Insulin pump therapy, pre-pump HbA_{1c} and metabolic improvement in children with type 1 diabetes at a tertiary Canadian children's hospital

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ABSTRACT

Background and Objectives: Indications for insulin pump therapy (IPT) in children with type 1 diabetes (T1D) are relatively non-specific and therefore subject to provider discretion. Health professionals' perceptions of which people will have difficulty with IPT, e.g., those with higher HbA_{1c}, may not be correct. This study examined the effect of IPT on HbA_{1c}, and the role of pre-pump HbA_{1c} on this effect.

Methods: All children with T1D started on IPT at British Columbia Children's Hospital from January 2011 through June 2016 were included if they had HbA_{1c} values available both before and after IPT (n=125). Generalized Estimating Equations was used to estimate the effects of IPT on HbA_{1c}, stratified by pre-pump HbA_{1c} levels (good: <7.5% [<58 mmol/mol], moderate: 7.5-9.0% [58-75 mmol/mol], poor: >9.0% [>75 mmol/mol]).

Results: After adjusting for potential confounders, mean HbA_{1c} decreased by 0.48% [5.2 mmol/mol] (95% confidence interval: –0.64, –0.33% [–7.0, –3.6 mmol/mol]; $P<0.0001$) after IPT initiation. The adjusted mean HbA_{1c} decreased by 0.14% [1.5 mmol/mol] (–0.35, 0.07% [–3.8, 0.8 mmol/mol]; $P=0.188$), 0.54% [5.9 mmol/mol] (–0.74, –0.34% [–8.1, –3.7 mmol/mol]; $P<0.0001$), and 1.08% [11.8 mmol/mol] (–1.69, –0.46% [–18.5, –5.0 mmol/mol]; $P=0.0006$) after pump initiation in the good, moderate, and poor pre-pump metabolic control groups, respectively.

Conclusions: Pre-pump HbA_{1c} appears to play a significant role in the effects of IPT on HbA_{1c}, with the largest decrease in HbA_{1c} seen in the poor pre-pump HbA_{1c} group. Eligibility and consideration for IPT should be expanded to routinely include these children.

KEY WORDS

Diabetes mellitus, type 1; pediatrics; insulin infusion systems; glycated hemoglobin A

INTRODUCTION

It is well established that intensive blood glucose management can reduce diabetes complications later in life.(1) Insulin pump therapy (IPT) has become an established form of treatment for T1D, and is currently the most physiologic method for insulin delivery that is widely available. Its use has been increasing over time, with increased uptake as universal funding has become more available.(2,3) The prevalence of IPT varies widely.(4,5)

In British Columbia, Canada, criteria for insulin pump coverage includes having access to a diabetes specialist, agreeing to a comprehensive and age-appropriate diabetes education by an interdisciplinary diabetes healthcare team, and making a commitment to have regular follow up. Additionally, the person must be checking blood glucose at least four times a day be and recording results. Additional considerations include frequent unpredictable hypoglycemic episodes, frequent unpredictable diabetic ketoacidosis episodes, or unpredictable swings in blood glucose.(6) Criteria for funding vary across Canadian provinces, with some including factors such as a minimum time from diagnosis,(7,8) an inability to consistently achieve a recommended HbA_{1c} target value in the setting of consistent multiple daily injection diabetes management,(9) actively attempting to meet and/or maintain a personalized HbA_{1c} target,(7,8,10) or needing to have HbA_{1c} below a pre-set threshold.(7,8,11,12) While all of these criteria exist for funding eligibility, Diabetes Canada's Clinical Practice Guidelines more simply state that insulin therapy should be individualized to reach HbA_{1c} targets, minimize hypoglycemia and optimize quality of life, and they note that IPT is safe and effective and can be initiated at any age.(13)

Given both the relatively non-specific indications for IPT and the variable funding criteria for these programs, decisions about which children are most likely to benefit from IPT may be largely based on the discretion of the diabetes specialist. It has, however, been shown that health care provider assumptions of who may be a good 'fit' for IPT may not in fact predict a successful transition to IPT (14). A bias may

well exist that children with high HbA_{1c} are not likely to succeed with IPT, as indeed multiple Canadian provincial government websites state that HbA_{1c} must be below a set threshold to be eligible for insulin pump therapy in those provinces.(7,8,11,12) Requiring a moderate or good HbA_{1c} for initiation of IPT does not seem well supported in the literature, as a multicenter study looking at responders to IPT found that it was actually those with HbA_{1c} greater than 9% who had increased odds of responding to insulin pump therapy with a lowered HbA_{1c}.(15) Prior studies addressing the effect of pre-pump HbA_{1C} on post-pump glycemic management have often used *target* HbA_{1C} rather than *improvement* in HbA_{1C} as the primary outcome of interest,(16–18) and of those that have looked as a primary or secondary focus at the *change* in HbA1c, it was not when adjusting for confounding variables.(18–21). We therefore set out in this single-site study in British Columbia, Canada to assess the effects of IPT on a child's HbA_{1c}, using *change* in HbA_{1c} as the outcome of interest, and to see if the effects of IPT on HbA_{1c} differ based on pre-pump HbA_{1C} strata when controlling for potential confounders.

METHODS

Data Source

This study was conducted at British Columbia Children's Hospital (BCCH), the only tertiary pediatric hospital serving British Columbia, Canada. All patients with T1D who had started IPT at BCCH between January 2011 and June 2016 were identified. Patients were included if they had HbA_{1c} values both before and after starting IPT.

Data Collection

Paper and electronic medical records were reviewed to collect data on gender, age at diagnosis, age at pump initiation, prior insulin routine, continuous glucose monitoring (CGM), and pump brand. HbA_{1c} values from 12 months before pump initiation to 18 months after pump initiation were collected. In order to avoid HbA_{1c} values taken during the partial remission after diagnosis ("honeymoon period"), HbA_{1c} values within 6 months of diabetes diagnosis were excluded and HbA_{1c} values between 6 and 12 months

after diabetes diagnosis were considered using the Insulin Dose Adjusted A_{1c} (IDAA1c). IDAA1c identifies values in the honeymoon period [IDAA1C = HbA_{1c} (percent) + [4 × insulin dose (units per kilogram per 24 hours)], and HbA_{1c} values that were associated with IDAA1c values ≤ 9 were excluded from analysis.(22)

Statistical Analysis

Continuous variables were presented as median and interquartile range (IQR), while categorical variables were presented as number and percentage. Characteristics were compared among three groups of metabolic control: good, moderate, and poor, as defined by pre-pump mean HbA_{1c} levels of <7.5% [<58 mmol/mol], 7.5 to 9.0% [58 to 75 mmol/mol], and >9.0% [>75 mmol/mol], respectively. Generalized Estimating Equations (GEE) method was used to estimate the pre-pump mean HbA_{1c}, and to examine the changes in mean HbA_{1c} before and after pump initiation. Variables for the regression analyses were selected a-priori (age at pump initiation, gender, and time from diagnosis to IPT initiation), or if the covariates were statistically significant at a level of 0.15 in the unadjusted analysis. The GEE models were also fit in the three pre-pump metabolic control groups separately. These stratified analyses could not be adjusted for CGM due to very small cell counts in the pre-pump metabolic control groups. All the regression analyses were additionally adjusted for the baseline HbA_{1c} to address the issue of *regression towards the mean*.(23) In a sensitivity analysis, we further adjusted for prior regimen despite its statistical non-significance at a pre-specified 0.15 threshold. Since the stratified analyses could not adjust for CGM, we did an additional analysis on the full cohort with and without CGM to examine any difference this variable makes. Statistical analyses were conducted in STATA/IC software version 14.2 (StataCorp, College Station, TX, USA) and SAS statistical software (version 9.4).(24)

Ethics Approval

The study protocol was reviewed and approved by the UBC Clinical Research Ethics Board (H16-01652).

RESULTS

A total of 125 children with T1D were started on IPT at BCCH between January 2011 and June 2016, and met study criteria with both pre- and post-pump HbA_{1c} values. There were 37, 72, and 16 patients in the good, moderate, and poor baseline HbA_{1c} groups, respectively. Table 1 highlights baseline characteristics for all patients included in the study as well as for the different baseline HbA_{1c} groups. There was a slight preponderance of female patients (51%), and the median age of the participants at diagnosis was 7.4 years (IQR 2.7, 10.1). Median age at pump initiation was 11.0 years (IQR 6.9, 14.4) and there was large variability in the time elapsed from diabetes diagnosis to pump initiation with a median of 29.0 months (IQR 16.7, 57.3). Of the three Health Canada approved insulin pumps available during the study period, 18%, 41%, and 41% had been started on brand A, B, and C respectively. Eighty-one percent of patients had been on a conventional regimen of insulin injections prior to starting pump therapy, which consisted of a fixed dose of neutral protamine Hagedorn (NPH) insulin in the morning, a sliding scale for rapid insulin analogue at both breakfast and dinner, and an intermediate or long-acting insulin analogue overnight. Nineteen percent of patients had been on a multiple daily injection basal-bolus regimen. Only 3% of all participants were on CGM either prior to, or concurrent with, the start of IPT (Table 1).

Compared to the moderate and good HbA_{1c} groups, the poor baseline HbA_{1c} group had a lower median age at diagnosis and an increased length of time to pump initiation; however, age at pump start was similar between all three groups. There was a similar distribution of conventional and multiple daily injection routines before initiating IPT in all three groups. The poor HbA_{1c} group had a higher proportion of females.

After adjusting for age at pump initiation, gender, time from diagnosis to pump start, BMI Z-score, insulin pump brand, continuous glucose monitoring status, and baseline HbA_{1c}, overall mean post-pump HbA_{1c} decreased by 0.48% [5.2 mmol/mol] (95% confidence interval: –0.64, –0.33% [–7.0, –3.6 mmol/mol]; $P<0.0001$) after pump-initiation (Table 2). A sensitivity analysis further adjusting for prior

regimen showed almost identical results (hence not shown). The results for IPT with and without CGM were also almost identical (hence the one without CGM is not shown). We also noted that age at pump initiation, higher BMI Z-score and a delay in pump initiation since diabetes diagnosis were associated with an increase in mean post-pump HbA_{1c}, compared to mean pre-pump HbA_{1c}, and that male gender was associated with a decrease in mean post-pump HbA_{1c}, compared to mean pre-pump HbA_{1c} (Table 2). Further analysis adjusting for the variables mentioned above (except CGM due to very small cell counts) shows that the mean HbA_{1c} decreased by 0.14% [1.5 mmol/mol] (–0.35, 0.07% [–3.8, 0.8 mmol/mol]; P=0.188), 0.54% [5.9 mmol/mol] (–0.74, –0.34% [–8.1, –3.7 mmol/mol]; P<0.0001), and 1.08% [11.8 mmol/mol] (–1.69, –0.46% [–18.5, –5.0 mmol/mol]; P=0.0006) after pump initiation in the good, moderate, and poor pre-pump metabolic control groups, respectively (Figure 1).

DISCUSSION

To our knowledge, this is the first study in young children to demonstrate the associated change in HbA_{1c} after insulin pump initiation for each of three categories of pre-pump metabolic control, when controlling for confounding variables. Being on IPT was associated with a decrease in HbA_{1c} over the next 18 months, and children with higher pre-pump HbA_{1c} levels had more improvement in HbA_{1c} during the post-pump follow-up period compared to those who started with lower HbA_{1c} levels. This result is consistent with several prior studies in children which observed an improvement in post-pump HbA_{1c} levels in youth with high baseline HbA_{1c} levels. (15,18–21)

Iafusco et al. highlighted whether good management should be a prerequisite for pump use by describing 19 older adolescents divided into two groups. Those with lower HbA_{1c} levels starting out had little change in HbA_{1c} after 6 months of insulin pump use, but those with higher pre-pump HbA_{1c} had a reduced HbA_{1c} after pump initiation.(19) In a larger study that included both children and young adults, Nimri et al. found that those with higher HbA_{1c} before IPT experienced the greatest reduction in HbA_{1c} after starting IPT.(21) Nabhan et al. presented a correlation plot showing that children and adolescents with higher

baseline HbA_{1c} had greater improvement on IPT, again suggesting IPT may have the ability to improve HbA_{1c} for patients with poorly controlled diabetes.(20) Finally, Pinas-Hamiel et al. observed that youth with higher HbA_{1c} before pump therapy had a statistically significant decrease in HbA_{1c} after starting IPT; however, their regression analysis did not look at HbA_{1c} *change* as an outcome of interest.(18) Overgaard Ingeholm et al. found that for youth with diabetes, a pre-pump HbA_{1c} >9% [>75 mmol/mol] was associated with the highest odds of responding to IPT with an HbA_{1c} decrease of at least 1% [10.9 mmol/mol].(15)

Our study chose to look at *change* in HbA_{1c} for each of the three groups of pre-pump metabolic control. This outcome was chosen because reduction in HbA_{1c} improves long-term health and reduces complications such as retinopathy, nephropathy, and neuropathy.(1) Alternately, some prior studies have chosen to look at the likelihood of children obtaining a 'target' HbA_{1c} (as opposed to an improvement of HbA_{1c}) when starting IPT. These studies showed that lower HbA_{1c} at pump initiation was associated with a lower (or target) HbA_{1c} after starting IPT.(16–18) While we propose that change in HbA_{1c} is a more useful marker of the impact of IPT, our study's findings are also in line with these prior studies as the "good" HbA_{1c} group before pump therapy maintained their metabolic management after starting pump therapy. Unlike the moderate and poor metabolic control groups, the effect estimate in the group with "good" metabolic control was not statistically significant, with an observed decrease in the mean HbA_{1c} of 0.14% [1.5 mmol/mol]. Thus, it is encouraging that youth who are meeting target HbA_{1c} at the time of starting IPT may obtain relatively equivalent metabolic management, while potentially harnessing other benefits of IPT.

This study addresses the long-time question of whether IPT should be used as a way to improve adherence to insulin therapy, or if adherence to therapy should be a pre-requisite to initiating IPT. Indeed, in Canada, criteria for IPT vary from province to province, with some requiring a moderate or good HbA_{1c} *prior* to initiation.(7,8,11,12) Informing the choice of which children will most likely succeed on

an insulin pump is an important goal, due to both the expense of insulin pump therapy and the importance of good metabolic management to improve long-term health. This study suggests that poor metabolic control is associated with the largest improvement in HbA_{1c}, and this has promising implications for the care of these youth. It is important to note, however, that reaching improved metabolic control should not be a reason to discontinue insulin pump use or its insurance coverage. IPT should not be used only to lower HbA_{1c}, as it can be an instrumental tool in maintaining glycemic management while providing manifold benefits to youth living with diabetes.

In an earlier study,(25) CGM usage was found to be associated with lower HbA_{1c} in similar aged children. We found the same regarding CGM in our unadjusted analysis, but CGM was no longer statistically significant in the adjusted analysis. Of note, CGM use was very infrequent in our study population. This was likely due to lack of universal or extended health coverage for CGM in British Columbia during the study period, in addition to lack of support for CGM within the province-wide diabetes in school program during the study period. As few children were on CGM, these results should be interpreted with caution.

The majority of children in our study transitioned directly from conventional insulin therapy to IPT. It is therefore interesting to consider if an improvement in HbA_{1c} might have also been seen if these patients were instead transitioned to a more intensive injection insulin routine rather than IPT. In this regard, there have been somewhat conflicting results from pediatric studies evaluating for differences in glycemic management between twice daily NPH with rapid analogue therapy and multiple daily injection basal-bolus therapy. A large international study demonstrated that children using NPH combined with rapid insulin analogues actually had lower HbA_{1c} compared to intensive regimens,(26) and a second large multicenter study found that change in HbA_{1c} over time was not different between conventional and multiple daily injection insulin regimens.(27) On the other hand, a national multicenter study in the United States demonstrated that an intensification of insulin regimen was associated with lower HbA_{1c} levels over time.(28) De Beaufort et al. commented that successful outcomes with the use of a

conventional regimen may be a result of optimal use of this regimen in specific centers.(26) At our center, families using 'conventional' insulin therapy do receive multidisciplinary diabetes education, use carbohydrate counting daily as they typically plan for a pre-determined amount of carbohydrates with each meal, and adjust doses of their rapid insulin analogue at breakfast and dinner based upon blood glucose levels. These site-specific factors may decrease the likelihood that the change in HbA_{1c} seen with IPT in our study represents factors associated with intensification or education rather than change to IPT. Indeed, prior regimen was not significant in univariate analysis, and a sensitivity analysis further adjusting for prior regimen showed almost identical results to the presented regression model. Nonetheless, it must be considered that 'intensification' for some or all families as they moved from injection to pump therapy could have played a role in the improvement seen with IPT. The specific characteristics of our study population must be kept in mind when considering the change in glycemic control that occurred with IPT.

The low percentage of youth on a multiple daily injection basal-bolus insulin regimen prior to IPT in our study highlights a significant limitation in insulin therapy options that face youth living in regions where schools are not able to support intensive insulin injection regimens. In such situations, IPT may well be the only feasible option for a child to receive intensive diabetes management in the school setting. Our study demonstrates that for youth for whom local factors dictate they are on a conventional insulin injection routine, such as in British Columbia under the timeframe of this study, transition to IPT can lead to improved HbA_{1c}.

Our analysis identified other factors associated with the change in HbA_{1c} after pump start. A higher age at pump initiation, BMI Z-score and a delay in pump initiation since diabetes diagnosis were associated with an increase in mean post-pump HbA_{1c}, compared to pre-pump mean HbA_{1c}, while male gender was associated with decrease in mean post-pump HbA_{1c}, compared to pre-pump mean HbA_{1c}. However, these

were not our primary hypotheses, so these findings should be interpreted with caution. Further studies are required to confirm these findings.

With regards to all study participants, we observed an overall decrease in HbA_{1c} over the 18-month follow-up period after pump initiation of 0.48% [5.2 mmol/mol]. This is consistent with two meta-analyses in adult and pediatric populations,(29,30) as well as several studies in children,(31,32) which demonstrated improved glycemic control with IPT. Of note, it has been shown in several pediatric studies that HbA_{1c} may decrease initially following pump initiation, and then gradually increase closer to baseline when followed long-term; however, still maintaining HbA_{1c} levels below the pre-pump values.(18,20,33,34) One possibility for this observed effect is the increased contact and follow-up by diabetes educators in the initial time after IPT initiation, as well as increased adherence while adjusting to a new routine.

Strengths of this study are that it represents all insulin pump starts at a tertiary Canadian hospital over a five-year period. Furthermore, the analysis of change in HbA_{1c} was rigorous in that it excluded honeymoon period HbA_{1c} values, and used robust statistical analysis to account for longitudinal and correlated data along with adjusting for the confounding variables.

Limitations of this study include the retrospective data collection, relatively small group size when stratified into levels of pre-pump HbA_{1c}, and the relatively short follow-up period of 18 months. Additionally, as this study was not randomized, there may be unmeasured confounding. Being a single-site study may limit the generalizability of the results to other heterogeneous populations, as the population of this study reflects the current state of diabetes care in British Columbia during this timeframe. Firstly, while there was universal coverage for insulin pumps, there was no universal or private coverage for CGM. This coupled with the small number of participants in the individual pre-pump metabolic control groups restricted our ability to adjust for CGM. However, the result from the

regression analysis on the full cohort with and without CGM was very similar reinforcing our confidence in the results. Secondly, there was initially no, and subsequently limited, ability for insulin administration at school, leading most children to be on conventional insulin routines prior to IPT. Even though our analysis adjusted for a range of potential confounding variables, socioeconomic status is as an important co-variant which the present data set is unable to address. Additionally, we did not have information on parental education and supplemental insurance coverage. Finally, this study excluded children who did not have sufficient pre-pump HbA_{1c} data available for analysis.

Our study demonstrates for the first time in a large cohort of young children the varying degree of *improvement* in HbA_{1c} after IPT initiation based on the children's pre-pump HbA_{1c} after controlling for other potentially confounding variables. Children who had poor metabolic control prior to IPT initiation showed the greatest improvement, followed by those with moderate and good pre-pump metabolic control. These results highlight that eligibility and consideration for IPT should be expanded to routinely include children with high HbA_{1c}.

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All authors were involved in study design and analysis plan, contributed to the data interpretation, and edited the manuscript. SB collected data and prepared the first draft of the manuscript. NI conducted the data analysis. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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TABLES

TABLE 1: Baseline characteristics of patients included in the analysis of effects of insulin pump therapy on HbA_{1c}, divided into pre-pump metabolic control groups

	Pre-pump metabolic control*			
Factor	Good (N=37)	Moderate (N=72)	Poor (N=16)	Overall (N=125)
Age at Diagnosis; median (IQR)	9 (6.7, 11.5)	6.1 (2.8, 10.1)	2.6 (1.7, 8.8)	7.4 (2.7, 10.1)
Gender; n (%)				
Male	20 (54)	36 (50)	5 (31)	61 (49)
Female	17 (46)	36 (50)	11 (69)	64 (51)
Continuous glucose monitoring; n (%)				
No	36 (97)	69 (96)	16 (100)	121 (97)
Yes	1 (3)	3 (4)	-	4 (3)
Age at pump initiation (years); median (IQR)	11.1 (9, 14.1)	10.3 (6.1, 14.4)	11.9 (5.6, 15.8)	11 (6.9, 14.4)
Time from diagnosis to pump initiation (months); median (IQR)	22.7 (13.5, 39.2)	31.6 (16.6, 58.4)	58 (24.5, 106.5)	29 (16.7, 57.3)
Height z-score; median (IQR)	0.3 (-0.5, 1.4)	0.2 (-0.6, 1.1)	0.1 (-0.3, 0.6)	0.2 (-0.5, 1)
Weight z-score; median (IQR)	0.4 (0.1, 1.4)	0.9 (0.2, 1.4)	0.7 (0.1, 1.4)	0.7 (0.1, 1.4)
BMI z-score; median (IQR)	0.4 (-0.2, 1.3)	0.9 (0.4, 1.5)	0.7 (0.5, 1.5)	0.7 (0.3, 1.4)
Insulin regimen prior to pump therapy; n (%)				
Multiple daily injections	7 (19)	14 (19)	3 (19)	24 (19)
Conventional	30 (81)	58 (81)	13 (81)	101 (81)
Pump Brand; n (%)				
1	8 (22)	13 (18)	1 (6)	22 (18)
2	16 (43)	29 (41)	6 (38)	51 (41)
3	13 (35)	29 (41)	9 (56)	51 (41)

*Mean HbA_{1c}: Good: <7.5% [<58 mmol/mol]; Moderate: 7.5-9.0% [58-75 mmol/mol]; Poor: >9.0% [>75 mmol/mol]

IQR: Interquartile range. BMI: Body mass index

Table 2: Unadjusted and adjusted analysis from generalized estimating equation showing changes in mean HbA_{1c} (%) before and after pump initiation

Characteristics	Unadjusted mean change in HbA_{1c} (%)	p-value	Adjusted mean change in HbA_{1c} (%)	p-value
Age at pump initiation	0.02 (-0.01, 0.05)	0.222	0.03 (0.01, 0.05)	0.002
Gender				
Male	-0.32 (-0.6, -0.04)	0.025	-0.16 (-0.31, -0.02)	0.028
Female	*Ref*		*Ref*	
Each year since diabetes diagnosis to pump initiation	-0.03 (-0.15, 0.09)	0.6	0.25 (0.10, 0.40)	0.001
Body mass index Z-score	0.19 (0.04, 0.34)	0.014	0.10 (0.03, 0.18)	0.007
Insulin regimen prior to pump therapy				
Multiple daily injections	-0.04 (-0.39, 0.3)	0.802		
Conventional	*Ref*			
Pump Brand				
1	-0.43 (-0.76, -0.1)	0.011	-0.12 (-0.30, -0.06)	0.192
2	-0.02 (-0.35, 0.3)	0.885	-0.21 (-0.38, -0.03)	0.021
3	*Ref*		*Ref*	
Continuous glucose monitoring				
No	*Ref*		*Ref*	
Yes	-0.75 (-1.40, -0.10)	0.024	0.04 (-0.53, 0.61)	0.893
Insulin Pump				
Pre-pump	*Ref*		*Ref*	
Post-pump	0.08 (-0.07, 0.23)	0.303	-0.48 (-0.64, -0.33)	<0.0001

Adjusted model was additionally adjusted for baseline HbA_{1c} to address the issue of regression towards the mean

FIGURES

Figure 1: Adjusted changes in mean HbA_{1c} before and after insulin pump initiation (stratified by pre-pump metabolic control groups) from generalized estimating equations