BMI (R-value -0.19 to 0.13).

Tables

Age at Menarche	**12.5 (1.1)**
Race/Ethnicity	
Caucasian	27 (51.95%)
Black or African American	10 (19.2%)
Asian or Pacific Islander	2 (3.8%)
Hispanic	13 (25%)
Insurance	
Private	26 (50%)
Medicaid	26 (50%)

Table 1: Demographics of studied population

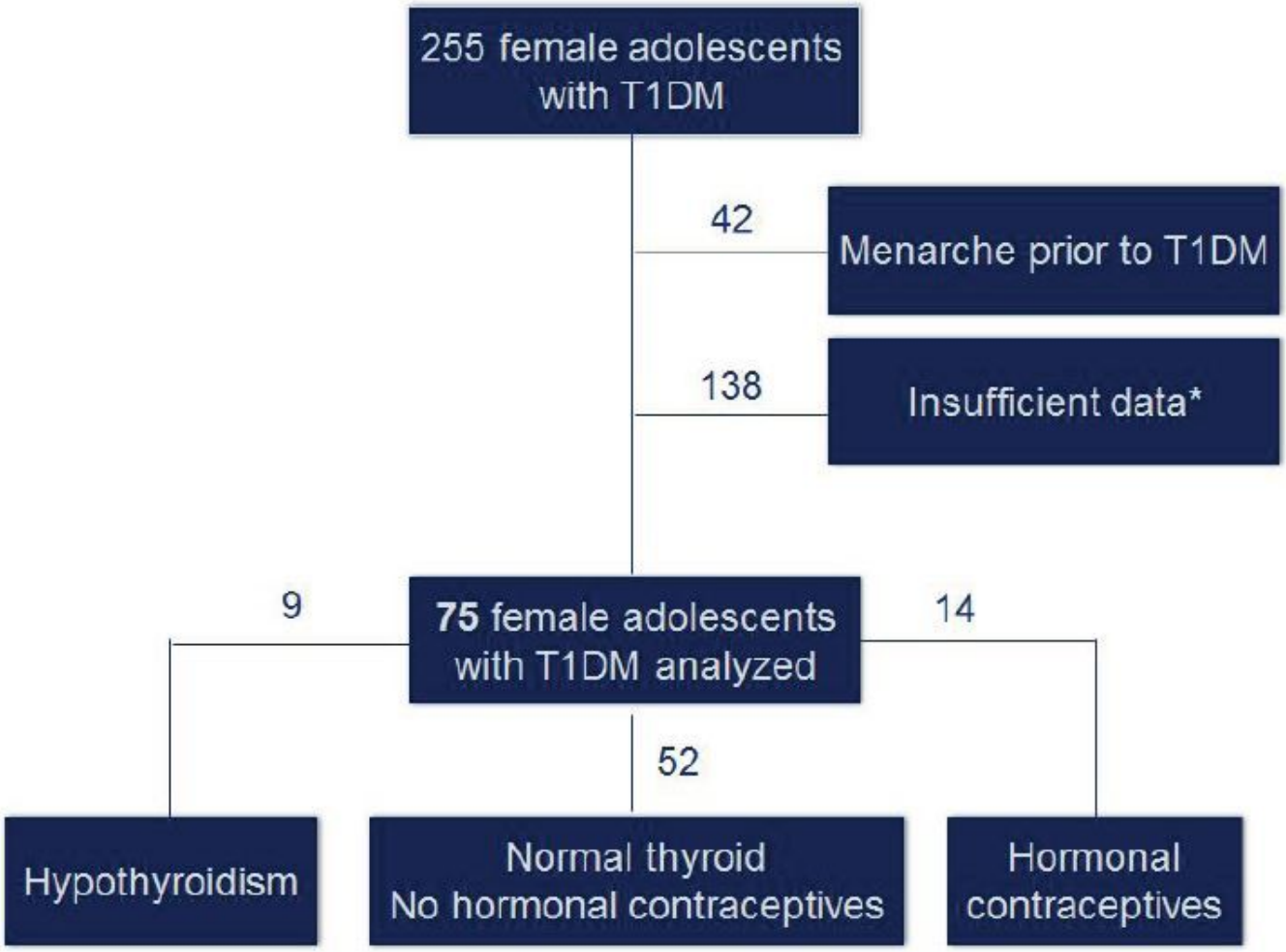
Characteristics at Menarche, median	
BMI (%)	74.0% (43.9%-89.0%)
HgbA1c (%)	8.9% (8.9%-10.4%)
Total daily dose (u/kg/day)	1.00 (0.75-1.20)

Table 2: Demographics of studied population at time of menarche

Statistical Analysis

Descriptive statistics were calculated including means and standard deviations for continuous variables and counts and percentages for nominal variables. Boxplots were constructed to visualize the distribution of total daily dose (TDD) at each time period. A linear mixed effect regression model was used to estimate mean TDD by time adjusted for age, BMI percentile, and HgbA1c. Pearson's correlation coefficient for HgbA1c and BMI percentile with TDD were estimated for each time period. Analyses were performed using R version 3.5.3 in RStudio.

Figures



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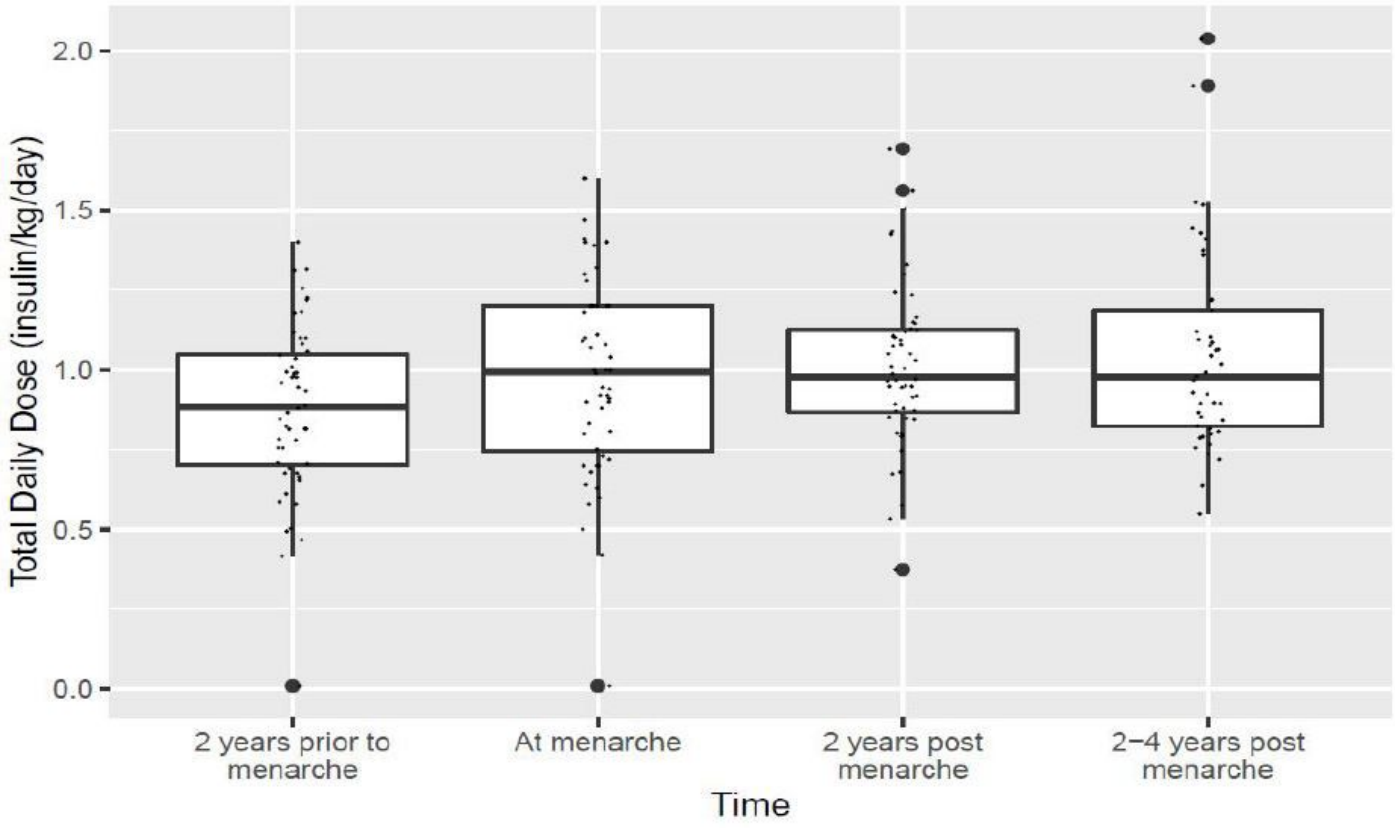

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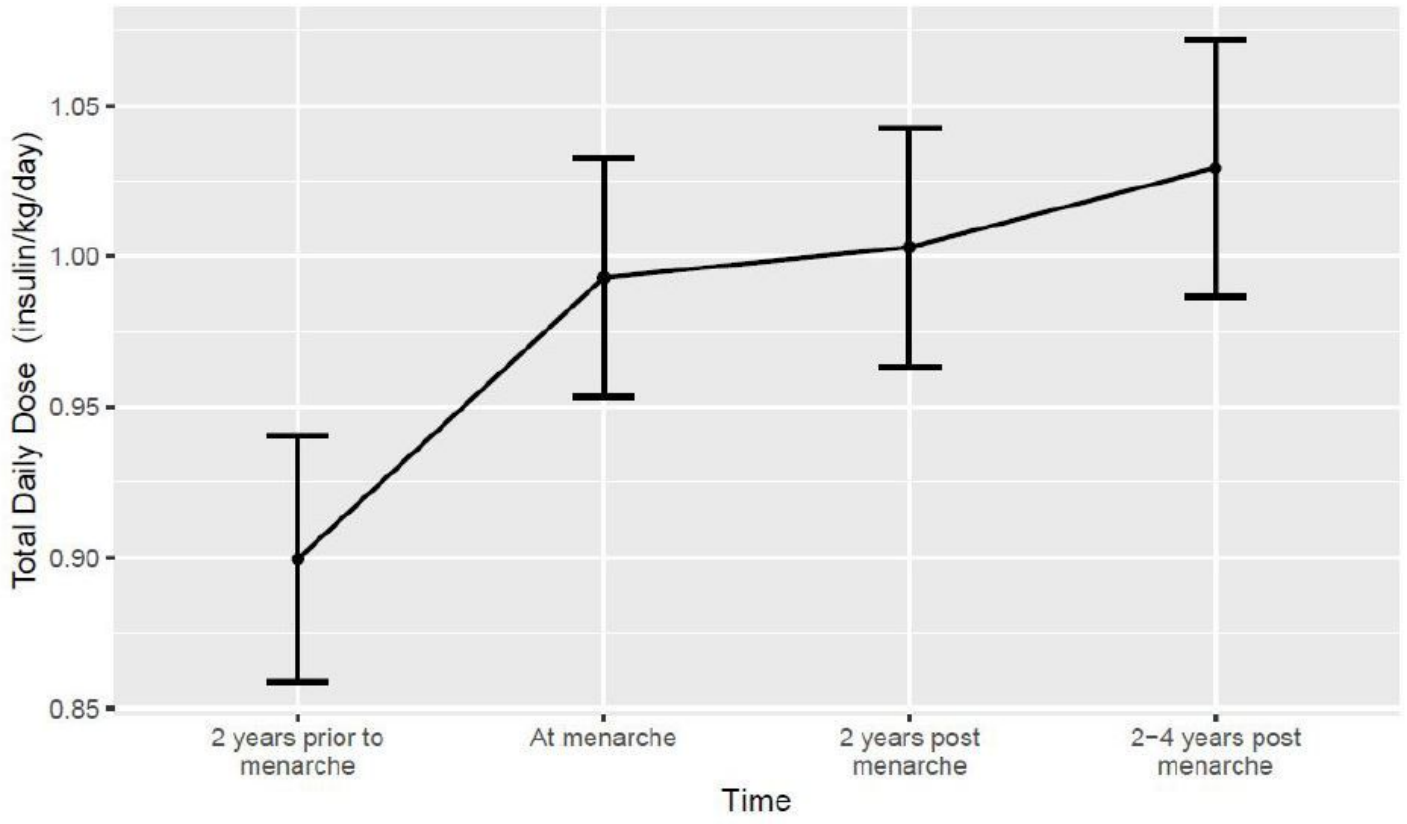

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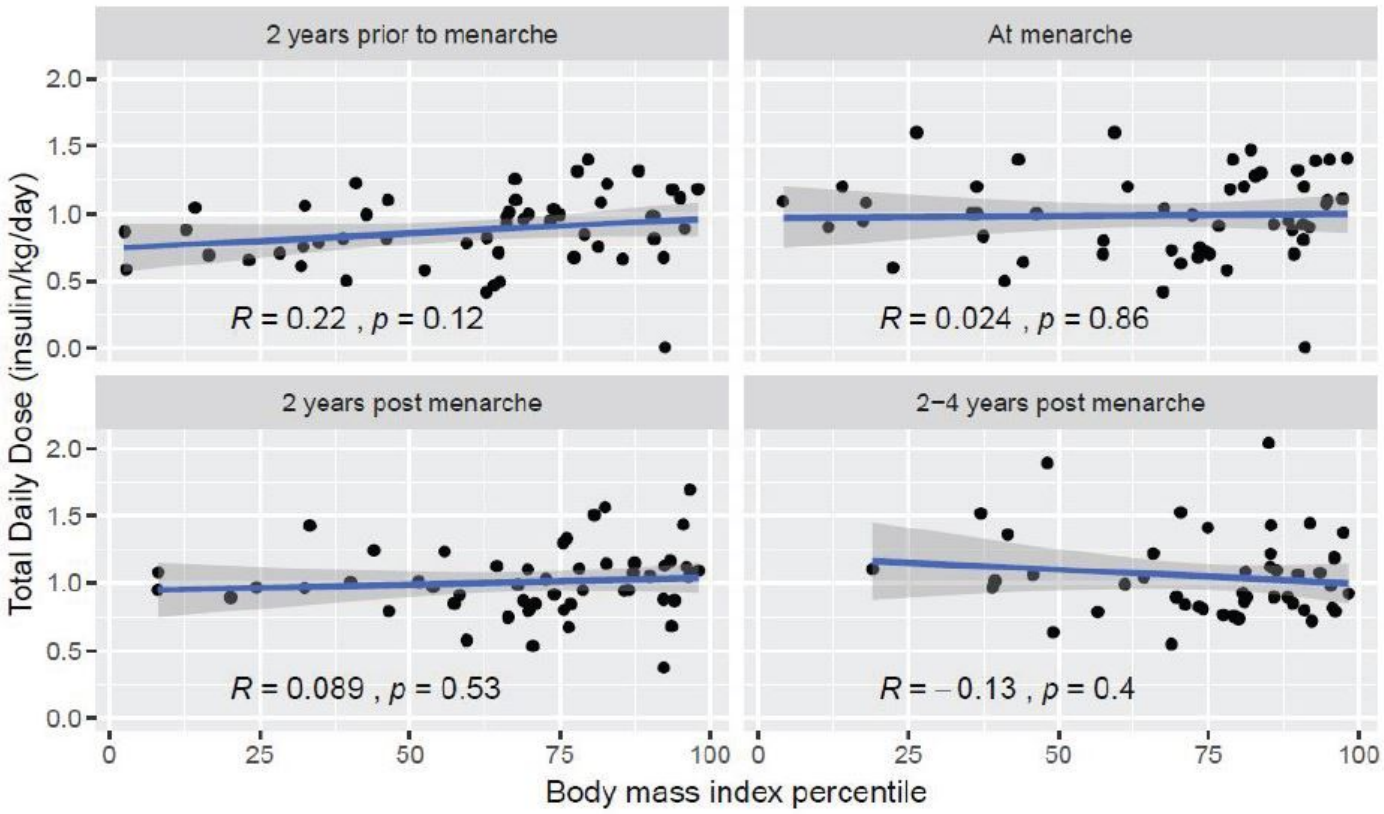

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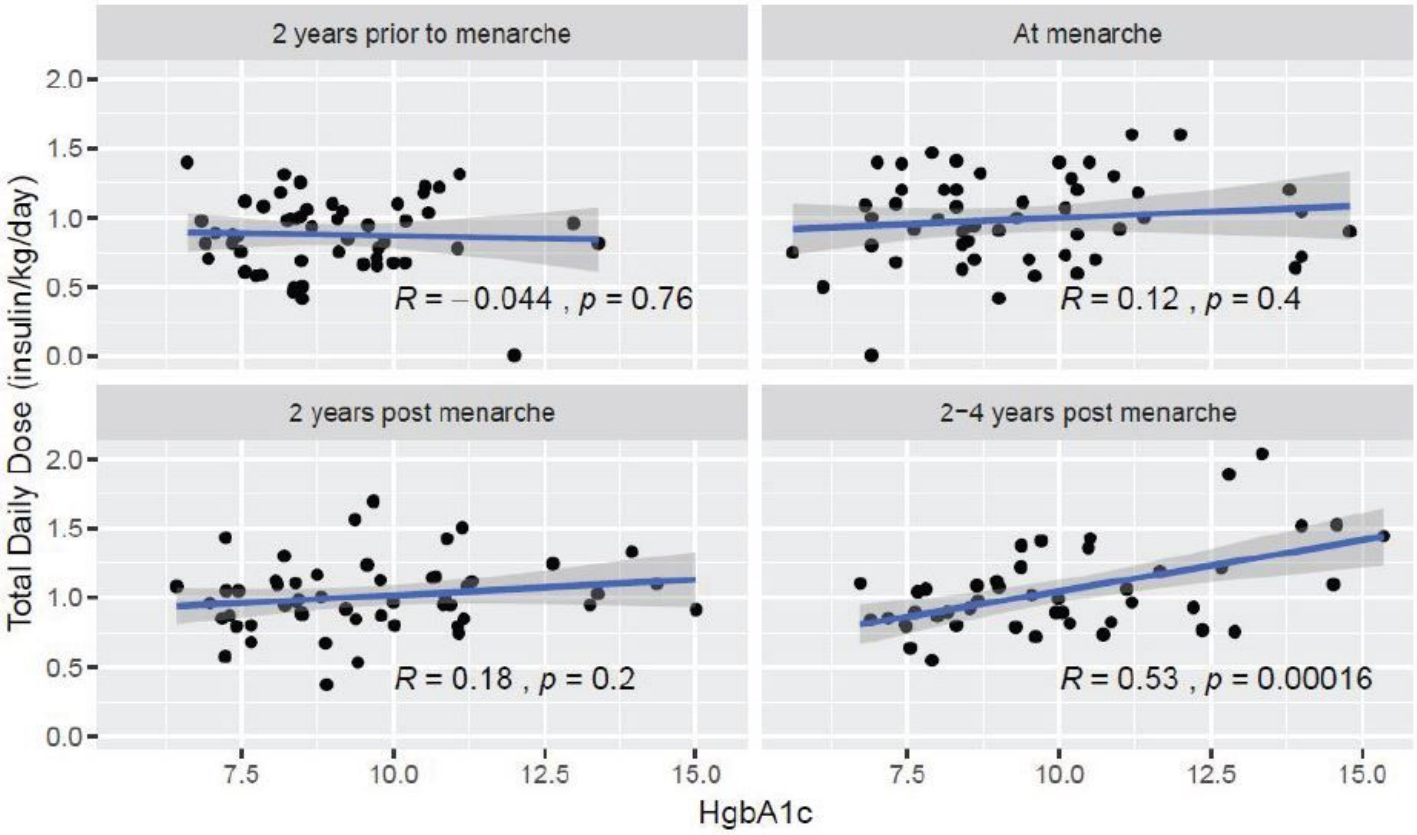

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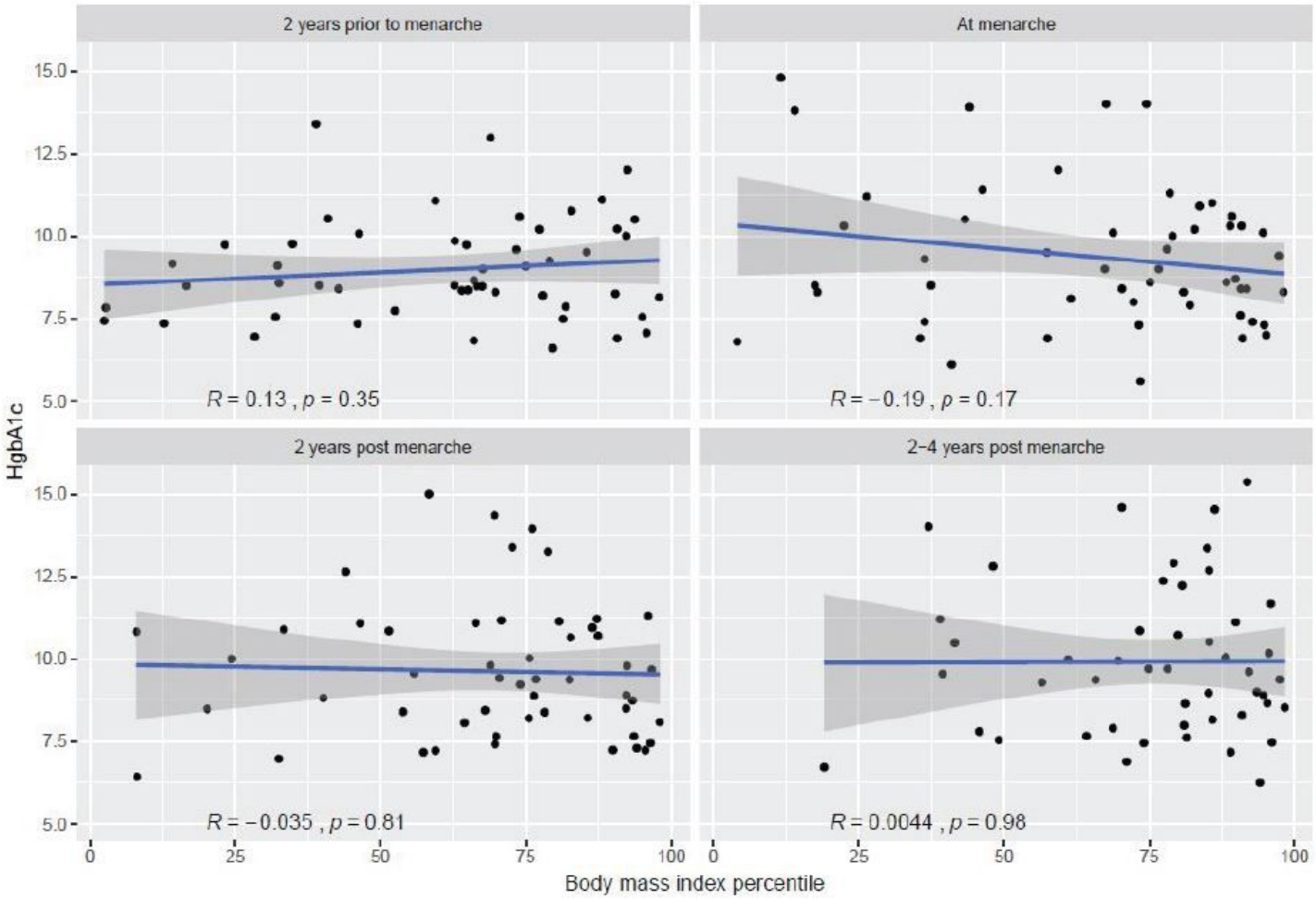

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