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Predictors of changing insulin dose requirements and glycaemic control in children, adolescents and young adults with Type 1 diabetes

G. H. Teló[1,2], **C. E. Dougher**[1], **L. K. Volkening**[1], **M. L. Katz**[1], and **L. M. Laffel**[1]

[1]Pediatric, Adolescent and Young Adult Section, Section on Clinical, Behavioral and Outcomes Research, Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

[2]Federal University of Rio Grande do Sul, Porto Alegre, Brazil/CAPES Foundation, Ministry of Education, Brasilia, Brazil

Abstract

Aims—To investigate trajectories of daily insulin dose requirements and glycaemic control in children, adolescents and young adults with Type 1 diabetes and to identify factors associated with changing insulin needs and deterioration in HbA_{1c}.

Methods—The sample was a dynamic cohort of 635 children, adolescents and young adults with Type 1 diabetes from one centre. Data from clinic visits occurring over 20 years (1993–2013) were extracted from medical records. From age 7–24 years, we evaluated HbA_{1c} and insulin dose according to sex, insulin regimen and weight status.

Results—Participants provided a mean ± SD of 10.7±4.3 years of insulin dose data and 12.0±4.6 years of HbA_{1c} data. At first observation, the mean ± SD age was 10.0±2.6 years, diabetes duration was 2.8±2.1 years, insulin dose was 0.8±0.2 units/kg and HbA_{1c} was 74±18 mmol/mol (8.9±1.6%). Insulin dose was higher in girls at ages 8–13 years ($P<0.0001$ to $P<0.01$), but higher in boys/young men at ages 16–21 years ($P<0.0001$ to $P=0.04$). HbA_{1c} was higher in girls/young women at ages 16–24 years ($P<0.0001$ to $P=0.01$). Compared with injection therapy, pump therapy was associated with lower insulin dose at ages 8–24 years ($P<0.0001$ to $P=0.03$) and lower HbA_{1c} at ages 8–22 years ($P<0.0001$ to $P=0.005$). HbA_{1c} did not differ between overweight/obese and normal weight individuals, but overweight/obese individuals had higher insulin dose at ages 8–13 years ($P<0.0001$ to $P=0.03$).

Conclusions—This longitudinal assessment identifies clinically meaningful modifiable (e.g. insulin regimen) and non-modifiable (e.g. sex) factors predictive of insulin requirements and HbA_{1c} levels in young people with Type 1 diabetes; anticipatory insulin adjustments may improve glycaemic control.

Correspondence to: Lori Laffel. lori.laffel@joslin.harvard.edu.
DR LORI M. B. LAFFEL (Orcid ID : 0000-0003-2202-492X)

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Introduction

Childhood, adolescence and young adulthood are developmental stages that affect insulin requirements and glycaemic control in people with Type 1 diabetes [1]. Optimizing glycaemic control substantially reduces the risk of microvascular and macrovascular complications [2,3]; however, achieving the recommended American Diabetes Association target levels of HbA_{1c} <58 mmol/mol (<7.5%) for individuals aged <18 years and <53 mmol/mol (<7%) for young adults remains a challenge [4,5]. In studies involving children and adolescents with Type 1 diabetes, poor glycaemic control has been associated with older age, black race and longer diabetes duration [6,7]; however, many studies analysing predictors of deterioration in glycaemic control during childhood and adolescence have been limited by short duration of follow-up [8,9], small sample size [10,11] and limited numbers of factors evaluated [10,12].

Although previous studies have described the impact of puberty on insulin resistance and insulin sensitivity in children and adolescents with Type 1 diabetes [13,14], the natural course of insulin requirements during childhood, adolescence and young adulthood, as well as factors associated with insulin dose requirements, is not entirely understood. It is recognized that obesity impairs insulin action [15]. Other reports have shown that girls have higher insulin requirements than boys during adolescence as a result of lower insulin sensitivity in girls, which is probably related to increasing adiposity and decreasing physical activity during puberty [16]. Additionally, insulin pump therapy has been associated with lower insulin requirements [16–18]; however, the impact of weight, sex and regimen on insulin requirements, as well as trajectories of insulin dose and HbA_{1c} according to age requires further study.

In an effort to identify factors associated with insulin dose requirements and deterioration of glycaemic control commonly observed during childhood, adolescence and young adulthood [4], we sought to investigate trajectories of daily insulin dose and glycaemic control in young people with Type 1 diabetes according to age. We also sought to identify the demographic and clinical characteristics associated with trajectories of insulin dose and glycaemic control. Understanding the impact of these characteristics on insulin requirements and HbA_{1c} levels may inform approaches to improving glycaemic control during childhood, adolescence and young adulthood.

Participants and methods

Participants

We compiled a dynamic cohort of children, adolescents and young adults with Type 1 diabetes identified by their enrolment in five short-term non-drug studies at a single paediatric diabetes centre [19–22]. These investigations provided an opportunity for rigorous data collection and careful ascertainment of clinical/demographic characteristics. Participants included in this analysis met the following inclusion criteria: diabetes duration ≥1 year and daily insulin dose ≥0.5 units/kg at first included observation; follow-up for ≥1 year; and ≥2 observations with insulin dose and HbA_{1c} data. The institutional review board approved retrospective and prospective data collection for the present study. All the young

people/their parents signed informed assent/consent, respectively, at the time of the short-term investigations.

Data collection and measures

Trained research staff reviewed paper and electronic medical records and extracted demographic/clinical data from participants' clinic visits that occurred during a 20-year period (January 1993 to December 2013). Glycaemic control was assessed by HbA_{1c}, which was performed in a clinical laboratory using an assay standardized to the Diabetes Control and Complications Trial (DCCT; reference range 4.0–6.0%). Insulin regimen was classified as use of multiple daily injections or insulin pump. Daily insulin dose was captured by clinician report for those using injection therapy and, for pump users, by pump downloads when available or clinician report when pump downloads were not available. After data extraction, we converted total daily insulin dose values to units/kg/day.

For individuals aged <20 years, we calculated age- and sex-adjusted BMI percentiles using normative data from the US Centers for Disease Control and Prevention [23]. For individuals aged ≥20 years, we calculated BMI (kg/m^2). Categories of weight status were defined as: underweight (age <20 years: BMI <5^{th} percentile; age ≥20 years: BMI <18.5 kg/m^2); normal weight (age <20 years: BMI 5^{th} to <85^{th} percentile; age ≥20 years: BMI 18.5 to <25 kg/m^2); overweight (age <20: BMI 85^{th} to <95^{th} percentile; age ≥20 years: BMI 25 to <30 kg/m^2); and obese (age <20 years: BMI ≥95^{th} percentile; age ≥20 years: BMI ≥30 kg/m^2). Because only 1% of individuals were underweight at first observation, we included underweight individuals in the normal weight category for the analyses. To account for differences in developmental stages, we assessed participants in three age categories: 7–13 years (representing pre-puberty to early puberty); 14–18 years (representing mid puberty to late puberty); and 19–24 years (representing post-puberty) [24]. The number of participants in each age group provided sufficient data for analyses.

Data analysis

Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA). Descriptive data are presented as means ± SD for continuous variables and percentages for categorical variables. Statistical analyses included unpaired *t*-tests for continuous variables and chi-squared tests for categorical variables. Because of the sparse availability of data for participants aged <7 years and >24 years, we only included participant data for those aged 7–24 years in the analyses. For each age between 7 and 24 years, we calculated annualized daily insulin dose (units/kg) and HbA_{1c} values by averaging all insulin dose and HbA_{1c} values within ±6 months of the participant's birthday. For annualized insulin regimen and weight status values, we used the insulin regimen and weight status closest to the participant's birthday for each age between 7 and 24 years.

Bivariate analyses included the impact of sex, insulin regimen and weight status (normal weight vs overweight/obese) on annual mean daily insulin dose and HbA_{1c} according to age. Because we aimed to investigate age trajectories of insulin dose and HbA_{1c}, we have only described in the results significant differences in which there was also a significant difference at 1 year younger or 1 year older; however, we included data for all comparisons

in the figures. In addition, we evaluated annual mean insulin dose and HbA_{1c} as dependent variables in multivariable analyses. Longitudinal mixed modelling assessed the impact of different predictors of insulin dose and HbA_{1c} according to age, using unstructured covariance matrices for repeated measure variables. In each of the models predicting insulin dose and HbA_{1c} over time according to age, covariates included sex, age at diabetes diagnosis, insulin regimen, weight status and calendar year. The variable of calendar year was included to control for historical changes in diabetes treatment and glycaemic control, given the changing availability of insulin analogues and technologies over time. In the model predicting insulin dose, we stratified HbA_{1c} into two groups [<75 mmol/mol (<9%) and ≥75 mmol/mol (≥9%)] according to the overall mean HbA_{1c} per person. In the model predicting HbA_{1c}, we stratified daily insulin dose into two groups (<1 units/kg and ≥1 units/kg) based on the overall mean insulin dose per person. An α level of <0.05 was used to determine statistical significance.

Results

Cohort characteristics

The study sample was a dynamic cohort of 635 children, adolescents and young adults with Type 1 diabetes identified at a single diabetes centre and followed over time. Table 1 shows participant characteristics for initial and final insulin dose and/or HbA_{1c} observation. At first observation, the mean age was 10.0±2.6 years and mean duration of Type 1 diabetes was 2.8±2.1 years. All were diagnosed in childhood at a mean age of 7.2±3.5 years. Approximately half of the cohort (54%) was female and the majority of participants (91%) were white. Insulin pump use increased from 4% at first observation to 36% at last observation.

The mean (median; interquartile range) time from first to last insulin dose observation was 10.7±4.3 (10.6; 7.5–13.7) years, with a mean of 4.4±3.7 months between observations. The mean number of insulin dose observations per person was 30.0±13.7 and the mean number of annualized insulin dose observations per person was 11.2±4.1. At first observation, the mean daily insulin dose was 0.8±0.2 units/kg. At last observation, the mean daily insulin dose was 0.9±0.3 units/kg.

The mean (median; interquartile range) time from first to last HbA_{1c} observation was 12.0±4.6 (12.1; 8.3–15.4) years, with a mean of 4.2±4.5 months between observations. The mean number of HbA_{1c} observations per person was 34.9±15.4 and the mean number of annualized HbA_{1c} observations per person was 12.2±4.5. At first observation, the mean HbA_{1c} was 74±18 mmol/mol (8.9±1.6%). At last observation, the mean HbA_{1c} was 75±19 mmol/mol (9.0±1.7%).

Insulin dose trajectories

To evaluate insulin dose trajectories over time as participants aged, we assessed daily insulin dose as units/kg by sex (female vs male), insulin regimen (pump vs injection therapy), and weight status (normal weight vs overweight/obese). In the analysis by sex, girls had significantly higher insulin dose than boys at ages 8–13 years (P<0.0001 to P<0.01) whereas

boys/young men had significantly higher insulin dose than girls/young women at ages 16–21 years (P<0.0001 to P=0.04; Fig.1a). In the analysis by regimen, those receiving pump therapy had a significantly lower insulin dose than those receiving multiple daily injection therapy throughout childhood, adolescence and young adulthood (P<0.0001 to P=0.03), except at age 7 years (Fig. 1b). In the analysis by weight status, overweight/obese individuals had significantly higher insulin dose than normal weight individuals at ages 8–13 years (P<0.0001 to P=0.03; Fig. 1c).

Glycaemic control trajectories

To evaluate glycaemic trajectories over time as individuals aged, we assessed HbA_{1c} by sex, insulin regimen and weight status, as above. In the analysis by sex, girls/young women had significantly higher HbA_{1c} levels than boys/young men at ages 16–24 years (P<0.0001 to P=0.01; Fig. 2a). In the analysis by regimen, those receiving pump therapy compared with multiple daily injections had significantly lower HbA_{1c} values throughout most of childhood, adolescence and young adulthood [ages 8–22 years; P<0.0001 to P=0.005 (Fig. 2b)]. In the analysis by weight status, there were no significant differences between normal weight and overweight/obese individuals over time (Fig. 2c).

Multivariable analyses

Given that the shapes of the insulin dose trajectories were not linear in the bivariate analyses, with trajectories resembling quadratic-cubic patterns, we performed separate longitudinal multivariable analyses in three age groups: 7–13, 14–18 and 19–24 years (Table 2). Generalized mixed models predicting daily insulin dose confirmed differences in the impact of sex on insulin dose according to age, with girls having significantly higher insulin doses than boys at ages 7–13 years, while young men had higher insulin doses than young women at ages 19–24 years. Similar to the bivariate analyses for insulin regimen, pump therapy predicted lower insulin doses in the longitudinal models for all three age groups. Overweight/obesity was only predictive of higher insulin dose in those aged 7–13 years. Attained age, age at diabetes diagnosis, and calendar year (used as a marker for the change in diabetes treatment over the observation period) had variable effects on insulin dose across the three age groups. As age increased, insulin dose increased in participants aged 7–13 years and decreased in those aged 14–18 and 19–24 years. Older age at diagnosis was associated with lower insulin dose in the two younger age groups. Calendar year was predictive of insulin dose in the two older age groups, with later calendar year being associated with higher insulin dose. Finally, daily insulin dose was lower for individuals with HbA_{1c} values <75 mmol/mol (<9%) in the two older age groups.

Given the variable HbA_{1c} trajectories according to sex, insulin regimen and weight status across the age span of 7–24 years, we performed separate longitudinal multivariable analyses in the same three age groups as above (Table 2). Generalized linear mixed models indicated that female sex predicted significantly higher HbA_{1c} in those aged 14–18 and 19–24 years. Pump therapy predicted significantly lower HbA_{1c} in all three age groups. Surprisingly, overweight/obesity predicted lower HbA_{1c} in those aged 14–18 and 19–24 years. Attained age predicted HbA_{1c} in all age groups; older age was associated with higher HbA_{1c} in the two younger age groups and lower HbA_{1c} in the oldest age group. Older age at

diagnosis was associated with lower HbA_{1c} in the two younger age groups. Calendar year was predictive of HbA_{1c} in the youngest age group, with later calendar year being associated with lower HbA_{1c}. Notably, daily insulin dose <1 unit/kg was significantly predictive of lower HbA_{1c} in all three age groups.

Discussion

Suboptimal glycaemic control is a common problem in young people with Type 1 diabetes [13]. In the present study we identified several factors associated with insulin requirements and deterioration in glycaemic control in children, adolescents and young adults with Type 1 diabetes. In this long-term dynamic cohort, age trajectories of insulin dose differed according to sex, insulin regimen and weight status, while age trajectories of HbA_{1c} differed according to sex and insulin regimen. Insulin doses were higher during the pubertal years, as expected. HbA_{1c} levels were higher in girls/young women in late adolescence and young adulthood and lower in insulin pump users over time, while overweight/obesity did not seem to negatively affect HbA_{1c} levels across ages. As age at diagnosis increased during childhood and adolescence, insulin dose requirement decreased as might be expected, given more aggressive β-cell destruction at younger ages of onset [25]. Insulin pump users and individuals of normal weight also required lower doses of insulin.

Adolescence is a period of cognitive, psychosocial and physical maturation. With the onset of puberty, glycaemic control usually deteriorates despite concomitant increases in insulin doses [13,26]. Reaching adulthood is then associated with decreases in insulin requirement and, hopefully, improved glycaemic control, although recent data from the T1D Exchange Clinic Registry indicate that glycaemic control does not appear to improve until the latter half of the third decade of life [4]. Adolescents in the T1D Exchange Clinic Registry had a mean HbA_{1c} of 9.0% compared with 9.5% in the same age group during the DCCT [2]. Similar to this finding, in the present study, calendar year did not have an impact on glycaemic control during adolescence, and suboptimal glycaemic control persisted over time, indicating that recent diabetes treatment advances have not been fully successful in overcoming the unique challenges of managing Type 1 diabetes during adolescence.

The rising insulin requirement during early adolescence corresponds to the physiological insulin resistance observed during puberty [13]. Considering that puberty happens earlier in girls than boys [24], it is reasonable to expect insulin requirements to increase in girls at a younger age [16]. Indeed, in the present study, girls had higher insulin doses than boys at ages 8–13 years. Notably, glycaemic control did not differ by sex in childhood but deteriorated in girls/young women in comparison to boys/young men in adolescence and young adulthood. The observation that glycaemic control deteriorates in the latter part of adolescence and during young adulthood suggests that puberty-associated insulin resistance is probably well managed with increased insulin dosing. Other factors, such as adherence and psychosocial issues, probably contribute to the deterioration in glycaemic control that follows the period of pubertal growth and development, when family involvement in diabetes management is waning [27]. Also, parental involvement is likely to decline as teens get older, at a time when teens may not be fully prepared for successful independent self-

management as a result of many competing social, emotional and academic demands, coupled with ongoing maturation of their cognitive function [28].

Many studies assessing the impact of pump therapy on glycaemic control in children with Type 1 diabetes have reported some improvement in glycaemic control, especially in the period immediately after pump initiation [17,18]. Considering this potential benefit, pump therapy may be considered a modifiable factor that could positively impact glycaemic control, particularly during adolescence when insulin needs increase because of puberty-related insulin resistance [13]. In the present study, pump therapy was associated with better glycaemic control and lower insulin doses across all ages. Although pump use considerably increased from first to last observation, glycaemic control did not improve over time. Insulin pump therapy may have helped prevent the expected deterioration in glycaemic control among adolescents in this study; however, our findings may also represent better adherence associated with individuals selected for pump therapy. The lack of information regarding adherence, as well as demographics such as socio-economic status, limits interpretation of possible insulin pump benefit among adolescents. The differences in insulin dose between pump and injection therapy were maintained throughout childhood, adolescence and young adulthood. This might be explained by the observation that pump therapy may deliver fasting and prandial insulin doses in a more physiological manner than injection-based therapy [16]. Recent data indicate that about one-third of children and adolescents with Type 1 diabetes are overweight or obese, similar to the general paediatric population [29,30]. In the present study, from first to last observation, overweight/obesity increased from 31% to 49%. It is well known that obesity increases insulin resistance, and our findings highlight the observation that young people who are overweight or obese require higher insulin doses, especially during adolescence when insulin resistance is already present as a result of pubertal needs; however, the association of BMI, HbA_{1c}, insulin dose and insulin resistance is complex and incompletely understood. In contrast to some literature, in which higher BMI has been associated with higher HbA_{1c} levels [30], there was no clear difference in HbA_{1c} between normal weight and overweight/obese individuals in the present study; however, the lack of information regarding demographics, physical activity, adherence and psychosocial issues limits the interpretation of this result.

It is important that we do not overstate our findings. First, this study was based on longitudinal follow-up data, mainly collected retrospectively, from a single centre, with many measurements obtained as part of routine clinical care rather than as part of a research study. Lack of information regarding demographics, adherence and clinical characteristics limits the interpretation of HbA_{1c} trajectories over time according to modifiable factors such as weight and insulin pump, especially when considering pump therapy to have a positive impact on glycaemic control. Also, insulin dose was captured mostly electronically for pump users and by clinician report for individuals using injection therapy. In individuals using injection therapy, insulin dose adjustments are based on reported insulin doses, which may differ from actual administered insulin doses [16]. Finally, interpretation of weight status was limited by the lack of information regarding diet and exercise.

Glycaemic outcomes in young people with Type 1 diabetes are suboptimal, with fewer than one in five children and adolescents achieving target HbA_{1c} levels [4]. This report identifies

clinically meaningful and actionable factors for which to adjust insulin doses in an anticipatory manner to improve glycaemic control in young people with Type 1 diabetes. To our knowledge, this is one of the largest cohort studies of young people with Type 1 diabetes providing extensive longitudinal data regarding trajectories of insulin dosing and glycaemic control across childhood, adolescence and young adulthood. Female sex, late adolescence and young adulthood, and injection therapy seemed to have a negative impact on glycaemic control. Further studies are needed to confirm these findings and investigate the impact of demographic and clinical characteristics, such as adherence, on insulin dose requirements and glycaemic control in children, adolescents and young adults with Type 1 diabetes.

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What's new?

- In a 20-year observational study (*N*=635), we assessed the impact of sex, insulin regimen and weight status on insulin requirements and HbA_{1c} levels in people with Type 1 diabetes from childhood to young adulthood.
- Age trajectories of insulin dose differed by sex, insulin regimen and weight status. Age trajectories of HbA_{1c} differed by sex and insulin regimen.
- Fewer than one in five children and adolescents with Type 1 diabetes achieve target HbA_{1c} levels. This report identifies clinically meaningful and actionable factors upon which to adjust insulin doses in an anticipatory manner to improve glycaemic control in young people with Type 1 diabetes.

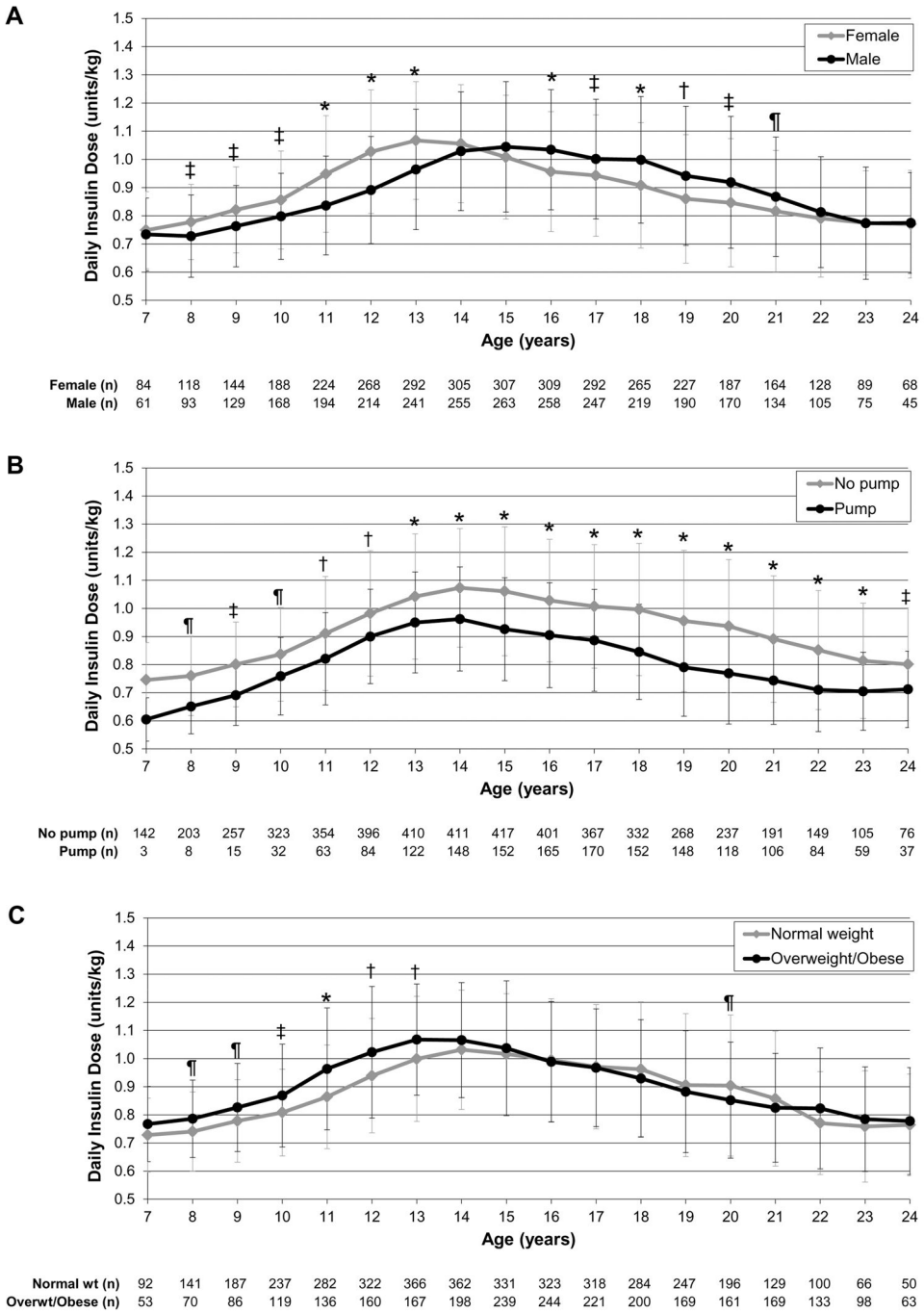

FIGURE 1.

Daily insulin dose trajectories by (a) sex, (b) regimen and (c) weight status. *P<0.0001, †P<0.001, ‡P<0.01, ¶P<0.05. Error bars represent standard deviation. (a) Girls had significantly higher insulin dose than boys during ages 8–13 years (P<0.0001 to P<0.01); boys/young men had significantly higher insulin dose than girls/young women during ages 16–21 years (P<0.0001 to P=0.04). (b) Those receiving insulin pump therapy had significantly lower insulin dose than those receiving multiple daily injection therapy during ages 8–24 years (P<0.0001 to P=0.03). (c) Overweight/obese individuals had significantly

higher insulin dose than normal weight individuals during ages 8–13 years ($P<0.0001$ to $P=0.03$).

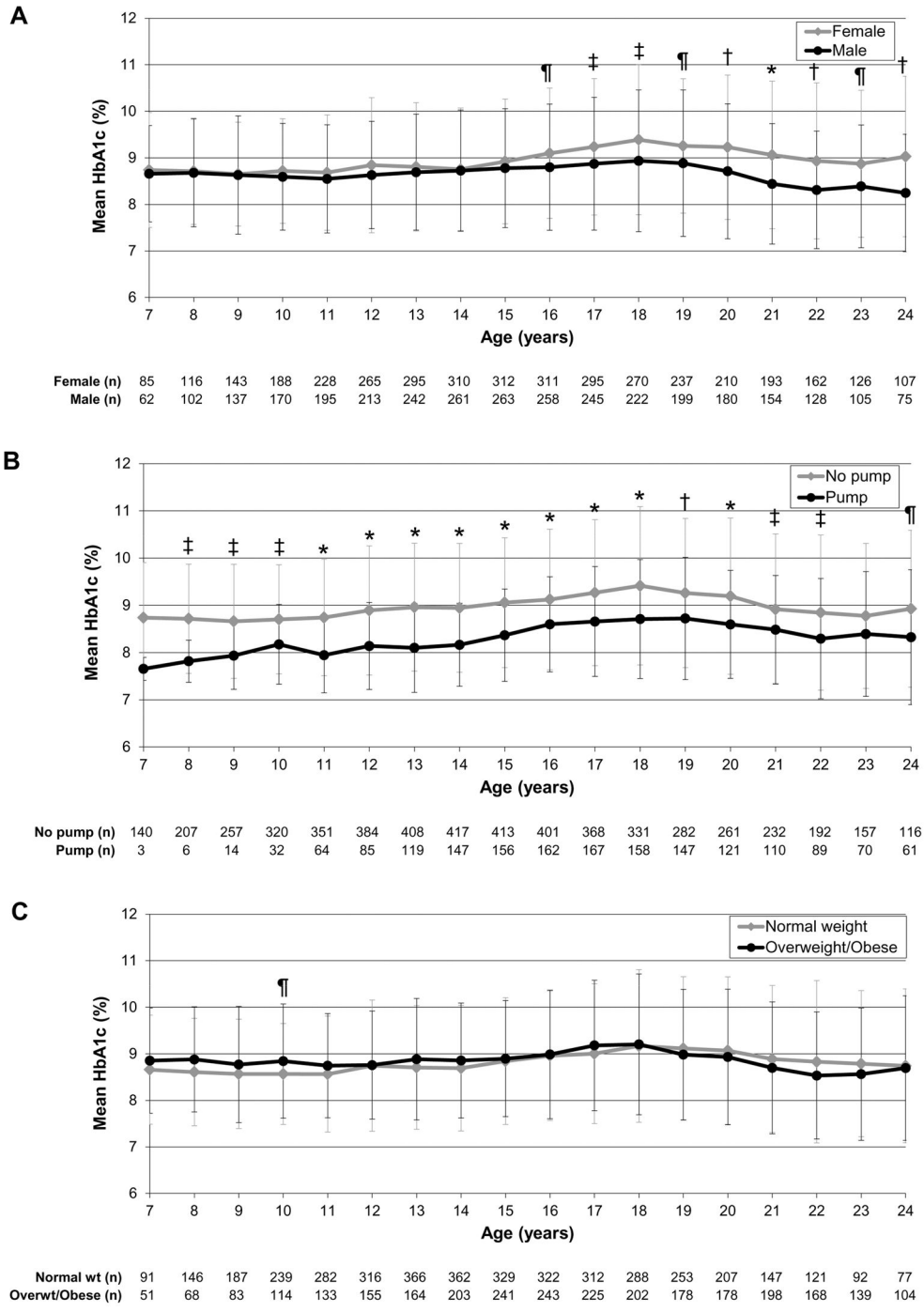

FIGURE 2.

HbA_{1c} trajectories by (a) sex, (b) regimen and (c) weight status. **P*<0.0001, †*P*<0.001, ‡*P*<0.01, ¶*P*<0.05. Error bars represent standard deviation. (a) Girls/young women had significantly higher HbA_{1c} levels than boys/young men during ages 16–24 years (*P*<0.0001 to *P*=0.01). (b) Those receiving pump therapy had significantly lower HbA_{1c} values than those receiving multiple daily injections during ages 8–22 years (*P*<0.0001 to *P*=0.005). (c)

There were no differences in HbA_{1c} over time by age between overweight/obese and normal weight individuals.

Table 1

Demographic and clinical characteristics of study participants

	First observation (*N*=635)	Last observation (*N*=635)
Age, years	10.0±2.6 (6.5–19.1)	20.8±3.2 (8.7–24.5)
Sex, % female	54	-
Race/ethnicity, % white	91	-
Age at Type 1 diagnosis, years	7.2±3.5	-
Diabetes duration, years	2.8±2.1 (1.0–12.6)	13.6±4.3 (2.2–22.9)
HbA_{1c}, mmol/mol	74±18 (37–201)	75±19 (40–149)
HbA_{1c}, %	8.9±1.6 (5.5–20.6)	9.0±1.7 (5.8–15.8)
Daily insulin dose, units/kg	0.8±0.2 (0.5–1.7)	0.9±0.3 (0.4–2.0)
Regimen, % pump use	4	36
Weight status, %		
Normal weight*	69	51
Overweight	22	34
Obese	9	15
Calendar year, years range	1993–2008	1997–2013

Data are mean ± SD (range), unless otherwise indicated.

Table 2

Longitudinal multivariable models predicting annual daily insulin dose and annual HbA_{1c} *

	Annual daily insulin dose (units/kg): effect estimates stratified by age						Annual HbA_{1c} (%): effect estimates stratified by age					
	7–13 years	***P***	**14–18 years**	***P***	**19–24 years**	***P***	**7–13 years**	***P***	**14–18 years**	***P***	**19–24 years**	***P***
Age (per 1 year increase)	0.061	<0.0001	−0.023	<0.0001	−0.029	<0.0001	0.079	<0.0001	0.144	<0.0001	−0.060	0.01
Sex (female vs male)	0.067	<0.0001	−0.027	.06	−0.054	0.003	0.127	0.15	0.196	0.04	0.521	<0.0001
Age at diagnosis (per 1 year increase)	−0.013	<0.0001	−0.006	.008	0.001	0.79	−0.052	0.0006	−0.035	0.01	−0.023	0.19
HbA_{1c} (<9% vs ≥9%)	−0.010	0.46	−0.051	.0005	−0.103	<0.0001	–	–	–	–	–	–
Daily insulin dose (<1 units/kg vs ≥1 units/kg)	–	–	–	–	–	–	−0.527	<0.0001	−0.813	<0.0001	−0.639	<0.0001
Regimen (pump vs multiple daily injections)	−0.060	<0.0001	−0.123	<0.0001	−0.119	<0.0001	−0.280	.0002	−0.438	<0.0001	−0.385	<0.0001
Weight status (overweight/obese vs normal weight)	0.027	0.0001	0.009	.29	0.010	0.32	−0.045	0.37	−0.239	<0.0001	−0.140	0.03
Calendar year (per year increase)	−0.000	0.90	0.005	.006	0.005	0.03	−0.089	<0.0001	−0.009	0.45	0.013	0.47

* Values for annual change in HbA_{1C} are presented in DCCT % units. To convert to mmol/mol, please refer to www.ngsp.org.