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Sex differences over time for glycemic control, pump use and insulin dose in patients aged 10–40 years with type 1 diabetes: a diabetes registry study

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ABSTRACT

Introduction To evaluate sex differences in people with type 1 diabetes concerning changes in glycemic control and trends in insulin pump use and insulin dose over two decades in adolescents and one-and-a-half decades in adults.

Research design and methods People aged 10–20 years (data years 1999–2018) and 21–40 years (data years 2004–2018) with type 1 diabetes were identified in the Diabetes Prospective Follow-up Registry (DPV). All available patients' data sets of the respective period were used for linear regression analyses to investigate trends in HbA1c, pump use, insulin doses and body mass index SD scores (BMI-SDS) in females and males. In addition, stratification by migrant background was made for the adolescent group.

Results In the youth group (n=68 662), both boys and girls showed an HbA1c decrease over the period examined. After stratification for migrant background, an HbA1c convergence between boys and girls was seen in those without migrant background as of 2016. Usage of insulin pumps increased continuously from 3% (boys and girls) to 47% (boys) and 54% (girls), respectively. The daily insulin dose in units per kilogram body weight and day increased continuously from 1999 to 2018. An insulin dose leveling between boys and girls occurred. BMI-SDS consistently increased in girls whereas only slight variations were observed in boys.

The adult group (n=15 380) showed constant HbA1c sex differences from 2004 to 2018 with lower HbA1c level in females. The use of insulin pump therapy rose from 18% to 35% (males) and 30% to 50% (females).

Conclusions The gap in metabolic control between boys and girls with type 1 diabetes seems to close, but predominantly in adolescents without a migrant background. Improved HbA1c was associated with increased insulin pump use, especially in girls.

In adult patients, sex differences in metabolic control and insulin pump use persist: women show constantly lower HbA1c values and higher insulin pump use.

Significance of this study

What is already known about this subject?
► Sex and gender differences exist regarding diabetes mellitus.

What are the new findings?
► Pre-existing HbA1c sex differences seem to clear in type 1 children and adolescents without migrant background.
► There is a time lag concerning HbA1c sex differences in adolescents with migrant background.
► HbA1c values declined among all youth groups from 2016 to 2018 onwards.
► Adults' sex differences for HbA1c and insulin pump use persist.

How might these results change the focus of research or clinical practice?
► Efforts are necessary to equalize gaps regarding sex and gender and to support vulnerable groups with type 1 diabetes.

INTRODUCTION

Over the last decades, sex and gender differences in medicine came into the focus of interest. Growing evidence suggests that sex and gender affect the pathophysiology, incidence, prevalence, symptoms and signs, course and response to therapy of many diseases, including diabetes mellitus.[1] For type 1 diabetes, for example, it is known that women have higher excess all-cause mortality than men.[2] In addition, a migrant background might aggravate sex and gender differences, as minority status itself is associated with a more unsatisfactory health outcome in youth with type 1 diabetes.[3] With this knowledge in mind, the new medical science gender medicine was—or is in the process of being—implemented into medical education institutions and networks.[4–8] The growing awareness about sex and gender differences accompanies an enormous encompassing change in diabetes therapy, due to new diabetes drugs and mainly due to technical innovation like sophisticated insulin pumps.[9]

The best possible metabolic control to avoid acute and long-term sequelae is the declared aim in diabetes therapy—for all sexes, males and females alike. The still most frequently used indicator for glycemic control is HbA1c, with an international guidelines' target of nowadays' <53 mmol/mol (<7%) for children, adolescents and adults.[10 11] Furthermore, diabetes registries for all age groups—national, international or regional—started documenting the progress in glycemic control and other clinical variables systematically since the late 1990s (see ref [12]), giving an excellent opportunity to investigate changes over time.

The present study aimed to evaluate sex differences and their changes over the last decades in two generations of individuals with type 1 diabetes against the backdrop of altering gender awareness. Glycemic control, insulin pump use, insulin dose and body mass index SD scores (BMI-SDS) were part of the investigation in a large international diabetes registry cohort.

RESEARCH DESIGN AND METHODS

As the basis for this study served the international multicenter, Diabetes Prospective Follow-up Registry (DPV). Currently, 495 pediatric and adult specialized diabetes centers from Germany (n=445), Austria (n=45), Switzerland (n=4) and Luxemburg (n=1) prospectively document demographic and clinical data of individuals with any diabetes, resulting in data of more than 560 000 patients (September 2019). For central analysis and quality assurance, participating DPV centers transfer locally collected and pseudonymized data twice a year to Ulm University, Ulm, Germany. In case of inconsistency or implausibility, data are reported back to the centers for verification or correction. The local/national review boards have approved the data collection of each participating center.

We searched the DPV database according to the following criteria: patients with type 1 diabetes (as documented in the registry's master data), aged 10–40 years, period 1999–2018 (for patients 10–20 years of age) or 2004–2018 (for patients >20–40 years of age) and documented HbA1c and type of diabetes therapy. The search resulted in a study sample of 84 042 patients originating from 489 centers. Demographic variables of our study group included age, patients' duration of diabetes, age at diabetes onset, sex and migrant background (defined as at least one parent and the patient born in another country than the participating four nations, or the patient alone born in another country than the participating four nations). We categorized the population into two age groups: 10–20 (youth group) and >20–40 (adult group) years of age. Further age grouping (10–15, >15–20, >20–30 and >30–40 years of age) was done for confounder adjustment. Individuals' duration of diabetes was grouped into ≤/>5 years. The use of insulin pumps was registered. Clinical data were HbA1c (mathematically standardized to the Diabetes Control

and Complications Trial reference range (21–43 mmol/mol/4.05%–6.05%)),[13] insulin dose in units per kilogram body weight and day and BMI-SDS based on the cohort of Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter.[14] For each patient, all available variables were aggregated per calendar year as a median, resulting in maximally 20 data sets per patient in the youth group (due to the time frame) and maximally 15 data sets in the adult group (also limited by the chosen period 2004–2018). Patients may have contributed data to the analysis in both age groups for a maximum of 20 years.

We calculated linear and logistic regression models (SAS PROC GLIMMIX) adjusted for repeated measurements and a simple autoregressive covariance structure to evaluate trends over time for HbA1c, insulin pump use, insulin dose and BMI-SDS. The autoregressive covariance structure considers that chronologically close measurement points correlate more closely than measurement points wide apart. Df were calculated using the between-within method. Year of treatment, sex, age group, diabetes duration group and an interaction term of year of treatment with sex were modeled as fixed effects. In a second step, we stratified the youth group by migrant background. We use the least square means for the interaction of year of treatment with sex to present results graphically. In a sensitivity analysis (SA) to test the model's robustness, we included only patients with at least two documented treatment years (online supplemental material).

A p value <0.05 indicated statistical significance. All statistical analyses were performed with SAS for Windows V.9.4 software (SAS Institute).

RESULTS

Description of the study cohort

Of the 564 734 individuals documented in DPV as 2019, 84 042 fulfilled the inclusion criteria. Of these, 68 662 were defined as the youth group and 15 380 as the adult group.

The baseline median age of the youth group included in this study was 12.0 (SA 11.6) years, baseline median diabetes duration 1.9 (SA 1.8) years, and baseline median HbA1c 7.73% (60.95 mmol/mol) (SA 7.67% (60.31 mmol/mol)). The adult group had a median age of 30.6 (SA 30.0 (IQR 25.3–34.7)) years, median diabetes duration of 8.6 (SA 9.2) years, and a median HbA1c value of 64.57 mmol/mol (8.06%) (SA 60.39 mmol/mol (7.68%)). Table 1 shows the population's characteristics in detail aggregated for the first available year per patient.

HbA1c trends

The linear regression model with adjustment for age, diabetes duration, migration and repeated measurements showed an overall decrease in the youth group for HbA1c: for boys from 65.62 (65.06–66.18) mmol/mol (8.15 (8.10–8.21) %) (least square mean (95% CI)) in the year 1999 to 64.03 (63.70–64.35) mmol/mol (8.00

Table 1 Characteristics of the study population, classified into youth and adult groups

Parameter	Youth group	n	Youth group SA	n	Adult group	n	Adult group SA	n
First year of analysis	2009 (2004–2014)	68 662	2009 (2003–2013)	56 620	2011 (2007–2015)	15 380	2010 (2006–2014)	6672
Age (years)	12.0 (10.4–14.6)	68 662	11.6 (10.4–14.1)	56 620	30.6 (25.6–35.45)	15 380	30.0 (25.3–34.7)	6672
Female/male sex (%)	46.8/53.2	68 662	46.9/53.1	56 620	49.5/51.5	15 380	51.0/49.0	6672
Migration background (%)	17.0	68 662	17.1	68 662	2.1	15 380	1.5	6672
Diabetes duration (years)	1.9 (0.2–5.6)	68 662	1.8 (0.2–5.4)	56 620	8.6 (0.6–17.3)	15 380	9.2 (1.2–17.51)	6672
Insulin pump use (%)	19.5	65 498	18.7	54 177	26,6	11 974	31.8	4569
HbA1c (%)	7.73 (6.87–9.02)	67 095	7.67 (6.83–8.84)	55 534	8.06 (6.89–9.91)	14 831	7.68 (6.72–9.11)	6478
HbA1c (mmol/mol)	60.95 (51.56–75.06)	67 095	60.31 (51.11–73.09)	55 534	64.57 (51.81–84.80)	14 831	60.39 (49.93–76.06)	6478
Insulin dose (IU/kg/day)	0.75 (0.57–0.95)	64 534	0.75 (0.56–0.94)	53 511	0.59 (0.43–0.78)	11 384	0.59 (0.42–0.772)	4366

Data are presented as median and lower upper quartile or as percentage and represent the first year available per patient.
SA, sensitivity analysis.

(7.98–8.04) %) in the year 2018. For girls, an even more pronounced decrease from 67.17 (66.59–67.76) mmol/mol (8.30 (8.24–8.35) %) to 64.70 (64.36–65.04) mmol/mol (8.07 (8.04–8.10) %) was seen, almost closing the earlier HbA1c gap between boys and girls (figure 1A). The SA confirmed this trend (see online supplemental figure S1A). Categorizing the youth population in individuals with and without migrant background revealed

that the group without migrant background underwent a convergence tour between boys and girls' HbA1c values (figure 1B), passing the significance level in the SA (p=0.039 for the interaction of year and sex, online supplemental figure S1B). The youth group with a migrant background showed a persistent distance between boys and girls' HbA1c values, although also with a trend toward convergence (figure 1C, verified by SA (online
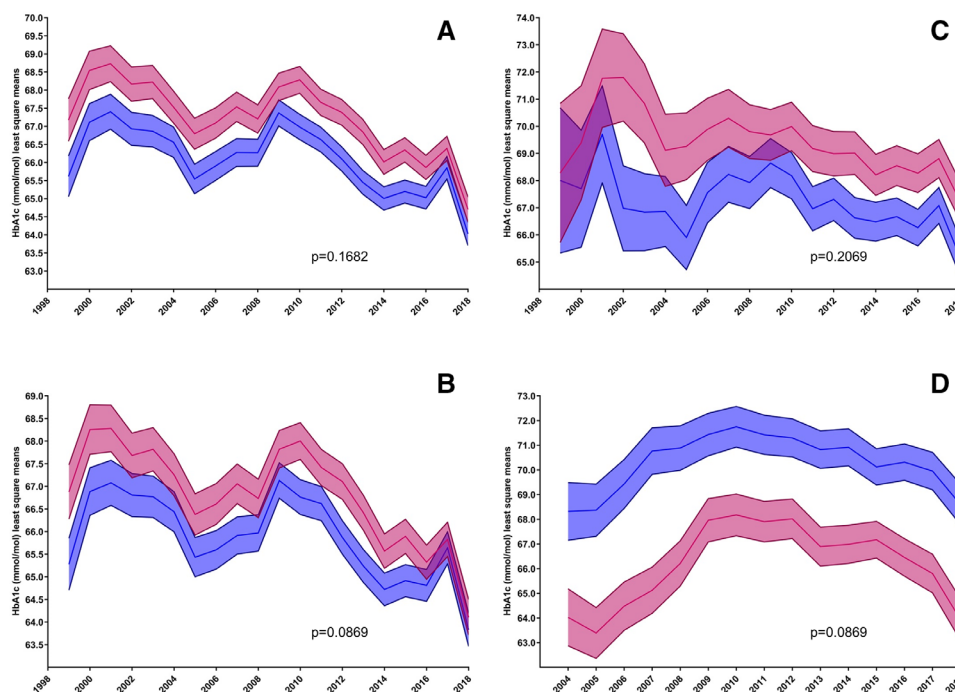

Figure 1 Least square means and 95% CI for HbA1c (%) over time for the whole youth group (A), for youth patients without (B) and with a migrant background (C) and adult group (D). Purple: females. Blue: males.

supplemental figure S1C)). Comparing girls with migrant background to girls without a migrant background and boys with migrant background to boys without migrant background showed a difference in HbA1c values, especially in boys (p=0.0037) (girls: p=0.0748), verified by SA (boys: p=0.0025; girls: p=0.1415). A pronounced decline in HbA1c values occurred among all youth groups 2016–2018 for girls and boys.

Adult male patients started with an HbA1c of 68.32 (67.15–69.49) mmol/mol (8.40 (8.29–8.51) %) in 2004, peaked in 2010 with 71.75 (70.93–72.57) mmol/mol (8.72 (8.64–8.79) %) and decreased until 2018 to 68.59 (67.77–69.41) mmol/mol (8.43 (8.35–8.50) %). The females paralleled this trend curve while displaying a constantly lower HbA1c (figure 1D). The SA, however, showed a (temporary) convergence of females and males' HbA1c values starting in 2009 and a divergence in 2018, leaving the males with an HbA1c of 63.14 (62.29–63.98) mmol/mol (7.93 (7.85–8.00) %) and the females with an HbA1c of 61.27 (60.40–62.14) mmol/mol (7.76 (7.68–7.84) %) (p=0.0039) (online supplemental figure S1D).

Insulin pump use

The use of insulin pumps underwent a steep and continuous increase from 1999 to 2018 in the youth group, favoring girls cumulatively over the years: approximately 2.6% of boys and girls used this technique in 1999. In 2018, the percentage of boys using insulin pumps was 45%, and in girls 53% (figure 2A). The SA showed a similar trend (online supplemental figure S2A). Stratifying the youth group by migrant background, the pattern remains similar for individuals with and without a migrant background. However, the percentage of girls and boys with a migrant background who received an insulin pump therapy was lower (girls 48%, boys 39% in 2018) than girls and boys without a migrant background (girls 54%, boys 47% in 2018). In the adult group, considerably more females than males used insulin pumps. Females started in 2004 with 28% pump use, males with 18%; in 2018, 49% (females) and 30% (males) used insulin pumps (figure 2B). The SA verified the findings (online supplemental figure S2B).

Insulin dose trends and BMI-SDS trends

The daily insulin dose in units per kilogram body weight per day in the youth group increased steeply from 1999 to 2005 and was divergent for boys and girls: In 1999, boys had a documented insulin dose of 0.77 (0.76–0.78) IU/kg/day, girls of 0.82 (0.81–0.83) IU/kg/day. From 2006 onwards, the differences almost vanished, ending up in 2018—after a continuous increase—at a daily dose of 0.90 (0.90–0.91) IU/kg/day in boys and 0.90 (0.89–0.90) IU/kg/day in girls (p<0.001 for the interaction of year and sex) (figure 3A). The SA reinforced this result (online supplemental figure S3A). A similar trend curve showing a convergence of insulin doses for boys and girls over time with an even earlier
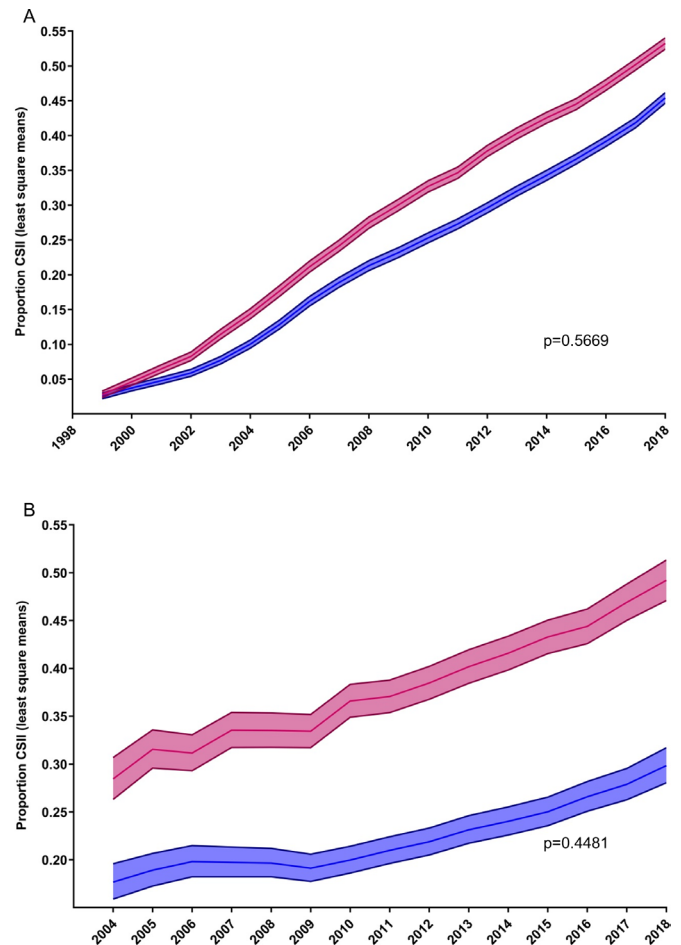
Figure 2 Least square means and 95% CI for proportion continuous subcutaneous insulin infusion (CSII) over time for youth group (A) and adult group (B). Purple: females. Blue: males.

beginning could be seen for those individuals without a migrant background (figure 3B), but not for individuals with a migrant background. With a migrant background, the gap between boys and girls closed as late as from 2015 onwards (figure 3C). For the adult group, the trend course shows fewer fluctuations: In 2004, there was no difference in the daily insulin dose in units per kilogram body weight in males (0.67 (0.65–0.69) IU/kg/day) and females (0.67 (0.65–0.69) IU/kg/day). After peaking in males in 2009 (0.73 (0.71–0.74) IU/kg/day), the insulin dose was 0.71 (0.69–0.72) IU/kg/day in males and 0.69 (0.68–0.71) IU/kg/day in females in 2018 (figure 3D).

The BMI-SDS constantly rose in the youth group girls over the observed period: in 1999, the girls' BMI-SDS was 0.33 (0.31–0.35), in 2018 0.63 (0.62–0.64) (figure 4A). Whether without a migrant background or with a migrant background, the gain in BMI-SDS was consistently higher in girls than in boys (figure 4B,C). In adults, males showed persistently lower BMI-SDS values than females (figure 4D). Online supplemental figure S4A–D shows the respective SA results.
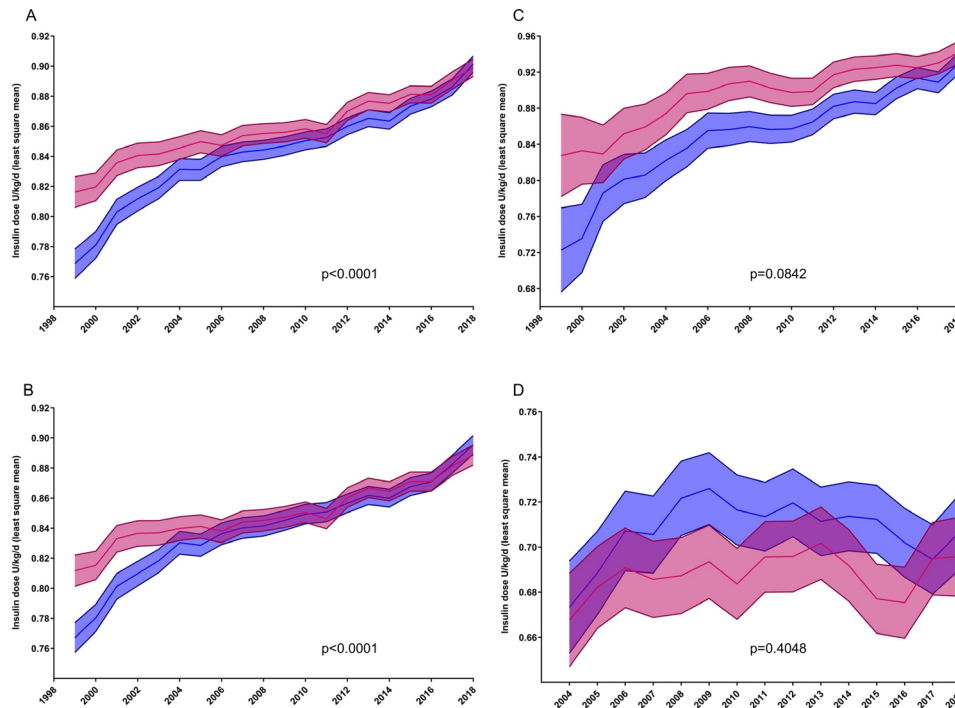
Figure 3 Least square means and 95% CI for insulin dose/kg/day over time for the whole youth group (A), for youth patients without (B), with a migrant background (C) and adults (D). Purple lines: females. Blue lines: males.

CONCLUSION

Our study about sex differences in glycemic control, pump use and insulin dose demonstrates many dynamic changes over time. One of the most important findings is that the boys and girls' (youth group) glycemic control, represented by HbA1c, drew nearer over the last 3 years—although this holds for patients without a migrant background mainly—settling on a lower level than 20 years ago for both sexes. Over decades, studies reported the girls' metabolic control to be poorer than the boys'.[15–17] The boys and girls' intrinsic physiology has not changed, so the root must lie in something extrinsic and behavioral. As the proportion of girls using pumps increased almost 20-fold from 1999 to 2018, but only
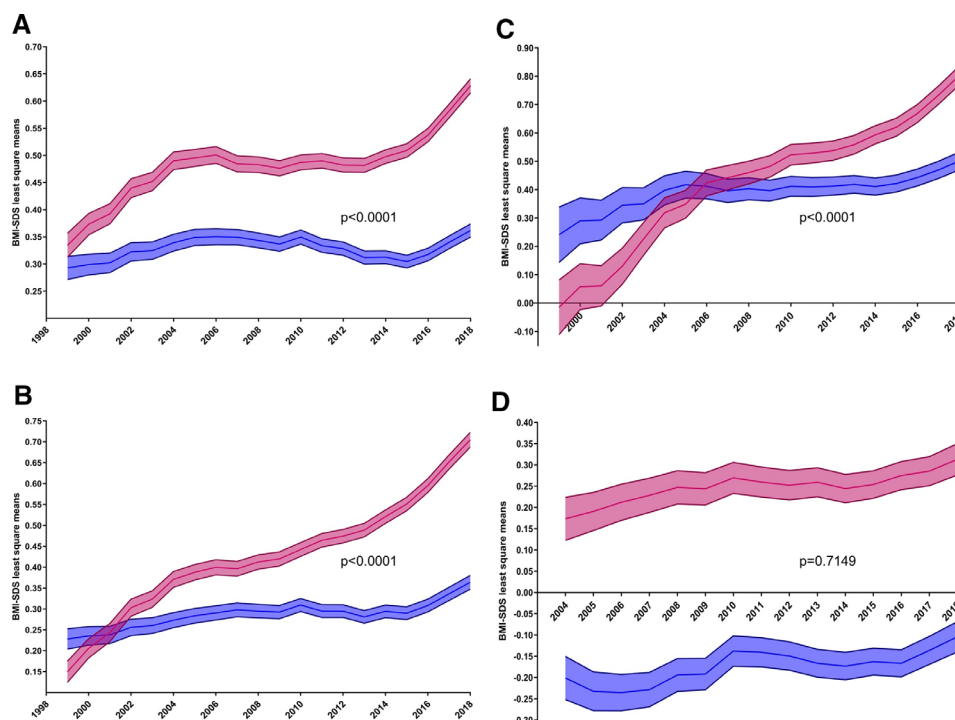

Figure 4 Least square means and 95% CI for body mass index SD scores (BMI-SDS) over time for the whole youth group (A), for youth patients without (B), with a migrant background (C) and adults (D). Purple lines: females. Blue lines: males.

18-fold in boys, this could be a partial explanation. Extensive cohort studies[18–20] and review papers[21] provided evidence for improved clinical outcomes by insulin pump use, especially in children, but also showed that boys were treated less often with a pump compared with girls.[18 22] A reason for treating more girls than boys with insulin pumps over the years might have been the long-standing worse glycemic control in girls,[15–17 23] as unsatisfying glycemic control is one of the primary and recognized indications for treatment with insulin pumps. Girls might even display more acceptance for insulin pumps than boys. Another explanation for the vanishing HbA1c sex difference is an altered daily insulin dose: earlier studies have shown that both daily insulin dosage and HbA1c were significantly higher in female children and adolescents.[24] However, we could demonstrate in this study that both girls and boys used continuously increasing insulin doses since 1999, leading to diminished and, in the end, non-existent insulin dose differences between girls and boys. The general insulin dose increase might be due to the attempt to achieve the international and national guidelines' HbA1c targets (53 mmol/mol (<7%)) via tighter glucose control, accompanied by increasing use of technical devices (flash/continuous glucose monitoring (CGM)) guaranteeing avoidance of hypoglycemic events particularly.[9] The increasing BMI-SDS might also contribute to the increased insulin dose indicating insulin resistance. However, the girls showed a steep increase in BMI-SDS but a less steep increase in insulin doses than boys. The girls' less steep increase might result from their higher insulin pump use: we know that this technique requires less insulin than multiple daily injections.[19 20] However, care should be taken not to overinterpret the longitudinal insulin dosage data: early study data originate from patients' statements linked with the possibility of under-reporting of meals and their corresponding insulin dosages. Data from recent years, partly from the reliable insulin pump and technical device readings, are probably closer to the accurate insulin dosage.

More factors contribute to the changes in glycemic control and the boys and girls' HbA1c convergence in the youth group. Greater self-control that is attributed to girls' behavior compared with boys', resulting, for example, in better grades,[25] is a trait that may lead to better or excellent glycemic control. However, these girls' characteristic is hardly something new for the last couple of years. More likely, a change in treatment and social interaction, particularly in girls and adolescent females, took place, perhaps partly due to the introduction of gender medicine in medical school,[5] partly due to generally changing gender stereotypes as stated in a meta-analysis by Eagly et al,[26] and partly maybe due to the increased number of female physicians. The female physician factor was associated with a higher quality of care in an Irish review and meta-analysis about the quality of diabetes management in primary care.[27] Besides the factors mentioned above, we must not forget the tighter HbA1c targets that were molded into International Society for Pediatric and Adolescent Diabetes (ISPAD)'s guidelines in 2018

but were anchored in diabetologists' minds long beforehand: The clinicians' treatment target for their patients matter in the management of children and adolescents with type 1 diabetes, as shown in a small Australian study by Cameron et al.[28] Especially those children and adolescents with inadequate glycemic control - namely girls - would have come to the fore with the lower HbA1c target to get their HbA1c closer to the pursued target.

The general and pronounced HbA1c decline from 2016 to 2018 in all adolescents might be an effect of increased use of CGM: in 2016 the reimbursement by health insurances started and resulted in a tremendous increase of CGM use.[29] A recent study confirmed the benefit of CGM in adolescents and young adults with regard to glycemic control.[30] Additional factors like newer drugs, for example, glucagon like peptide 1 (GLP1) receptor agonist, are unlikely to have contributed to the HbA1c decline, as they had no approval for children and adolescents in the mentioned period.

Unfortunately, the general and the girls' glycemic control improvement has not yet reached the same level in those children and adolescents with a migrant background, although a convergence trend can be observed. Moreover, the use of insulin pumps turned out to be somewhat lower than in those patients without a migrant background, although increasing over time and showing the same pattern with more girls than boys using pumps. There seems to be a time lag in improvements for people with type 1 diabetes and migrant background. For years, we have known that minorities with type 1 diabetes are disadvantaged in health systems.[3 31–34] We have not yet found an optimal way of communicating with children and adolescents with a migrant background and their families. Similar to the implementation of gender medicine since the 1990s, there are attempts to create an enabling environment for migration and health research at national, regional and global levels.[35] An active part for diabetologists in this process will hopefully lead to success over the next decade.

Glycemic control trends for the adult group showed a temporary increase of HbA1c up to 2010 and a decrease until 2018, ending up (SA) with a marginally improved HbA1c compared with 2004. One reason for the downward direction of HbA1c values might be the pronounced use of CGM since 2016, especially in young adults.[29] Additional contributing factors could be a change towards new long-acting insulins. Other influencing newer diabetes drugs like sodium dependent glucose co-transporter 1/2 (SGLT1/2) inhibitors can be excluded as they were not approved for type 1 diabetes during the study period.

From 2004 to 2018, females had lower HbA1c and needed lower daily insulin doses per kilogram body weight, despite constantly higher BMI-SDS and potentially negatively influencing factors like menstrual cycles, luteal phase changes in insulin sensitivity or use of hormonal contraception.[36] This glycemic control observation contrasts with other European or US studies: from 2004 to 2016, Scottish women with type 1 diabetes had consistently slightly higher average HbA1c than

men.[37] The same pattern was seen in young Italian adults aged 18–30 years with type 1 diabetes.[38] Data from the T1D Exchange Registry showed similar HbA1c results in women and men with type 1 diabetes.[39] One possible explanation for this sex difference in the DPV cohort might be that more women than men use insulin pumps—undoubtedly due to the recommendation to use insulin pumps during pregnancy and preconceptionally. The Scottish registry and the T1D Exchange study mentioned above report the same gender distribution for insulin pump use. However, they show no or even reversed HbA1c sex differences. The known sex differences in energy balance and metabolic homeostasis (inter alia higher skeletal muscle mass, higher visceral adiposity, and higher glucose oxidation in men, higher total fat mass, higher subcutaneous adiposity, and higher insulin sensitivity in woman) that influence glycemic control (reviewed in ref 40) are expected to be similar within the human species worldwide, and therefore cannot explain these contradictive findings. That leaves us with environmental factors that theoretically might play a role. A European study using data from the Survey of Health, Aging and Retirement showed that sex differences in cognitive functions vary systematically across birth cohorts and regions. The authors stated that improved living conditions and less gender-restricted educational opportunities are associated with increased gender differences favoring women in cognitive functions and decreasing or eliminating differences in other cognitive abilities.[41] Nevertheless, whether this changing face of cognitive gender differences is actually associated with the sex differences seen in our DPV cohort remains more than speculative and has to be entrusted for further studies. It also remains speculative whether factors, such as, for example, socioeconomic status or the time spent at home or at work, influence glycemic control and explain sex differences. These data are not systematically recorded in DPV.

Our study has a few more limitations: the adult DPV cohort is the 'younger' group in the DPV, as DPV started initially in 1995 as a pediatric diabetes registry. While the sizeable pediatric cohort is now population based and represents approximately 90% of the children with type 1 diabetes in Germany, the adult cohort—although growing—is still clinic based. Hence, the period of the adult group in our study is shorter than the youth group's period. Moreover, the SA reduces the initial cohort by a factor of 2.3 from n=15 380 to n=6672 participants. Despite still comprising a large number of adult patients, this is a limitation of our study. Another limitation is the incomplete documentation of migrant background in the adult group: in Germany alone, about 26% of the population had a migrant background in 2019;[42] thus, the documented proportion of 1.5% in the study population is highly underestimated. We have to assume that many adults with a migrant background have been included in the non-migration subgroup. Stratification by migrant background was therefore not carried out.

In summary, we identified a closing gap concerning sex differences regarding improved glycemic control over time in a population of children and adolescents with type 1 diabetes without a migrant background. Sex differences seem to persist longer in patients with a migrant background, showing a time lag. Improvements in glycemic control are accompanied by increased insulin pump use, favoring girls, and an increased daily insulin dose, favoring boys. In the adult population, women persistently show better glycemic control and use insulin pumps more often than men. The discussed explanations for the observed sex differences remain speculative.

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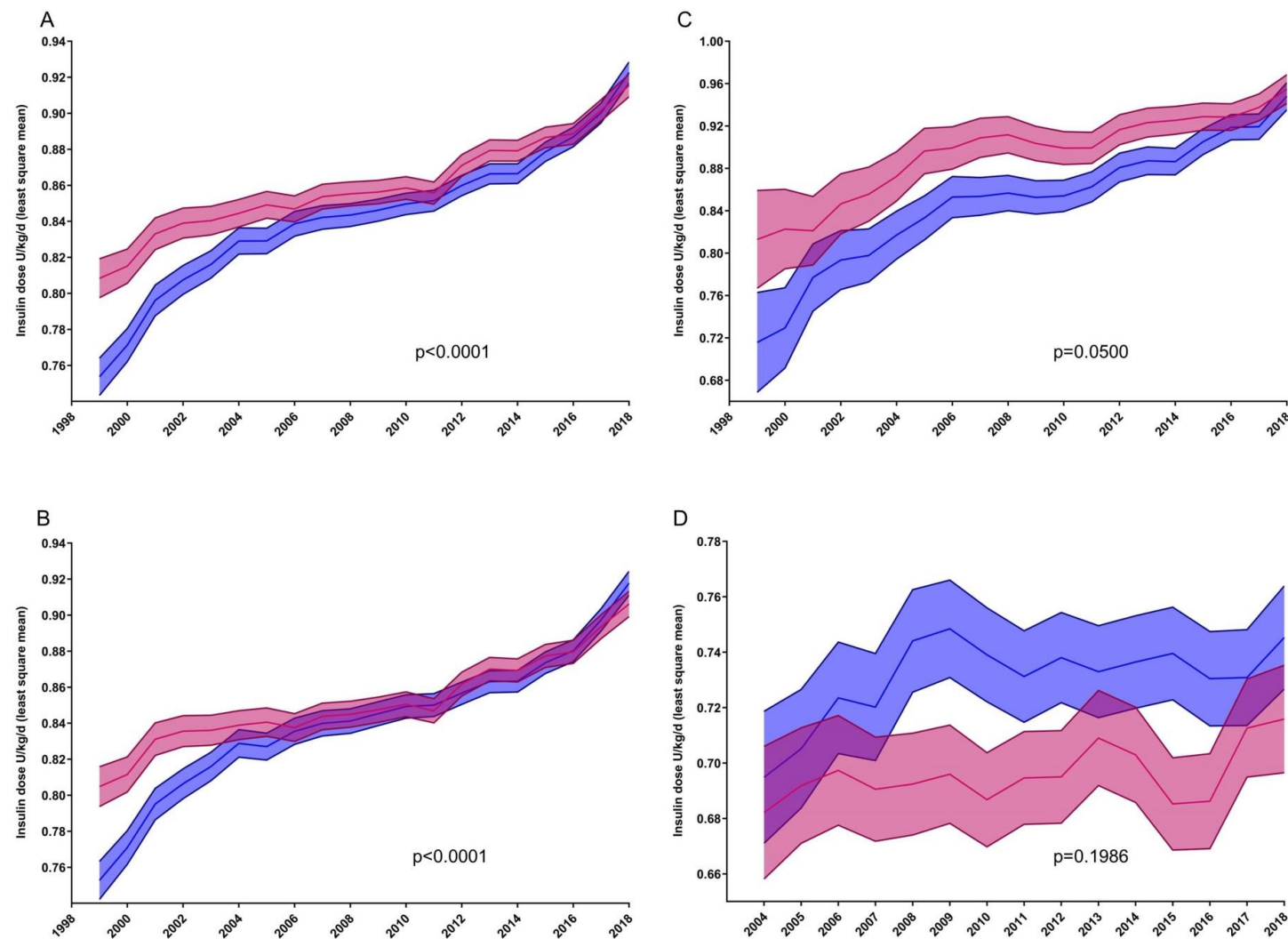6. Legato MJ, Johnson PA, Manson JE. Consideration of sex differences in medicine to improve health care and patient outcomes. *JAMA* 2016;316:1865–6.
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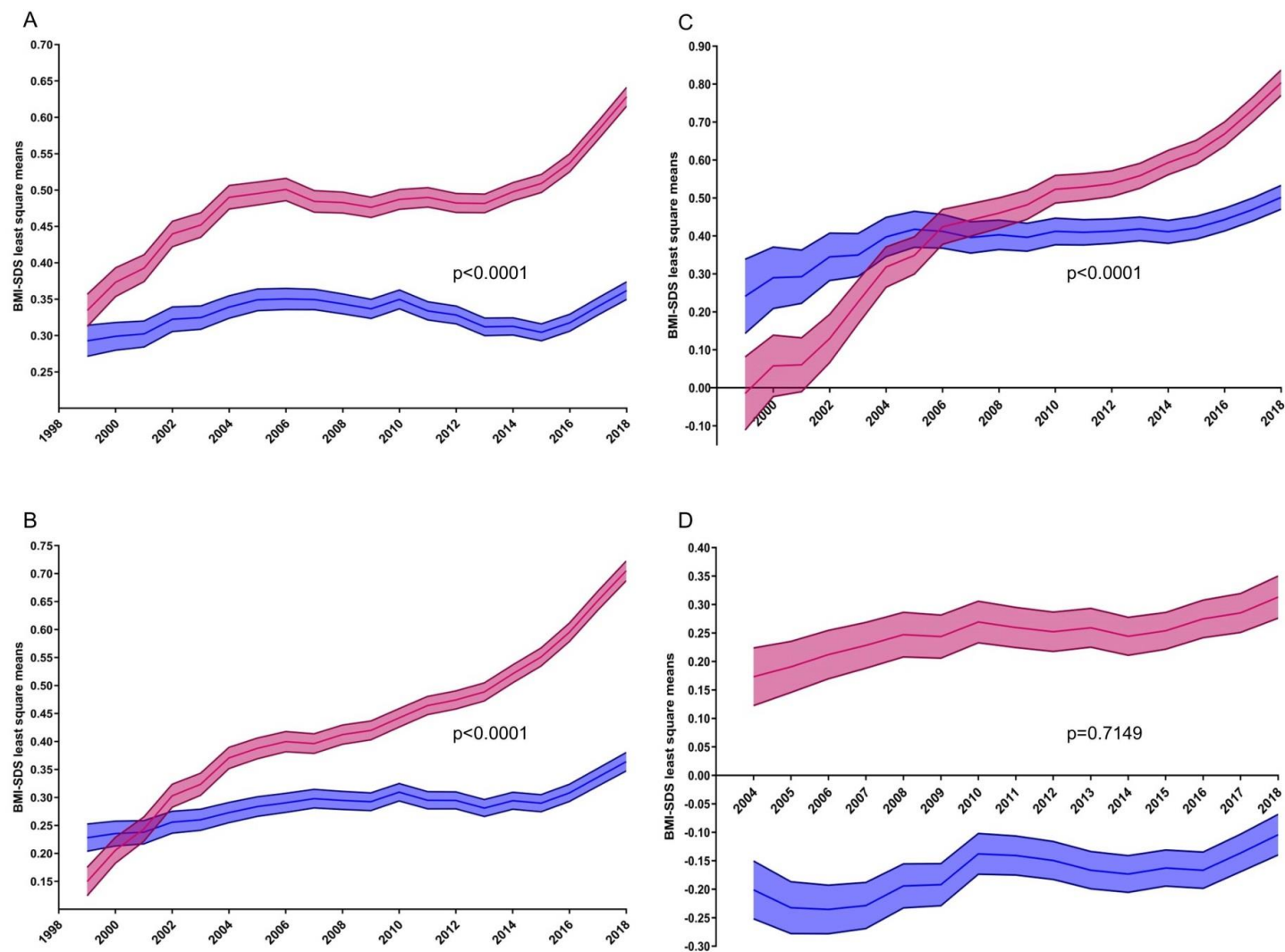
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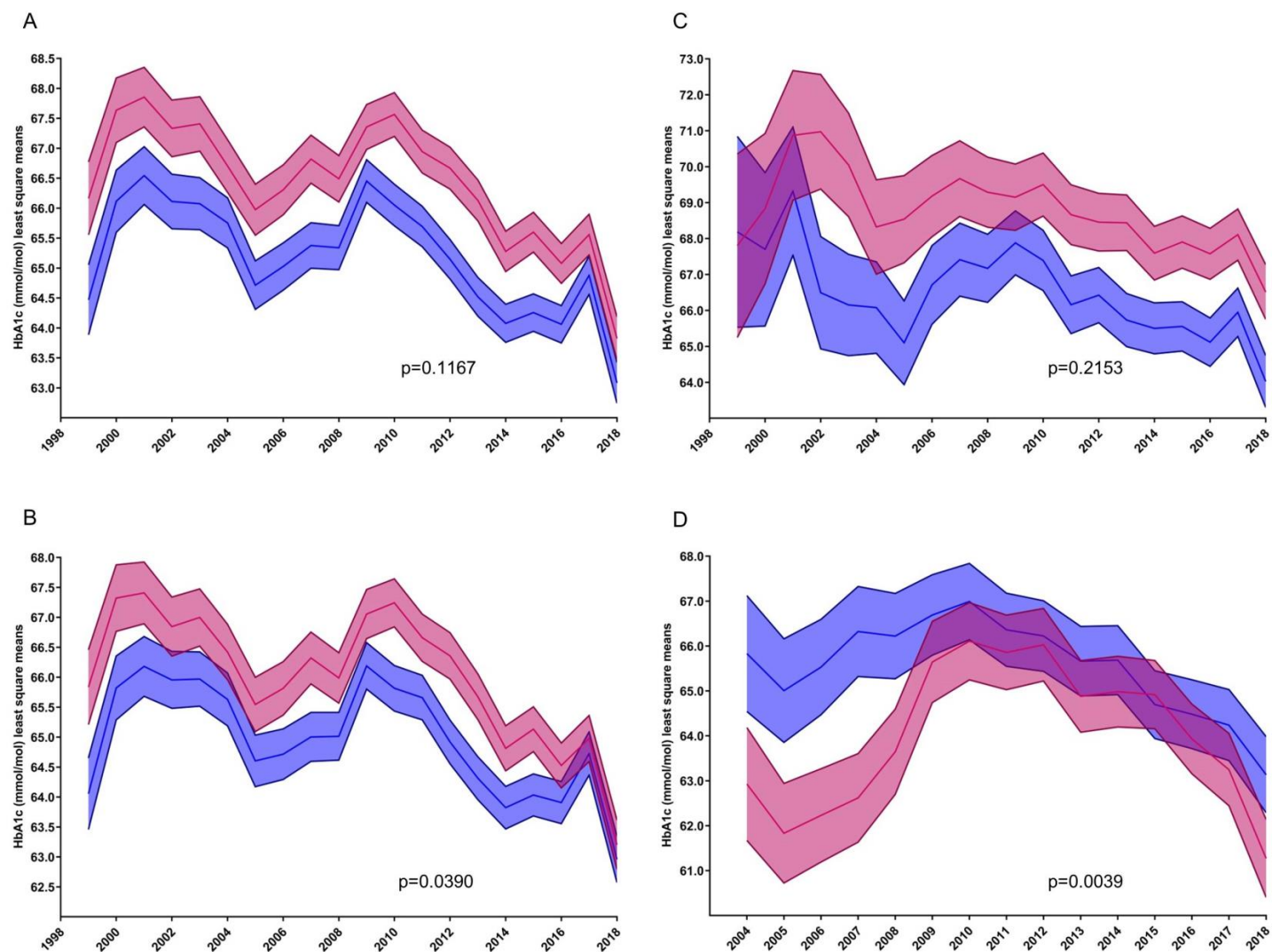
Supplemental material Figure S1, A-D: Sensitivity analysis. Least square means and 95% CI for HbA1c (mmol/mol) over time for the whole

youth group (A), for youth patients without (B) and with migration background (C) and adult group (D). Purple: females; blue: males.
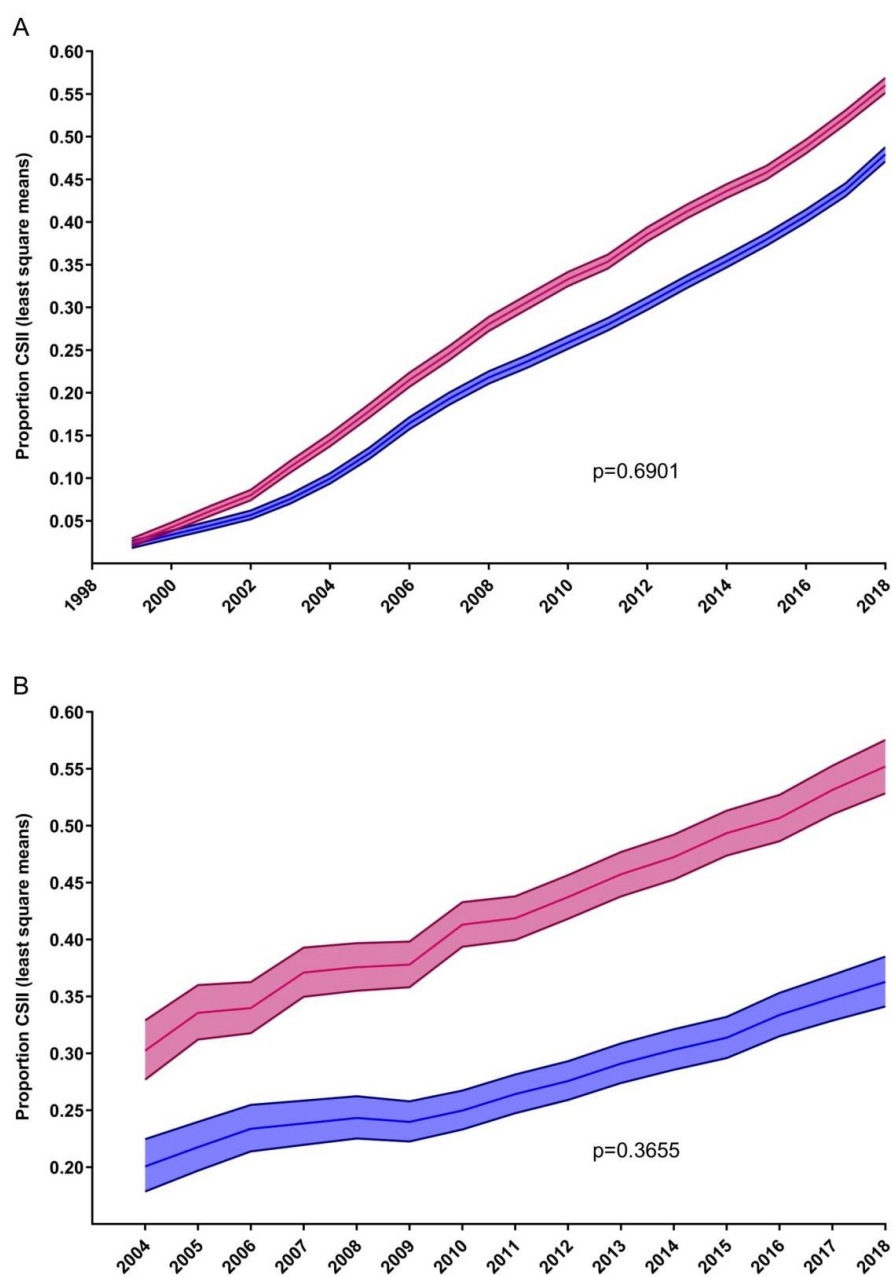
Supplemental material Figure S2, A, B: Sensitivity analysis. Least square means and 95% CI

for proportion CSII over time for youth group (A) and adult group (B). Purple: females; blue:

males.

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Supplemental material Figure S3, A-D: Sensitivity analysis. Least square means and 95% CI for Insulin dose U/kg/d over time for the whole youth group (A), for youth patients without (B), with migration background (C) and adults (D). Purple lines: females; blue lines: males.

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Supplemental material Figure S4, A-D: Sensitivity analysis. Least square means and 95% CI for BMI-SDS over time for the whole youth group

(A), for youth patients without (B), with migration background (C) and adults (D). Purple lines: females; blue lines: males.