Ulm University
Institute of Epidemiology and Medical Biometry
Director: Prof. Dr. med. Dietrich Rothenbacher

Socioeconomic and demographic factors associated with diagnosis, treatment, and outcomes in pediatric type 1 diabetes

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Marie Auzanneau
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Acting dean: Prof. Dr. Thomas Wirth
1st reviewer: Prof. Dr. Reinhard Holl
2nd reviewer: Prof. Dr. Reinhold Kilian
3rd reviewer: Prof. Dr. Michael Laxy

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Abbreviations

ADA	American Diabetes Association
AID	Automated insulin delivery
BMI	Body mass index
BMI-SDS	Body mass index standard deviation score
CGM	Continuous Glucose Monitoring
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complication Trial
DKA	Diabetic ketoacidosis
DPV	Diabetes-Patienten-Verlaufsdokumentation
GIMD	German Index of Multiple Deprivation
GISD	German Index of Socioeconomic Deprivation
HbA1c	Hemoglobin A1c
HCL	Hybrid closed-loop
OR	Odds Ratio
PY	Person-year
Q1, Q5	Quintile 1, Quintile 5
SAS	Statistical Analysis Software
SES	Socioeconomic status
SMBG	Self-monitoring of blood glucose
T1D	Type 1 diabetes mellitus
T1DX	Type 1 Diabetes Exchange Clinic Registry
T2D	Type 2 diabetes mellitus
US	United States (of America)

1. Introduction

1.1. Background

Type 1 diabetes mellitus (T1D) is caused by a chronic autoimmune-mediated destruction of pancreatic-ß-cells, generally leading to absolute insulin deficiency [1]. In most western countries, especially in populations of European ancestry, T1D accounts for more than 90% of childhood and adolescent diabetes [1, 2]. The prevalence of T1D in children and adolescents younger than 20 years in Germany has been estimated by 37,655 in 2020 and even if the increase in prevalence has slowed in the last years, T1D prevalence continues to increase in the age group 15-19 years [3].

The main objective of diabetes treatment is to achieve and maintain good glycemic control through near-physiologic insulin replacement to reduce short and long-term complications [4]. Glycemic control is usually evaluated by the average blood glucose level over the last two to three months (HbA1c, glycated hemoglobin), but also increasingly by the proportion of time spent in the recommended glucose target range of 70–180 mg/dl (TIR, Time in Range) [5].

In the past decades, considerable advances have occurred in diabetes care. In particular, diabetes technologies, which are able to offer better blood glucose monitoring and more physiological insulin delivery, are now widely available. Continuous glucose monitoring systems (CGM, also called “sensors”) and continuous subcutaneous insulin infusion (CSII, also called “insulin pumps”) have become the gold standard in pediatric diabetes care in high-income countries [6]. In addition, innovative systems connecting both devices with algorithms to facilitate automated insulin delivery (AID, sometimes called “hybrid closed loop”) have been increasingly used by children and adolescents since 2015 [6–9].

Despite the growing use of advanced technologies, achieving optimal glycemic control (HbA1c < 53 mmol/mol or < 7.0% according to current ISPAD guidelines [5]), remains challenging for many young people with diabetes, in particular for adolescents [10–12]. T1D management is complex, and as a chronic condition, diabetes requires that patients and their parents or caregivers invest time and resources to manage the disease in their everyday life [13]. Moreover, they need theoretical and practical knowledge related to diabetes physiology, food intake and physical activity. Repeated participation in education programs delivered by multidisciplinary teams is therefore necessary [13]. In addition, the use of specific diabetes technology can be challenging, especially for individuals with less technical knowledge, and therefore requires up-to-date education sessions focused on each device. One general goal of diabetes education is to “empower” patients and families to make appropriate decisions about their daily diabetes management [13]. Despite all efforts to individualize education programs, and ideally to adapt them to families with limited resources or minority cultural backgrounds, educational level of the family is known to be an important factor of the success of these interventions [13].

Comparisons of mean HbA1c-levels with other high-income countries indicate a good quality of care in pediatric diabetes in Germany. In a representative population of 19,820 children and adolescents under 18 years of age, the mean HbA1c level was estimated at 7.7% in 2013-2014, which was at the lower end of a range from 7.6% in Sweden to 8.7% in Wales [14]. Moreover, in Germany, nearly all pediatric medical care is covered by health insurance, either statutory (about 90%) or private (about 10%), so that access to diabetes care should not be restricted [15]. Nevertheless, significant regional differences in treatment modalities and clinical outcomes have been described [14, 16]. For example, in 2012-2013, the percentage of children and adolescents treated with rapid-acting insulin analogues ranged from 57% in Bremen to 96% in Saxony-Anhalt, and for long-acting analogues varied from 42% in Hamburg to 97% in Mecklenburg-Western Pomerania [16].

These observations raise several questions, in particular: are differences in T1D treatment only due to medical differences or also to non-medical factors? Are differences in T1D outcomes influenced by differences in treatment? And if so, can we modify some factors associated with treatment differences in order to reduce disparities in T1D outcomes?

To answer these questions, our first aim was to identify potential causes for these disparities. Besides specific regional factors related to the federal structure of Germany, that cannot be easily changed [16], other factors at smaller area level or individual level needed to be explored. Numerous studies, including systematic reviews and meta-analyses, have shown the importance of socioeconomic factors for the incidence and outcomes of type 2 diabetes (T2D) [17–24]. Associations between lower individual or neighborhood socioeconomic status and higher body mass index (BMI), lower level of physical activity, and more mental health problems, have often been reported [23, 25–30]. Regarding care and outcomes in children and adolescents with T1D, evidence of socioeconomic influences is weaker [31]. Nonetheless, as described above, the management of T1D is challenging for patients and their families and requires many educational and psychosocial resources in everyday life. We therefore aimed to investigate to what extent socioeconomic and demographic factors are associated with the observed differences in T1D treatment and outcomes.

One further question was whether socioeconomic or demographic factors are associated with a timely diagnosis of T1D, at onset of the disease. In fact, a timely diagnosis and treatment of T1D is of primary importance to reduce the risk of diabetic ketoacidosis (DKA). This severe complication, which affects one-quarter of all newly-diagnosed children with T1D, is associated with adverse long-term metabolic and neurocognitive consequences. The continuous increase of children diagnosed too late remains a serious problem, even in many high-income countries, despite considerable prevention efforts [32, 33], and the causes are not well understood. We therefore aimed to analyze whether socioeconomic or demographic factors are associated with the rate of DKA at T1D onset. Unlike the previous questions, this research question addresses the potential influence of socioeconomic or demographic factors not at the level of specialized diabetes care, but at primary care level.

To investigate socioeconomic factors, the individual socioeconomic status (SES), based on the three dimensions education, income and occupation, is a well-known indicator [34, 35]. However, accurate and complete documentation of SES at individual level is difficult to obtain, especially in a country where personal privacy is highly respected like in Germany. When collected by questionnaires, the item “household income” is frequently missing, leading to a selection bias, and responses are often influenced by “social desirability” [36]. In social epidemiology, indices of area deprivation have been increasingly used as proxy for SES [37, 38]. Based on aggregate data at a regional level, measures of area deprivation are indeed less accurate when used to assess individual socioeconomic situations. However, they are valuable to investigate area-based living conditions, like transport, housing, greenspaces, sport facilities or other resources of the community [38, 39]. Indices of area deprivation have been used for over 40 years in the UK [38]. In 1979, the sociologist Peter Townsend was the first author who defined the concept of “relative deprivation” as a lack of resources for people in comparison to the society to which they belong [40]. The resources he mentioned were multiple, not only financial, but also social and environmental. Since then, indices of multiple deprivation have been created in several countries, including Germany, and are now commonly used in social sciences and epidemiological research to investigate associations between socioeconomic living conditions and health outcomes [21, 25, 38, 41–44].

In addition to area deprivation, used to assess area-based socioeconomic factors, we investigated the role of demographic factors in pediatric diabetes care, either at the individual level (gender, migration background) or at the area level (degree of urbanization).

1.2. Aims of the research

Using the nationwide Prospective Diabetes Follow-up Registry (DPV), a large and for pediatrics representative real-world diabetes database, we aimed to explore whether socioeconomic and demographic factors are associated with diagnosis, treatment, and outcomes in pediatric diabetes in Germany. We therefore investigated the following research questions, listed below with the references of the corresponding publications (presented here in the sequence they were performed):

1. Are treatment modalities and outcomes in children and adolescents with T1D in Germany associated with area deprivation? [45]

2. Have socioeconomic disparities in technology use narrowed or widened from 2010–2012 to 2016–2018 in children and adolescents with T1D in the US and in Germany, with increasing use of diabetes technology? And are more pronounced socioeconomic disparities in technology use associated with larger socioeconomic disparities in glycemic control? [46]

3. How has the use of insulin pumps and of CGM evolved from 2016 to 2019 in Germany by federal state, area deprivation, gender, and migration background, in children, adolescents, and young adults with T1D? [47]

4. Are socioeconomic deprivation and urbanization, associated with the frequency of diabetes ketoacidosis (DKA) at diagnosis of pediatric T1D? [48]

The full-length articles and complete biographical references can be found in the Appendix (Chapter 7).

2. Materials and methods

2.1. Data sources

The four studies contributing to the present dissertation are based on data provided by two registries.

2.1.1. Diabetes-Follow-up Registry (DPV)

Data from the German Prospective Diabetes Follow-up Registry (DPV, www.d-p-v.eu) were used in all four studies of this dissertation. The DPV registry was launched in 1995 in Germany to collect standardized information on pediatric diabetes treatment and outcomes and to improve the quality of diabetes care. In 1997, the documentation was extended to adults with any type of diabetes [49, 50]. Since then, all participating diabetes centers prospectively document demographic and clinical data of patients (treatment, comorbidities, complications) using the DPV standardized electronic health record [49]. Twice a year, centers transmit the collected data in pseudonymous form to the University of Ulm. After plausibility checks, inconsistent data are sent back to the centers for verification and correction. Data are then anonymized and aggregated into a longitudinal database, which is used for nationwide benchmarking and epidemiological research. Data collection and analysis of pooled anonymized data from the DPV registry was approved by the Ethics Committee of the Medical Faculty of the University of Ulm (vote number 314/21), as well as the local review boards of the participating centers.

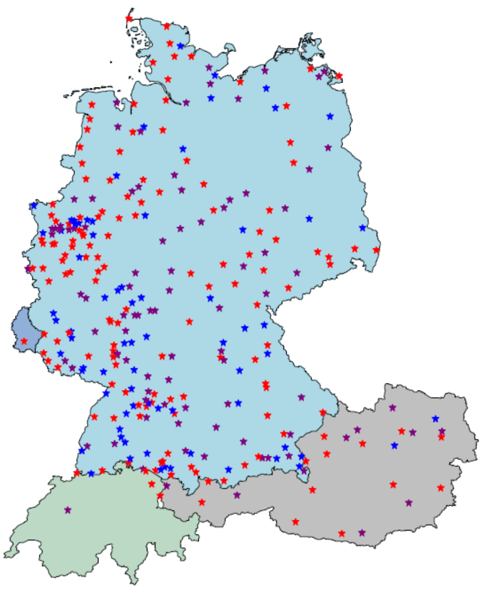

Fig. 1: Participating centers in the DPV registry (November, 2022)
The map represents the DPV centers in Germany (light blue), Luxembourg (dark blue), Switzerland (green), and Austria (grey). Red stars represent pediatric centers, blue stars represent internal medicine centers, and the purple stars both pediatric and internal medicine centers. Source: map created by K. Fink, updated by S. Tittel. Both conferred the right to use the map in this dissertation.

Currently, 502 diabetes care centers predominantly located in Germany, but also in Austria, Luxembourg, and Switzerland, are participating in the DPV registry (Fig. 1). As of September 2022, the DPV registry encompassed 6,405,586 visits of 654,400 patients with any type of diabetes, including 159,244 with T1D and 453,348 with T2D. The DPV registry contains longitudinal data of more than 85% [45] of all children and adolescents with T1D in Germany, so that it could be considered as highly representative for this population.

2.1.2. T1D Exchange Clinic Registry (T1DX)

Data from the T1D Exchange Clinic Registry (T1DX) were used for the second study of this dissertation. This registry was initiated in 2010 as the first large longitudinal database of individuals with T1D in the USA [51]. As of January 2018, the registry included data of 18,001 patients documented by 73 pediatric and adult diabetes and endocrinology centers (Fig. 2) [46]. Data have been prospectively collected from visits (electronic medical records) and/or from questionnaires completed by participants and/or their legal representatives. Centers received approvals from their respective institutional review boards and informed consent to participate were obtained from patients or their legal representatives. The Jaeb Center for Health Research, Tampa, Florida, coordinated the registry until 2019 and has been responsible for the management and quality assurance of the anonymized data [51].

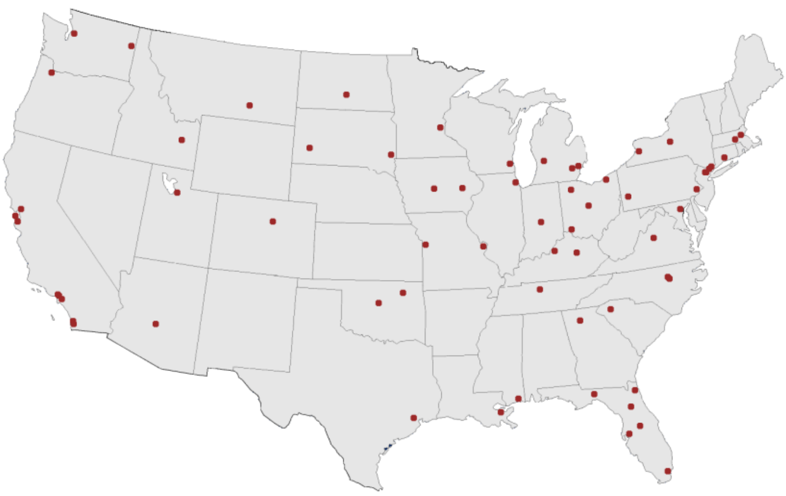

Fig. 2: Participating centers in the T1DX registry (February 2019)
The map represents the T1DX centers in the USA. Red stars represent pediatric and internal medicine centers. Source: map created by J. Saunders who conferred the right to use the map in this dissertation.

2.2. Main exposure variables

To explore associations with demographic and socioeconomic factors, we used the following exposures variables in the four studies of this dissertation: migration background, area deprivation, socioeconomic status (SES), and degree of urbanization.

2.2.1. Migration background

In the DPV registry, migration background is defined as place of birth outside Germany for the patient or at least for one of his/her parents. The US-based T1DX registry does not use the concept of migration background, but that of minority status, defined as race/ethnicity other than non-Hispanic white.

Migration background was used as an exposure in the third study of this thesis, and Migration background / minority status as a confounder variable in all other analyses. In the third publication of this thesis, we additionally categorized patients with migration background into two groups depending on their place of birth: patients born outside Germany were defined as “first-generation immigrants” and patients born in Germany with at least one parent born outside Germany as “second-generation immigrants” [47].

2.2.2. Area Deprivation

To date, two indices of area deprivation have been created for Germany: The German Index of Multiple Deprivation (GIMD) and the German Index of Socioeconomic Deprivation (GISD). Both indices were defined at district level. A continuous deprivation score was attributed to each district in Germany and subsequently districts were categorized into deprivation quintiles from Q1 (lowest deprivation) to Q5 (highest deprivation). We assigned patients to districts and consequently to deprivation quintiles using the 5-digit postal code of their residence.

2.2.2.1. German Index of Multiple Deprivation (GIMD)

We used the GIMD in the first three studies of this dissertation. The GIMD was created by Werner Maier in 2010 at the Helmholtz Center in Munich [19, 52, 53], according to the methodology developed by Noble et al. [41]. The GIMD comprises seven domains of deprivation differently weighted: income (25%), employment (25%), education (15%), municipal/district revenue (15%), social capital (10%), environment (5%), and security (5%) [52]. Associations between the GIMD and health outcomes have been found in many studies [19, 39, 53].

2.2.2.2. German Index of Socioeconomic Deprivation (GISD)

We used the GISD in the fourth study of this dissertation. The GISD has been created by Lars Eric Kroll at the Robert Koch Institute, Berlin [54]. This index is available for research in open access at the data repository of the German GESIS Leibniz-Institute for the Social Sciences (https://doi.org/10.7802/1460). The GISD includes regional data on education, occupation, and income [54].

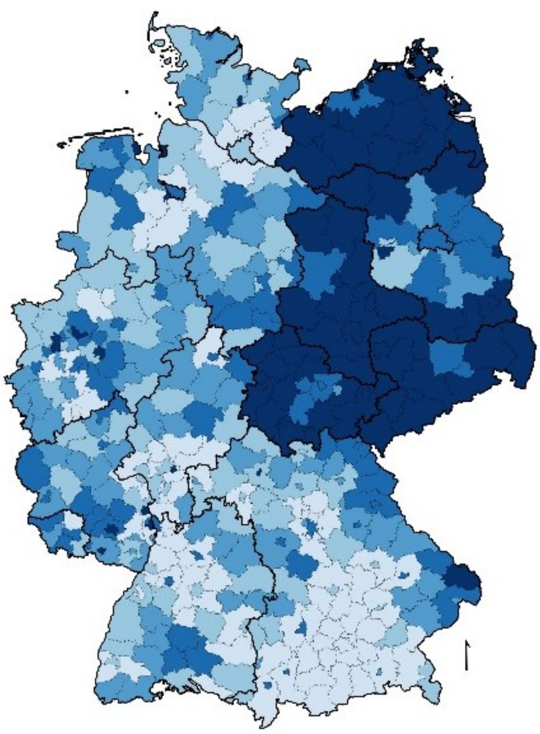

Fig. 3: German Index of Multiple Deprivation (GIMD, version 2010)
The map represents the districts of Germany, categorized into deprivation quintiles from Q1 (light blue, lowest deprivation) to Q5 (dark blue, highest deprivation). Scale 1:4,000,000 for A4 prints. [45]

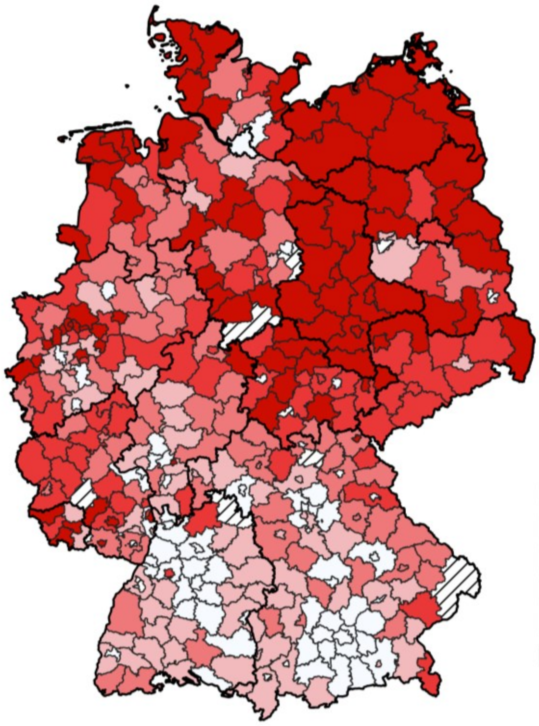

Fig. 4: German Index of Socioeconomic Deprivation (GISD, version 2012)
The map represents the districts of Germany, categorized into deprivation quintiles from Q1 (white, lowest deprivation) to Q5 (dark red, highest deprivation). Scale 1:4,000,000 for A4 prints. [48]

2.2.3. Socioeconomic status (SES)

In the second study of this dissertation, we used for the T1DX population a SES score composed of three individual variables equally weighted: education level (highest of either parent), insurance type (private, public, and no insurance), and annual household income.

2.2.4. Degree of Urbanization

In the fourth study of this dissertation, we categorized the districts into three degrees of urbanization, based on the population density as provided by Eurostat, 2015 [55]: "cities" (≥ 50% of the population living in a urban center with ≥ 1,500 inhabitants/km2, and ≥ 50,000 inhabitants collectively), "rural areas" (≥ 50% of the population living in areas with < 300 inhabitants/km2, and < 5,000 inhabitants collectively), and all other areas called "towns and suburbs."

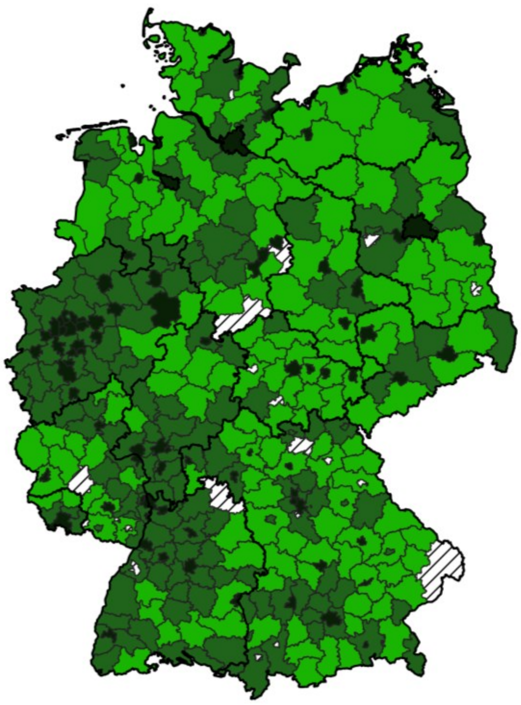

Fig. 5: Degree of Urbanization (2015)
The map represents the districts of Germany, categorized into three degrees of urbanization: rural areas in light green, towns and suburbs in green, and cites in dark green. Scale 1:4,000,000 for A4 prints. [48]

2.3. Outcome variables

Outcome variables investigated in the four studies of this dissertation were either related to treatment modalities (use of insulin pump, use of CGM, use of rapid- and long-acting insulin analogs, frequency of self-monitoring of blood glucose, participation in diabetes education) or to clinical status and complications (HbA1c, rate of severe hypoglycemia, rate of DKA at diagnosis or in the subsequent course of the disease, BMI-SDS [56], presence of overweight, presence of obesity, number of hospital days per year). These variables are defined in detail in the Methods section of each publication (see Appendix, Chapter 7).

2.4. Statistical analysis

Wilcoxon tests (continuous variables) and X^2 tests (categorical variables) were used to compare demographic and clinical characteristics. We adjusted for multiple comparisons according to the Holm-Bonferroni stepdown procedure.

To investigate associations between exposures and outcomes, we performed multivariable linear, logistic, or Poisson (considering overdispersion) regression models, depending on the outcome measure. Results of regression analyses were presented as adjusted estimates (least square means) with 95%-confidence intervals (95%-CI). P-values were adjusted for multiple testing using the false discovery rate (FDR) controlling Benjamini-Hochberg procedure.

According to the size of the study population, we set the level of significance of two-sided tests at $P < 0.01$ (publications 1 and 2, [45, 46]) or at $P < 0.05$ (publications 3 and 4, [47, 48]). All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

3. Results – summary of the publications

3.1. Area Deprivation and Regional Disparities in Treatment and Outcome Quality of 29,284 Pediatric Patients With Type 1 Diabetes in Germany: A Cross-sectional Multicenter DPV Analysis

Published in: Auzanneau M, Lanzinger S, Bohn B, Kroschwald P, Kuhnle-Krahl U, Holterhus PM, Placzek K, Hamann J, Bachran R, Rosenbauer J*, Maier W*, on behalf of the DPV Initiative. Area deprivation and regional disparities in treatment and outcome quality of 29,284 pediatric patients with type 1 diabetes in Germany: a cross-sectional multicenter DPV analysis. Diabetes Care 2018; 41 (12): 2517-2525. doi: 10.2337/dc18-0724 [IF: 15.270] **shared senior authorship.*

Research question 1: Are treatment modalities and outcomes in children and adolescents with T1D in Germany associated with area deprivation?

Background: In the last twenty years, considerable advancements in diabetes management and technology have contributed to globally improved glycemic control and quality of life for children and adolescents with T1D. Nevertheless, important variations in diabetes-related outcomes continue to be described, not only between low and high-income countries, but also within high income-countries. These disparities and the underlying reasons are not completely understood. Associations of socioeconomic factors with prevalence and outcomes of T2D have still been reported, but evidence of associations with care and outcomes of T1D is weaker. In this study, we aimed to analyze whether area deprivation is associated with treatment and outcomes in pediatric T1D in Germany.

Methods: Data of all children and adolescents younger than 20 years with T1D living in Germany, documented in the DPV database (see Chapter 2.1) in the years 2015 and 2016, were included and aggregated per patient as median, percentage or rate. We estimated the use of insulin pump, mean HbA1c, rate of severe hypoglycemia, rate of DKA, and prevalence of overweight by district, using logistic, linear or Poisson regression models adjusted for sex, age group, migration background, and diabetes duration. For each outcome, we categorized all adjusted estimates per district into quintiles and illustrated them on a map. In a second step, we estimated the use of insulin pump, CGM, rapid- and long-acting insulin analogs, frequency of self-monitoring of blood glucose (SMBG), participation in diabetes education, mean HbA1c, rates of severe hypoglycemia (all and with coma), rate of DKA (all and only severe DKA), BMI SDS [56], prevalence of overweight, prevalence of obesity, and number of hospital days by area deprivation quintile. We adjusted for all covariates used in the first model, and additionally for German federal states.

Results: Overall, data of 29,284 youths with T1D were analyzed. With increasing area deprivation, *from Q1 to Q5,* we observed the following results:

- Following treatment modalities were *significantly less frequently used:*
  - CGM use decreased from 6.3% [95%-CI: 5.7-7.0%] to 3.4% [2.7-4.3%]
  - Pump use decreased only from Q2 (48.0% [46.6-49.4%]) to Q5 (42.4% [39.6-45.1%]); and was lowest in Q1: 41.7% [40.3-43.2%]
  - Use of long-acting analogs decreased from 80.8% [79.4-82.2%] to 64.3% [60.4-68.0%]

- And the following outcomes *significantly worsened:*
  - Mean HbA1c increased from 7.84% [7.80-7.88%] to 8.07% [8.00-8.15%]
  - BMI-SDS increased from 0.26 [0.24-0.29] to 0.46 [0.41-0.50]
  - Prevalence of overweight increased from 11.8% [11.0-12.7%] to 15.5% [13.7-17.5%]

- By contrast, the following treatment modalities were *used significantly more frequently:*
  - Use of rapid-acting analogs increased from 74.7% [73.1-76.2%] to 79.0% [75.8-81.8%]

- And the following outcomes *significantly improved:*
  - Rate of severe hypoglycemia decreased from 12.1 [10.5-13.8] to 6.9 [5.0-9.5] events/ 100 PY

Associations with the following parameters were not significant:

- frequency of SMBG
- participation in diabetes education programs
- rate of severe hypoglycemia with coma
- rate of DKA or severe DKA
- prevalence of obesity
- number of hospital days / PY

Conclusion: This study revealed for the first time that the use of diabetes technology, BMI, and HbA1c in pediatric T1D in Germany was significantly associated with area deprivation, independently of the federal states. Associations between use of diabetes technology and improved glycemic control have been reported. Furthermore, some studies have shown that promoting equity in access to diabetes technology can help to reduce the association between socioeconomic disparities and glycemic control as the main outcome indicator of diabetes care. Our results indicate that facilitating access to CGM and insulin pump in the most deprived regions in Germany could contribute to improve diabetes-related outcomes in children and adolescents with T1D living in these regions. In addition, further research is needed to investigate more precisely the reasons of these disparities.

3.2. A Decade of Disparities in Diabetes Technology Use and HbA1c in Pediatric Type 1 Diabetes: A Transatlantic Comparison.

Published in: Addala A*, Auzanneau M*, Miller K, Maier W, Foster N, Kapellen T, Walker A, Rosenbauer J, Maahs DM*, Holl RW*. A Decade of Disparities in Diabetes Technology Use and HbA1c in Pediatric Type 1 Diabetes: A Transatlantic Comparison. Diabetes Care 2021 Jan; 44:133–140. doi: 10.2337/dc20-0257. Epub 2020 Sep 16. [IF: 19.112] **shared first and senior authorship.*

Research question 2: a) Have socioeconomic disparities in technology use narrowed or widened from 2010–2012 to 2016–2018 in children and adolescents with T1D in the US and in Germany, with increasing use of diabetes technology? and b) are more pronounced socioeconomic disparities in technology use associated with larger socioeconomic disparities in glycemic control?

Background: Insulin pumps and CGM are increasingly used in pediatric diabetes worldwide. Their utilization is associated with better glycemic control and a reduced rate of acute complications. A growing evidence indicates that most diabetes-related outcomes further improve with newest AID-technologies, including hybrid closed-loop (HCL) systems. However, in many countries, socioeconomic disparities have been reported in the use of diabetes technology as well as in glycemic outcomes. Thus, there is a concern that: a) socioeconomic disparities in technology use increase with wider use of technology and further technological advancement, and that b) greater socioeconomic disparities in technology use exacerbate socioeconomic disparities in glycemic control.

Methods: Children and adolescents younger than 18 years with T1D and a diabetes duration ≥ 1 year documented in the T1DX (US) or in the DPV (Germany) registries (see Chapter 2.1) in the 2010-2012 period or/and 2016-2018 period were included. In each time period, we used data from the last visit (T1DX) or from the last treatment year after aggregation (DPV). Individuals were categorized into SES-quintiles based either on individual insurance type, education level and annual income for T1DX, or on area deprivation (GIMD 2010) using districts of residence for DPV (see Chapter 2.2). SES-quintiles were sorted from Q1, the lowest SES (or highest deprivation), to Q5, the highest SES (or lowest deprivation). We estimated the mean use of insulin pump, use of CGM and mean HbA1c by SES quintiles in each time period, and then compared SES slopes between time periods (interaction of SES modelled as an ordinal variable with time periods). We therefore used logistic or linear regression models adjusted for sex, age group, diabetes duration group, migration background, and interaction of migration background with SES. For HbA1c, we performed the regression model again with additional adjustment for pump and CGM use.

Results: We found socioeconomic disparities in technology use and HbA1c in both registries. With higher SES / lower area deprivation, insulin pump and CGM use increased whereas HbA1c decreased as following (all P for trend < 0.001):

- T1DX (n= 16,457):
  - Pump use from 28.6% [95%-CI: 26.5–30.8] to 70.3% [66.9–73.5] in 2010-2012 and from 36.5% [34.2–38.9] to 75.8% [72.4–78.9] in 2016-2018
  - CGM use from 2.9% [95%-CI: 2.2–3.7] to 11.0% [9.1–13.2] in 2010-2012 and from 15.0% [13.2–17.0] to 52.3% [47.9–56.6] in 2016-2018
  - HbA1c from 9.0% [95%-CI: 8.9–9.0] to 7.8% [7.7–7.9] in 2010-2012 and from 9.3% [9.3–9.4] to 8.0% [7.9–8.1] in 2016-2018. With additional adjustment for pump and CGM use: HbA1c decrease from 8.7% [8.6–8.8] to 7.7% [7.6–7.8] in 2010-2012 and from 9.1% [9.1–9.2] to 8.1% [8.0–8.2] in 2016-2018

- DPV (n = 39,836):
  - *(Pump use: associations not linear)*
  - CGM use from 48.5% [95%-CI: 45.9–51.1] to 57.1% [55.4–58.7] in 2016-2018 *(not significant in 2010-2012)*
  - HbA1c from 8.0% [95%-CI: 7.9–8.0] to 7.6% [7.6–7.7] in 2010-2012 and from 7.8% [7.8–7.9] to 7.5% [7.5–7.6] in 2016-2018. With additional adjustment for pump and CGM use: HbA1c decrease from 7.9% [7.8–7.9] to 7.5% [7.5–7.5] in 2010-2012 and from 7.8% [7.8–7.9] to 7.5% [7.5–7.6] in 2016-2018

Socioeconomic disparities increased significantly between time periods for CGM use in the DPV registry, and for HbA1c in the T1DX registry (both P < 0.001). However, the increase of socioeconomic disparities in HbA1c in T1DX was no longer significant after additional adjustment for pump and CGM use.

Conclusion: The second article of this thesis reports that except for pump use in Germany (association non-linear), socioeconomic disparities in technology use and metabolic control in children and adolescents with T1D have persisted or even increased over time, from 2010-2012 to 2016-2018, both in the US and in Germany. However, associations with area-based socioeconomic deprivation in Germany were weaker than those with individual SES in the US. For the US, we found that the increase of disparities in HbA1c over time was no longer significant after adjustment for technology use; this result indicates that disparities in diabetes technology use probably exacerbate disparities in glycemic control. Measures promoting an equal access to diabetes technologies regardless of the socioeconomic situation, in particular access to CGM (greatest disparities), are important to reduce inequalities in glycemic control in pediatric diabetes, even in high-income countries.

3.3. Heterogeneity of Access to Diabetes Technology Depending on Area Deprivation and Demographics Between 2016 and 2019 in Germany

Published in: Auzanneau M, Rosenbauer J, Maier W, von Sengbusch S, Hamann J, Kapellen T, Freckmann G, Schmidt S, Lilienthal E, Holl RW. Heterogeneity of Access to Diabetes Technology Depending on Area Deprivation and Demographics Between 2016 and 2019 in Germany. J Diabetes Sci Technol. 2021 Sep;15(5):1059-1068. doi: 10.1177/19322968211028608. Epub 2021 Jul 12. [IF: 3.123].

Research question 3: How has the use of insulin pump and of CGM evolved from 2016 to 2019 in Germany by federal state, area deprivation, gender, and migration background, in children, adolescents, and young adults with T1D?

Background: Management of T1D improved considerably in the two last decades. Despite this, only a minority of adolescents and young adults achieve the recommended glycemic control. Insulin pumps and CGM are established diabetes technologies, which are widely used in pediatric diabetes. In 2016-2018 in Germany, 57% of children and adolescents with T1D under 18 years of age used an insulin pump and 49% used CGM [46]. These devices, as well as newest technologies like HCL, have the potential to improve diabetes outcomes. However, access to these technologies remains unequal, not only depending on clinical factors, but also largely on demographics and socioeconomic factors. We therefore sought to investigate how these disparities evolved over the last years in Germany, as diabetes technology use further increased in children, adolescents, and young adults with T1D.

Methods: Individuals with T1D aged younger than 26 years, with diabetes duration ≥ 3 months, living in Germany, and documented between 2016 and 2019 in the DPV registry (see Chapter 2.1) were included. Data were aggregated per patient and year as median (age, diabetes duration, HbA1c, BMI SDS, and BMI) or maximum (pump use, CGM use). We performed logistic regression models adjusting for gender, age group, diabetes duration group, and migration background, to estimate the use of pump and of CGM in 2016 and 2019 for each federal state. We categorized the estimates in three groups to create tertile-based choropleth maps. To assess the association of area deprivation, migration background, and gender with pump or CGM use by year, we repeated the same regression models with the following interaction-terms: area deprivation*year, migration background*year or gender*year, additionally adjusting for area deprivation and an interaction between migration background and area deprivation, and using sandwich variance estimators. P-values for trend (area deprivation, total time period) and OR were derived from the regression models.

Results: From 2016 (n = 25,442) to 2019 (n = 26,628):

- the use of insulin pump increased from 51.7% to 57.6%, and the use of CGM from 17.9% to 70.3% (unadjusted data)

- the distribution of the use of insulin pumps by federal state did not change substantially, with the lowest use in Baden-Württemberg and Bavaria, and the highest use in Schleswig-Holstein, Brandenburg, and Lower-Saxony. By contrast, the regional distribution of the use of CGM changed considerably

- the use of insulin pumps by area deprivation was not linear with the lowest use in the 20% least deprived districts (Q1) and thereafter a decreasing use with increasing deprivation (from Q2 to Q5). The use of CGM decreased with higher area deprivation from 2016 to 2018 (2018: $OR_{\text{Q1 vs. Q5}}$: 1.52 [95%-CI: 1.37-1.67]), but this effect diminished over the years and eventually disappeared in 2019 ($OR_{\text{Q1 vs. Q5}}$: 0.97 [0.88-1.08])

- individuals without migration background used both devices more frequently than individuals of the second-generation immigrants, who themselves used these devices more frequently than individuals of the first-generation immigrants. In 2019, $OR_{\text{with vs. without migration background}}$ were 1.36 [1.28-1.45] for the use of insulin pump and 1.30 [1.22-1.39] for the use of CGM. The effect of migration background on CGM use decreased significantly over the years

- when analyzed by gender: girls used more frequently an insulin pump than boys (2019: $OR_{\text{girls vs. boys}}$: 1.25 [1.18-1.31], whereas no gender difference was reported for the use of CGM (2019: $OR_{\text{girls vs. boys}}$: 1.02 [0.97-1.08])

Conclusion: The third article of this thesis revealed that even if inequalities in diabetes technology use by area deprivation were not clear (insulin pump) or disappeared (CGM), strong disparities by gender (insulin pump) and by migration status (both technologies) persist in Germany in 2019. With further technological advancement and the introduction of new devices (HCL), there is a concern that the disparities in access to technology based on migration background persist or even increase, and exacerbate the disparities in diabetes outcomes. Thus, efforts to identify barriers in access to diabetes technology are required.

3.4. Frequency of Ketoacidosis at Diagnosis of Pediatric Type 1 Diabetes Associated With Socioeconomic Deprivation and Urbanization: Results From the German Multicenter DPV Registry.

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Research question 4: Are socioeconomic deprivation and urbanization associated with the frequency of diabetes ketoacidosis (DKA) at diagnosis of pediatric T1D?

Background: DKA at diagnosis of T1D is a potentially life-threatening complication associated with long-term adverse consequences, such as poorer metabolic control and impaired neurocognitive function. In many high-income countries, including in Germany, the prevalence of DKA at diagnosis has increased over the last years and even further during the COVID-19 pandemic. The reasons for this increase are not completely understood. Besides non-modifiable biological risk factors, like younger age, one frequent factor could be theoretically modified: the delay in treatment. This delay is itself associated with other risk factors, and thus often acts as a mediator between other risk factors and the prevalence of DKA at diagnosis. Identifying these risk factors is therefore crucial to develop appropriate prevention strategies. Some individual risk factors associated with an increased rate of DKA at diagnosis, such as lower parental education or migration background, have been identified. In contrast, contextual factors have been hardly investigated. We therefore analyzed whether socioeconomic deprivation and urbanization are associated with the prevalence of DKA at diagnosis in Germany.

Methods: We included all visits in diabetes care centers documented between 2016 and 2019 in the DPV registry (see Chapter 2.1) at the time of T1D diagnosis (-/+7 days) in children aged 6 months-18 years, living in Germany. Data of repeated visits within this time-period were aggregated per patient as median, minimum (pH, bicarbonate) or maximum (DKA at diagnosis). DKA at diagnosis of T1D was defined according to the ISPAD guidelines as either pH < 7.3, bicarbonate < 15 mmol/L or "DKA" documented as the reason for hospitalization. Using logistic regression models with district as random effect, adjusted for migration background, sex, and age-group of the whole study population, we estimated smoothed (i.e. reduction in the effects of sampling variation across districts using shrinkage estimator) DKA rates by district. Smoothed DKA rates categorized into quintiles, socioeconomic deprivation (GISD 2012) quintiles, and degrees of urbanization (see Chapter 2.2) were represented on choropleth maps at district level. Using logistic regression models with a sandwich estimator, we analyzed the association between socioeconomic deprivation (modeled as categorical and ordinal variable) or degree of urbanization and the frequency of DKA at diagnosis. In addition, we tested interactions of deprivation or urbanization by age group, sex, or migration background.

Results: A total of 10,598 children and adolescents with newly T1D were included. The unadjusted DKA prevalence at diagnosis was 24.9%.

- The percentage of DKA at diagnosis significantly increased with higher socioeconomic deprivation (P for trend < 0.001): from 20.6% [95%-CI: 19.0–22.4] in the least deprived districts (Q1) to 26.9% [25.0–28.8%] in the most deprived districts (Q5).

- The percentage of DKA at diagnosis was significantly higher in rural areas than in towns and suburbs or in cities (27.6% [95%-CI: 26.0–29.3] vs. 22.7% [21.4–24.0], P < 0.001, or vs. 24.3% [22.9–25.7], P = 0.007, respectively).

These associations did not differ significantly by age groups, by sex, or by migration background (interaction terms with urbanization and with socioeconomic deprivation not significant). All results remained significant with different sensitivity analyses (associations of the frequency of DKA with urbanization and with socioeconomic deprivation after additionally adjusting for the other variable; districts modeled as random intercept in the regression models).

Conclusion: The fourth article of this thesis identified two contextual factors significantly associated with the frequency of DKA at T1D diagnosis in Germany. The focus on area-based factors is useful to understand the whole context beyond individual factors and thus, enables to organize targeted prevention campaigns where they are most needed. Publications have shown that prevention of DKA at diagnosis can be achieved by the mean of awareness campaigns and screening for presymptomatic stages of T1D, which both contribute to reduce delayed diagnosis. Our study provides evidence that such prevention campaigns would be more effective if they particularly target socioeconomically disadvantaged regions and rural areas.

4. Discussion

Real-world data, collected for example through representative patient registries, are very valuable to complete results of randomized control trials (RCT) [57]. RCT are considered to be the gold standard to evaluate the safety and effectiveness of new diabetes technologies [58]. However, patients (or their parents) who volunteer to participate in these studies are not representative of the entire population with diabetes: they are mostly technophile individuals with good health literacy. They are generally highly motivated to use new technologies and have a certain expectation that the new device will offer benefits. Moreover, some groups of patients, such as individuals with many comorbidities or with migration background, are systematically underrepresented in RCT [59, 60]. These studies present high internal validity, avoiding a number of possible biases, and are indispensable to determine the effect of treatments. However, they do not give any information on the actual use of these devices in the real world [61] nor on the real-world outcomes in patient groups underrepresented in the initial RCTs. The value of registry data based on electronic health records (EHRs) to explore the real distribution of the use of new technologies after approval and market launch, is increasingly recognized [57, 59, 60]. Observational studies using EHRs make investigation of real-world evidence possible, without selection bias, allowing therefore for generalizations (external validity), highly relevant for routine practice [59, 60].

Using data of the DPV registry, which covers more than 85% of the pediatric population with diabetes in Germany [45], we were able to investigate the real world distribution of diabetes technology use in Germany in the last years, and to analyze the effect of socioeconomic factors and demographics (sex, migration background) on diabetes diagnosis, treatment and outcomes. In the first three publications we found that in more deprived regions, the use of CGM and insulin pump was lower and that HbA1c was higher compared to less deprived regions [45–47]. In 2019, the association between CGM use and area deprivation disappeared, but considerable disparities by migration background were persistent for the use of insulin pump and CGM, irrespective of the year [47]. In addition, when looking at the influence of socioeconomic and contextual factors at primary care level, upstream from the care in specialized diabetes centers, the frequency of DKA at T1D diagnosis was also significantly higher in more deprived regions and in rural areas [48].

Compared to the situation in the US, socioeconomic and ethnic disparities in diabetes care are much weaker in Germany [46, 62]. However, these disparities were not really expected in pediatric diabetes care in Germany for several reasons. First, if health insurance status is playing a crucial role in access to health care in the US [46, 63–65], nearly all children and adolescents with diabetes are covered by health insurance in Germany, and the nature of the insurance (statutory or private) is not expected to have notable consequences in access to diabetes care [47, 66]. Second, the situation of individuals with migration background is very different in the US and in Germany. In the US, structural racism is still identified as a factor leading to significant health inequities, including pediatric diabetes care [62, 64, 67–69]. Moreover, in Germany, in contrast to the US-situation, there is a lower proportion of individuals with migration background in the most deprived area, so that both factors are not acting together, but probably inversely, potentially leading to a decrease of the effect. Nevertheless, we always adjusted for the other variable when we investigated associations with one factor (area deprivation or migration background), and thus, the effect of each factor is assumed to be assessed independently.

The most evident limitation of the use of indices of area deprivation is that they are based on aggregate data at district level and thus, they are only able to give a rough estimation of individual socioeconomic situations in these areas [70]. Moreover, German districts are very heterogeneous in population size (from about 35,000 to more than one million inhabitants), and the measure of deprivation is assumed to be less accurate in larger districts [45]. Therefore, in these districts, association with individual socioeconomic factors are probably underestimated when assessed by indices of area deprivation. However, districts are an administrative unit that correspond well to the structure of pediatric diabetes care in Germany. In addition, indices of multiple deprivation are able to take an “area effect” into account, which cannot be captured by individual indicators. In several publications, associations with area deprivation remained significant even after adjusting for individual SES [19, 39]. There is some evidence that individual and area-based deprivation, despite moderate to high correlation, act through partly different pathways [53, 71]. Indeed, area deprivation is partly reflecting the individual socioeconomic situation of the inhabitants in one area, but it also takes area-based resources into account, such as green spaces, availability of sport equipment, public transports, as well as neighborhood influences (social structure of the schools, neighborhood perceived safety, availability and quality of hospitals and outpatient medical services) [39, 53].

As a consequence, associations with area deprivation may be partly explained by structural factors at district level. For instance, regional medical services of health insurance funds may have different rules (less or more restrictive) regarding the reimbursement of diabetes technologies. Degree of affinity for innovative or advanced technology may also differ between regions, depending on the teams of the diabetes centers [72], on individual preferences of patients, and on the local reimbursement rules. Other regional characteristics may be more related to health outcomes (HbA1c, DKA at diagnosis). A large part of the most deprived regions, as measured by the GIMD or by the GISD, are located in former East Germany [70, 73]. Although living conditions converge since the fall of the Berlin Wall, lower physician density [16] as well as a higher proportion of individuals with low SES are still characterizing these regions [70]. Both could contribute to worse HbA1c and higher risk of DKA at diagnosis.

In line with the individual SES, both indices of area deprivation are based on three main dimensions: income, education, and occupation [19, 70]. Therefore, each of these dimensions is assumed to play a role in the association between deprivation and diabetes treatment and outcomes. Income might partly explain associations with technology use. Even if nearly every child and adolescent benefits from health insurance in Germany, applications are necessary for reimbursement of CGM or insulin pumps, and this procedure could discourage families with low resources. Education is assumed to play a role both for technology use and outcomes. A good general educational level is important for appropriate diabetes education, which is a condition for reimbursement of diabetes technology. Education is also related to self-efficacy, which is defined as “individual's belief in his or her capacity to execute behaviors necessary to produce specific performance attainments” [74]. Perceived self-efficacy has been identified as an important psycho-social component for the self-management of chronic diseases, including diabetes [75, 76]. Moreover, a low self-efficacy may discourage from technology use in patients with low affinity for technology. On the other side, provider implicit biases have been identified as the tendency of some clinicians to avoid the recommendation of technologies to some population groups, because they estimate their resources as not sufficient to afford the cost of such technologies or to use it appropriately [65]. Last but not least, lower health literacy is associated with lower level of education [77]. Health literacy correlates with healthier lifestyle and good health outcomes in general, and it has been identified as a factor for better glycemia [77]. In case of new T1D symptoms, health literacy could be related to the capacity to seek rapidly for medical advice, and thus, be associated with timely diagnosis and treatment of T1D at onset and lower risk of DKA. Similarly, occupation is associated with higher social support, which could also contribute to a timely treatment in case of symptoms, for example, if workmates encourage or help to see a doctor.

We also found strong associations between lower technology use and presence of migration background, independent of socioeconomic deprivation. Sufficient language proficiency is required not only to participate in education programs, which are mandatory for technology use, but also for the management of the devices in daily life, for example to get information via hotlines. In addition, some cultural barriers could exist with regard to technology use.

Contrary to disparities in health outcomes (HbA1c, DKA at diagnosis), disparities in technology use present the advantage to be directly modifiable if the underlying reasons are understood. In the US, the T1D Exchange Quality Improvement Collaborative (T1DX-QI) developed in 2020 a health equity program with six approaches to address inequalities in T1D care [78]. In Germany, awareness of socioeconomic disparities in diabetes care is lower, especially in pediatric T1D. Measures to improve diabetes technology uptake in disadvantaged populations should probably combine efforts in three directions: simplify reimbursement by health insurance, give more time and resources to adapt teaching programs to individuals with lower education, and find ways to enhance empowerment and perceived self-efficacy of the patients living in deprived areas. Regarding individuals with migration background, language is assumed to be a major barrier, in particular to participate in appropriate education programs [79]. A solution could be to engage interpreters and to translate education programs into several languages.

We found that disparities in glycemic control were not disappearing when adjusting for technology use in Germany [46]. Thus, socioeconomic or ethnic disparities in technology use do not explain entirely the disparities in glycemic outcomes. Nevertheless, reducing disparities in technology use is essential to avoid that diabetes outcomes become even more divergent [46, 80]. In fact, there is now a large evidence that the use of CGM and insulin pump can improve glycemic control and reduce the risk of complications [81–84]. With the arrival of more innovative technologies (from hybrid closed-loop to full closed-loop systems representing an artificial pancreas), the risk of growing disparities in diabetes care and outcomes remains in the coming years [85].

Another finding was that DKA at T1D onset was significantly more frequent in more deprived areas as well as in rural regions [48]. DKA is a serious acute complication, occurring in about one quarter of all newly diagnosed T1D and associated with deleterious long-term consequences [48]. The fact that its prevalence has increased in many high-income countries in the last years [33, 86], including in 2020 during the COVID-19 pandemic [32], represent a major issue, especially because the causes of this increase are not well understood. Our results are therefore useful because they indicate in which areas prevention measures could be more effective to reduce the prevalence of this complication. Possible prevention strategies include screening for pre-symptomatic stages of T1D [87], awareness campaigns describing the most frequent symptoms of T1D onset in kindergarten, schools as well as at primary care level (pediatricians, general practitioners, emergency rooms). Our study brought evidence that such prevention measures could be particularly effective when focused on rural or socioeconomically deprived areas.

In conclusion, outside from the USA [88–91] and UK [92], but in comparable countries with similar level of diabetes care, evidence on socioeconomic and demographic disparities in pediatric treatment and outcomes of T1D was scarce. The four publications contributing to this thesis provide real-world recent evidence on associations between socioeconomic / demographic factors and treatment / outcomes in children and adolescents with T1D in Germany. In the past few years, similar inequities in pediatric diabetes care have been described in many other high-income countries, as in France [42], in New-Zealand [93] or in in Canada [80, 94].

Outlook: Our findings highlight the importance of considering the impact of factors based on socioeconomic characteristics and demographics (migration background, type of region), even in Germany, where the pediatric population benefits from a comprehensive health insurance. Our research based on real-world data gives some indications of possible concrete measures to reduce socioeconomic and demographic inequities in pediatric diabetes care and homogenize outcomes. In a similar way, analyses to investigate disparities in adult diabetes care are in preparation. Preliminary results indicate large socioeconomic discrepancies in the uptake of SGLT2 inhibitors or GLP-1 receptor agonists in adult T2D care in Germany. These findings raise the concern that many adults with T2D and cardiovascular disease, heart failure, or chronic kidney disease in Germany are not treated appropriately with newer drugs [95] due to their socioeconomic situation.

5. Summary

At the end of 2020, around 37,700 children and adolescents under the age of 20 in Germany had type 1 diabetes (T1D). Compared with other high-income countries, studies reporting pediatric diabetes outcomes indicate a relatively good quality of care in this country. However, statistics of central tendency conceal differences between different population groups.

Longitudinal data collected in the multicenter Prospective Diabetes Follow-up Registry (DPV), which is highly representative for the pediatric population with diabetes in Germany, provide useful information on the heterogeneity of diabetes treatment and outcomes across different population groups. Analysis of these data linked with demographic and socioeconomic indicators, such as migration background, socioeconomic deprivation, or degree of urbanization, allows to provide real world evidence on potential differences in the use of newest technologies and related outcomes between different population groups and regions. The results are presented in four articles summarized in the present dissertation.

The first article revealed significant associations between area deprivation and treatment modalities and outcomes in 29,284 children and adolescents with T1D younger than 20 years in the years 2015 and 2016 in Germany. In particular, the use of continuous glucose monitoring systems (CGM) decreased from 6.3% in the least deprived regions (Q1) to 3.4% in the most deprived regions (Q5) and the use of insulin pump decreased from 48.0% in Q2 to 42.4% in Q5. The main indicator for glycemic control, HbA1c, deteriorated from 7.8% in Q1 to 8.1% in Q5. Because many studies showed that increased use of diabetes technology potentially improves diabetes related outcomes, our findings suggest the possibility of an association between lower use of diabetes technologies in the most deprived regions in Germany and worse glycemic outcomes. Therefore, measures promoting a more equitable access to advanced technologies in pediatric diabetes are required.

The second article aimed to compare associations between socioeconomic factors and diabetes treatment and outcomes between time periods (2016-2018 vs. 2010-2012) and between countries (US vs. Germany). Higher insulin pump and CGM use and improved HbA1c were observed with higher socioeconomic status (SES) / lower area deprivation in both time periods and both countries, except in Germany for CGM in 2010-2012 (trend not significant probably due to the very low proportion of individuals using CGM in this time period), and for insulin pump in both time periods (non-linear association). Overall, disparities were much more pronounced in the US compared to Germany. In the US, disparities in glycemic control worsened between the two time-periods but after adjustment for technology use, this was no longer significant. This result suggests that disparities in technology use partly contribute to disparities in glycemic outcomes in the US. In Germany, disparities in both diabetes treatment and outcomes are present and persisted until 2016-2018 and this issue should be followed longitudinally, especially in the context of the increasing use of more advanced technologies (systems with automated insulin delivery, including hybrid-closed-loop systems).

The third article investigated disparities in insulin pump and CGM use by area deprivation, migration background, and gender between 2016 and 2019. One objective was to analyze the evolution of these associations over the years, with increasing use of technology. Whereas associations between socioeconomic deprivation and use of CGM disappeared in 2019, all other associations persisted until 2019. Insulin pump was significantly less used with increasing deprivation from Q2 to Q5, by migrants of the second and even lesser by migrants of the first generation, and less used by males. CGM was less used by migrants, but no differences in use by gender have been be observed. Overall, disparities in technology use by migration background were the strongest, even after adjustment for socioeconomic deprivation. Cultural and language barriers might limit access for children and adolescents of the second- and especially first-generation migration. Sufficient language skills are required for diabetes education, which is mandatory for the use and reimbursement of these technologies. Efforts to involve interpreters in medical consultations and to translate diabetes education programs could be effective to reduce these disparities.

The fourth article of this thesis broadens the question of socioeconomic influences to primary / emergency care for timely diagnosis of diabetes, upstream of the treatment in specialized diabetes care centers. Diabetic ketoacidosis (DKA) is a very serious complication that accompanies about 25% of pediatric T1D onset, and no decrease in trend has been observed over the last years. This is a relevant cause of concern in many high-income countries because DKA at T1D diagnosis is associated with deleterious long-term health consequences. The reasons for the still high frequency of this complication are not well understood. In many cases, DKA is due to a delay in diagnosis that could have been avoided. Studies on prevention measures like awareness campaigns and screening for pre-symptomatic T1D show only moderate and often not lasting effects on DKA reduction. However, these measures could have more impact if targeted on specific population groups. Including 10,598 children and adolescents with newly diagnosed T1D, we found that the prevalence of DKA at T1D diagnosis was significantly higher in rural areas as well as socio-economically deprived regions. These contextual factors should be taken into account to organize prevention measures in targeted areas, where they are most needed.

In conclusion, the four articles of this thesis revealed significant disparities by socioeconomic deprivation and migration background affecting health outcomes of children and adolescents already from onset of T1D. Our research based on real world data indicated potential ways to improve equality in treatment and outcomes of pediatric T1D in Germany. Further research is currently in progress to examine disparities in care of adults with type 2 diabetes (T2D). Important socioeconomic influences in the prevalence and outcomes of T2D have been described. The impact of socioeconomic factors in the prescription and uptake of the new, more effective but also more expensive, drugs will be investigated using real world data of the DPV registry.

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Appendix – articles of this thesis

The dissertation is submitted as a 'cumulative thesis' and contains four original articles.

1st article: Auzanneau M, Lanzinger S, Bohn B, Kroschwald P, Kuhnle-Krahl U, Holterhus PM, Placzek K, Hamann J, Bachran R, Rosenbauer J*, Maier W*, on behalf of the DPV Initiative, **shared last authorship*. Area deprivation and regional disparities in treatment and outcome quality of 29,284 pediatric patients with type 1 diabetes in Germany: a cross-sectional multicenter DPV analysis. Diabetes Care 2018; 41 (12): 2517-2525. doi: 10.2337/dc18-0724 [IF: 15.270]

Own contribution:
I was the first and corresponding author of this publication and contributed to the following parts:

- co-formulation of the research question
- co-development of the methodology and study design
- interpretation of the results of the statistical analysis
- creation of the figures
- literature research
- writing of the manuscript
- revision of the manuscript according to comments and suggestions of the co-authors
- submission of the manuscript to the journal
- revision of the manuscript after peer review

Area Deprivation and Regional Disparities in Treatment and Outcome Quality of 29,284 Pediatric Patients With Type 1 Diabetes in Germany: A Cross-sectional Multicenter DPV Analysis

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Marie Auzanneau,[1,2] Stefanie Lanzinger,[1,2] Barbara Bohn,[1,2] Peter Kroschwald,[3] Ursula Kuhnle-Krahl,[4] Paul Martin Holterhus,[5] Kerstin Placzek,[6] Johannes Hamann,[7] Rainer Bachran,[8] Joachim Rosenbauer,[2,9] and Werner Maier,[2,10] on behalf of the DPV Initiative

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

This study analyzed whether area deprivation is associated with disparities in health care of pediatric type 1 diabetes in Germany.

RESEARCH DESIGN AND METHODS

We selected patients <20 years of age with type 1 diabetes and German residence documented in the "diabetes patient follow-up" (Diabetes-Patienten-Verlaufsdokumentation [DPV]) registry for 2015/2016. Area deprivation was assessed by quintiles of the German Index of Multiple Deprivation (GIMD 2010) at the district level and was assigned to patients. To investigate associations between GIMD 2010 and indicators of diabetes care, we used multivariable regression models (linear, logistic, and Poisson) adjusting for sex, age, migration background, diabetes duration, and German federal state.

RESULTS

We analyzed data from 29,284 patients. From the least to the most deprived quintile, use of continuous glucose monitoring systems (CGMS) decreased from 6.3 to 3.4% and use of long-acting insulin analogs from 80.8 to 64.3%, whereas use of rapid-acting insulin analogs increased from 74.7 to 79.0%; average HbA_{1c} increased from 7.84 to 8.07% (62 to 65 mmol/mol), and the prevalence of overweight from 11.8 to 15.5%, but the rate of severe hypoglycemia decreased from 12.1 to 6.9 events/100 patient-years. Associations with other parameters showed a more complex pattern (use of continuous subcutaneous insulin infusion [CSII]) or were not significant.

CONCLUSIONS

Area deprivation was associated not only with key outcomes in pediatric type 1 diabetes but also with treatment modalities. Our results show, in particular, that the access to CGMS and CSII could be improved in the most deprived regions in Germany.

[1]Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany
[2]German Center for Diabetes Research (DZD), Neuherberg, Germany
[3]Children's Hospital, Ruppiner Kliniken GmbH, Hochschulklinikum der Medizinischen Hochschule Brandenburg, Neuruppin, Germany
[4]Practice for Pediatric Endocrinology and Diabetology, Gauting, Germany
[5]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University Hospital of Schleswig-Holstein, Campus Kiel/Christian-Albrechts University of Kiel, Kiel, Germany
[6]Pediatric and Adolescent Medicine, University Hospital, Martin-Luther University, Halle, Germany
[7]Department of Pediatrics, St. Marien Hospital Landshut, Landshut, Germany
[8]Pediatric Practice, Oberhausen, Germany
[9]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany
[10]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

Corresponding author: Marie Auzanneau, marie.auzanneau@uni-ulm.de.

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J.R. and W.M. share last authorship.

Despite considerable advances in the management of pediatric type 1 diabetes over the last two decades, major geographic variations in metabolic control and diabetes-related complications have persisted between countries around the world (1). Treatment and outcome quality of patients with type 1 diabetes also vary within countries. In Brazil, large discrepancies were found in clinical care across different regions (2). In Germany, significant disparities in the use of insulin pumps and rapid-acting or long-acting analogs, HbA_{1c} levels, the prevalence of overweight, and the rate of severe hypoglycemia have been reported between the federal states (3). However, regional variations in treatment and outcome quality of care of patients with type 1 diabetes are not completely explained.

Relative material and social deprivation (i.e., the lack of resources for people compared with the societies to which they belong) show significant area-level disparities associated with health (4). Therefore, indices of multiple deprivation have been used increasingly since 2000 to assess area deprivation, not only for epidemiological research but also for public health policy (5). According to Noble et al. (6), area deprivation refers not merely to the proportion of deprived people in an area but also to an "area effect" and to the negative consequences of "the lack of facilities in that area." Correspondingly, indices of multiple deprivation provide multidimensional information on living conditions at the regional level.

Concerning type 2 diabetes, a notable number of studies have shown that area deprivation is associated with worse indicators of outcome quality, such as BMI, HbA_{1c}, lipid profile, and short-term or long-term diabetes-related complications (7,8). However, evidence is weaker with regard to type 1 diabetes (9–13). Moreover, to date, studies on type 1 diabetes focused on associations between area deprivation and metabolic control but not medical treatment (9–13).

Nevertheless, regional socioeconomic disparities may be a major determinant of the use of insulin pump therapy (continuous subcutaneous insulin infusion [CSII]), continuous glucose monitoring systems (CGMS), and insulin analogs. In Germany, CSII is reimbursed by the statutory health insurance (covering ~90% of the population) if poor glycemic control persists despite intensified conventional insulin treatment (14). Patients and diabetologists have to apply to the health insurance company for reimbursement by providing comprehensive documentation of the blood glucose levels and insulin therapy over the last 3 months. Exigent documentation and uncertainty of reimbursement may discourage some families in socioeconomically disadvantaged areas. Application for reimbursement of real-time CGM by statutory health insurance is also necessary and only possible since 2016. For patients covered by private health insurance (~10% of the population), reimbursement depends on specifications in the insurance contract. Different proportions of patients with private versus statutory health insurance between areas in Germany could also lead to regional variation in diabetes treatment (15).

The objective of our study was therefore to analyze whether area deprivation is associated with regional disparities in the treatment and outcome quality of pediatric patients with type 1 diabetes in Germany.

RESEARCH DESIGN AND METHODS

Study Population

We used data from the multicenter "diabetes patient follow-up" registry (Diabetes-Patienten-Verlaufsdokumentation [DPV]). Currently, 459 diabetes care centers, mainly in Germany (n = 416) and Austria (n = 40), participate in the DPV initiative and prospectively document demographic and clinical data on treatment and outcome quality. Twice a year, centers transmit locally collected and anonymized data to the University of Ulm, Germany, for central analysis and quality assurance (16). Inconsistent or implausible data are reported back to centers for verification or correction. Data collection and analysis of anonymized data from the DPV registry were approved by the Medical Faculty Ethics Committee of the University of Ulm, Germany, and by the local review boards of participating centers.

As of March 2017, 484,365 patients with any type of diabetes were documented in the DPV database. We included only patients younger than 20 years of age with type 1 diabetes and German residence documented in the DPV for 2015 and 2016. The definition of type 1 diabetes in the DPV database is based on a physician's diagnosis according to the international guidelines (17) and can be revised based on the course of the disease. For each patient, we aggregated clinical data for the years 2015 and 2016 as median, percentage, or rate per 1 or 100 patient-years (PYs) for continuous, categorical, and event variables, respectively.

Area Deprivation

Area deprivation was assessed using the German Index of Multiple Deprivation from 2010 (GIMD 2010). This index was developed by Maier et al. (18,19) and is a validated measure of area deprivation for Germany (5,8,19,20). The GIMD includes seven domains of deprivation with different weighting: income (25%), employment (25%), education (15%), municipal/district revenue (15%), social capital (10%), environment (5%), and security (5%) (18,19). The GIMD 2010 was generated for all 412 districts of Germany (boundaries at 31 December 2010). Districts were categorized into deprivation quintiles, with quintile 1 (Q1) representing the least deprived and quintile 5 (Q5) the most deprived districts. We used the five-digit postal code of the patient's residence to assign the district of residence. The postal code of residence was not available for 2.6% of the patients (n = 766), so we used the postal code of the treating diabetes center as proxy.

Indicators of Diabetes Care

Indicators of medical treatment in our analysis were use of insulin pump therapy (CSII), use of CGMS, frequency of self-monitoring of blood glucose (SMBG), use of rapid-acting insulin analogs and use of long-acting insulin analogs in patients on injection therapy, and participation in diabetes education programs. CGMS includes real-time CGM and CGM with intermittent scanning, also called "flash glucose monitoring." Diabetes education was documented if a teaching session lasted for at least 45 min and if the patient and/or members of his or her family or other caregivers participated (21).

Indicators of outcome quality were BMI, presence of overweight or obesity, HbA_{1c}, rates of severe hypoglycemia (with or without coma) and of severe hypoglycemia with coma, rates of diabetic ketoacidosis (DKA) and of severe DKA, and number of hospital days per person and year (/PY). BMI values, expressed as weight in kilograms/squared height in meters (kg/m^2), were transformed to a BMI SD score (BMI SDS) using national reference data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (22). A BMI above the 90th or 97th percentile of this reference population was defined as overweight (including obesity) or obesity, respectively (22), according to the German national guideline (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [AGA]) (23) and the European Childhood Obesity Group (ECOG) guideline (24). HbA_{1c} was standardized to the Diabetes Control and Complications Trial (DCCT) reference of 4.05–6.05% (21–43 mmol/mol), applying the "multiple-of-the-mean" transformation method to adjust for differences between local laboratories (25). Severe hypoglycemia (with or without coma) was defined as self-reported unconsciousness, convulsion, or being unable to take glucose without third-party assistance (26) or, in preschool children, as an altered mental status and an inability to assist in hypoglycemia treatment (27). DKA was defined as pH $<$7.3 and/or requirement of hospital treatment; severe DKA was defined as pH $<$7.1. DKA at diabetes onset was not considered in this analysis.

Statistical Analysis

We present descriptive data as median (lower–upper quartile), percentage, or rate per 1 or 100 PYs for continuous, categorical, and event variables, respectively.

To illustrate the regional distribution of CSII, HbA_{1c}, prevalence of overweight, rate of severe hypoglycemia, and rate of DKA at district level in Germany, we created quintile-based choropleth maps (Fig. 1*B*–*F*). Choropleth maps display areas that are shaded or patterned in relation to the level of the variable of interest. They are frequently used to visualize the geographical distribution of health outcomes (28) and also in the field of diabetes research (29). For this purpose, we derived district-specific adjusted mean estimates (least square means) for each of these outcomes from multivariable regression models (linear, logistic, or Poisson considering overdispersion) with district as the categorical independent variable, adjusting for sex, age group ($<$6 years, 6 to $<$12 years, 12 to $<$20 years), migration background (defined as at least one parent or the child born outside Germany), and diabetes duration ($<$2 years, $\geq$2 years). Adjusted mean estimates for districts were then categorized into outcome quintiles.

To investigate the association between the GIMD 2010 quintiles and indicators of diabetes care, we performed multivariable regression models (linear, logistic, or Poisson considering overdispersion) with GIMD 2010 quintiles as the categorical independent variable and adjusting for sex, age group, migration background, and diabetes duration. In a second step, we also adjusted for German federal state in regression models to investigate whether the effects of area deprivation were independent of the federal structure of Germany. All analyses were repeated stratified by sex to examine possible differences in the associations of GIMD 2010 with indicators of care between girls and boys.

The number of cases used in the analysis of each variable is indicated in the tables and figures. Results of regression analyses are presented as adjusted mean estimates (least square means) with 95% CIs. *P* values were adjusted for multiple testing using the false discovery rate (FDR)-controlling Benjamini-Hochberg procedure (30). The level of significance of two-sided tests was set at $P < 0.01$. Statistical analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC). Choropleth maps were created using QGIS 2.14 open source software.

RESULTS

The study population comprised 29,284 children and adolescents with type 1 diabetes (selection presented in Supplementary Fig. 1). Of all subjects included, 45.6% used CSII, 6.3% used CGMS, and 46.8% had participated in a diabetes education program. Median HbA_{1c} was 7.62% (60 mmol/mol; interquartile range 6.94–8.50% [52–69 mmol/mol]). The rate was 10.2 events/100 PYs for severe hypoglycemia and 1.8 events/100 PYs for DKA. Data showed that 13.4% of the patients were overweight (including obesity) and 3.5% were obese. The number of hospital days was 4.9/PY. Demographic data of the study population stratified by GIMD 2010 quintiles are given in Table 1. Results of regression models for CSII, HbA_{1c}, prevalence of overweight, rate of severe hypoglycemia, and rate of DKA are illustrated graphically (Fig. 2); results for other outcomes are presented in Table 2.

Medical Treatment

Visual comparison of the regional distributions of CSII and GIMD 2010 (Fig. 1) indicated that CSII was used less frequently in the least deprived districts. Regression analyses with and without adjusting for federal state confirmed this impression (CSII use was 41.7% in Q1 and 42.4–48.0% in other quintiles, in the model adjusting for federal state), but showed further that use of CSII decreased from Q2 to Q5 (Fig. 2*A*). Regression analyses, with and without adjusting for federal state, showed that CGMS was used less frequently in districts with higher deprivation (3.4% in Q5 vs. 6.3% in Q1 in the model adjusting for federal state) (Table 2). Rapid-acting insulin analogs among patients on injection therapy tended to be used more frequently with increasing area deprivation according to the model not considering federal states. However, differences between deprivation quintiles became smaller after adjusting for federal state (79.0% in Q5 vs. 74.7% in Q1). In the model without federal states, the pattern of association between long-acting insulin analogs and area deprivation appeared to be more complex (highest use in Q1 and Q5, lowest use in Q2 and Q3). After adjustment for federal state, long-acting insulin analogs tended to be used less frequently with increasing area deprivation (64.3% in Q5 vs. 80.8% in Q1 and Q3). In all models, associations with frequency of SMBG were not significant. With increasing area deprivation, patients and their families participated more often in diabetes education programs, but these associations were no longer significant after additional adjustment for federal state.

Outcome Quality

Visual comparison of the regional distributions of HbA_{1c} and GIMD 2010 (Fig. 1) indicated that HbA_{1c} was higher in the most deprived districts. Regression analyses with and without adjusting for federal state confirmed this finding.

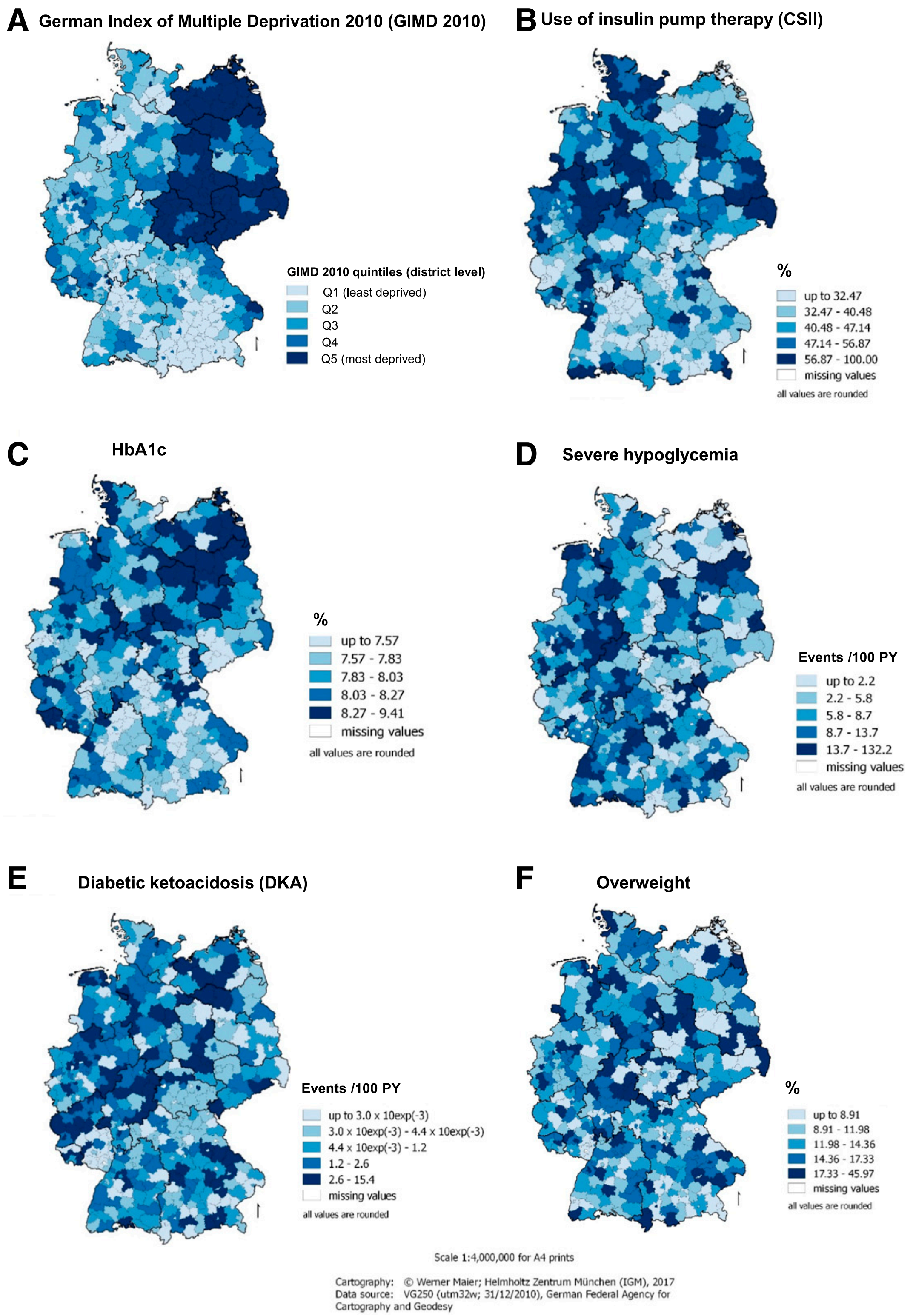

Figure 1—Quintile-based distribution of the GIMD 2010 (*A*) and of selected indicators of type 1 diabetes care at district level (*B*–*F*). *B*–*F*: Adjusted mean estimates (least square means) from regression models (linear, logistic, and Poisson), adjusting for sex, age-group, migration, and diabetes duration, with district as the categorical independent variable, categorized into outcome quintiles.

Average HbA_{1c} increased almost linearly from the least to the most deprived districts (from 7.84% [62 mmol/mol] in Q1 to 8.07% [65 mmol/mol] in Q5, after adjusting for federal state) (Fig. 2*B*). In contrast to HbA_{1c}, the rate of severe hypoglycemia (with or without coma) decreased in all models with higher area deprivation (from 12.1 events/100 PYs to 6.9 events/100 PYs in the model adjusted for federal state) (Fig. 2*C*), whereas the rate of severe

Table 1—Characteristics of the study population by GIMD 2010 quintiles

	All patients n = 29,284	Q1 n = 7,109	Q2 n = 7,541	Q3 n = 5,353	Q4 n = 5,804	Q5 n = 3,477
Girls, %	47.2	46.7	48.1	48.2	46.2	46.6
Age, years*	13.4 (9.8–16.2)	13.5 (9.9–16.3)	13.4 (9.9–16.2)	13.3 (9.8–16.2)	13.3 (9.7–16.2)	13.1 (9.7–16.0)
Age at onset, years*	7.7 (4.4–11.1)	7.8 (4.4–11.2)	7.6 (4.4–11.1)	7.8 (4.4–11.1)	7.6 (4.4–11.1)	7.7 (4.5–11.1)
Diabetes duration, years*	4.0 (1.3–7.5)	4.0 (1.4–7.5)	4.1 (1.4–7.6)	4.0 (1.3–7.5)	3.9 (1.2–7.5)	3.7 (1.2–7.3)
Migration background, %	21.6	21.1	23.7	22.5	23.9	13.3
East German residence (new federal states), %	15.9	0.0	0.4	3.1	30.5	77.3

Unadjusted data. *Data are median (lower–upper quartile).

hypoglycemia with coma did not vary significantly with area deprivation level (Table 2). Positive associations between area deprivation and DKA (Fig. 2*D*) or severe DKA (pH $<$7.1) (Table 2) were not significant. The prevalence of overweight (including obesity) increased steadily with area deprivation, and this association was stronger when additionally adjusting for federal state (from 11.8% in Q1 to 15.5% in Q5) (Fig. 2*E*). The pattern of association was similar for BMI SDS (Table 2). The increase in obesity prevalence was not significant. The number of hospital days (rate/PY) increased with higher area deprivation in the model not adjusting for federal state, but this association was no longer significant after controlling for federal state (Table 2).

Analysis by Sex

Considering the model adjusting for federal state, stratified by sex, the results were similar in boys and girls except for a slightly but significantly less frequent SMBG only in boys in Q5 compared with other deprivation quintiles (Supplementary Table 2).

CONCLUSIONS

We found that area deprivation was associated with the use of CSII, CGMS, rapid-acting or long-acting insulin analogs, HbA_{1c} levels, the rate of severe hypoglycemia, BMI SDS, and the prevalence of overweight, independently of the federal states. Associations of other factors with area deprivation were not significant regardless of the model considered or no longer significant after adjustment for federal state.

Our analysis showed a significantly less frequent use of CSII in the least deprived districts (Q1) compared with others (Q2–Q5). In Germany, CSII is reimbursed on a case-by-case basis, if certain medical criteria have been met (leading to approval by the health insurance company), for instance, if intensified conventional insulin therapy is not sufficient to achieve goals for glycemic control (14). We found the lowest HbA_{1c} levels in the least deprived districts (Q1) where pump use was also less frequent. It is possible that HbA_{1c} goals in these districts (Q1) are more often achieved with intensified conventional insulin therapy compared with more deprived districts, so that medical criteria for reimbursement of CSII are less frequently met. Further, in districts in deprivation quintiles Q2 to Q5, CSII was used less frequently with increasing area deprivation. This pattern may be associated with the uncertainty of reimbursement of the insulin pump, which may constitute an obstacle for some families in more deprived regions. Associations between socioeconomic factors and the use of CSII have been rarely investigated. However, some studies have indicated that individuals in higher socioeconomic groups injected insulin more frequently and were also more likely to use insulin pumps (13).

We found that CGMS was used less in more deprived districts. Associations between area deprivation or individual socioeconomic status (SES) and CGMS have not been investigated yet. Since June 2016 only, real-time CGM but not intermittent scanning CGM has been reimbursed by statutory health insurance in Germany. Absence of reimbursement until this date may have led to avoidance of CGMS use, particularly in more deprived regions.

Use of rapid-acting insulin analogs was positively associated with area deprivation, whereas long-acting insulin analogs were used less frequently with increasing area deprivation, after adjustment for federal state. Here, many factors may interact in a complex manner. Possible explanations include differences in patients' health insurance (private vs. statutory) or regionally different local discount agreements with pharmaceutical companies (15).

With regard to indicators of outcome quality, our results concerning the association between area deprivation and HbA_{1c} are in line with the findings from previous studies. Several reports on patients with type 1 diabetes have shown significant associations between higher area deprivation and poorer metabolic control in children (9) and adults (11).

We also found a positive association between area deprivation and overweight or BMI SDS, and these findings are also consistent with previous reports in the general population (8,31). For example, significant associations between area deprivation and obesity have been reported in adults in Germany, after controlling for education (8). A strong association between area deprivation and weight status was also confirmed in British children: children living in more deprived locations had both greater waist circumference and greater body mass, even after controlling for confounders (age, sex, stature, hip circumference) (31).

In contrast to previous reports (32), we found a negative association between area deprivation and the rate of severe hypoglycemia (with or without coma). Recent studies have demonstrated that the evidence for an association between low HbA_{1c} and hypoglycemia risk in type 1 diabetes no longer exists (33). However, we cannot exclude the possibility that in our setting, the lower rate of severe hypoglycemia in the most deprived districts is associated with higher

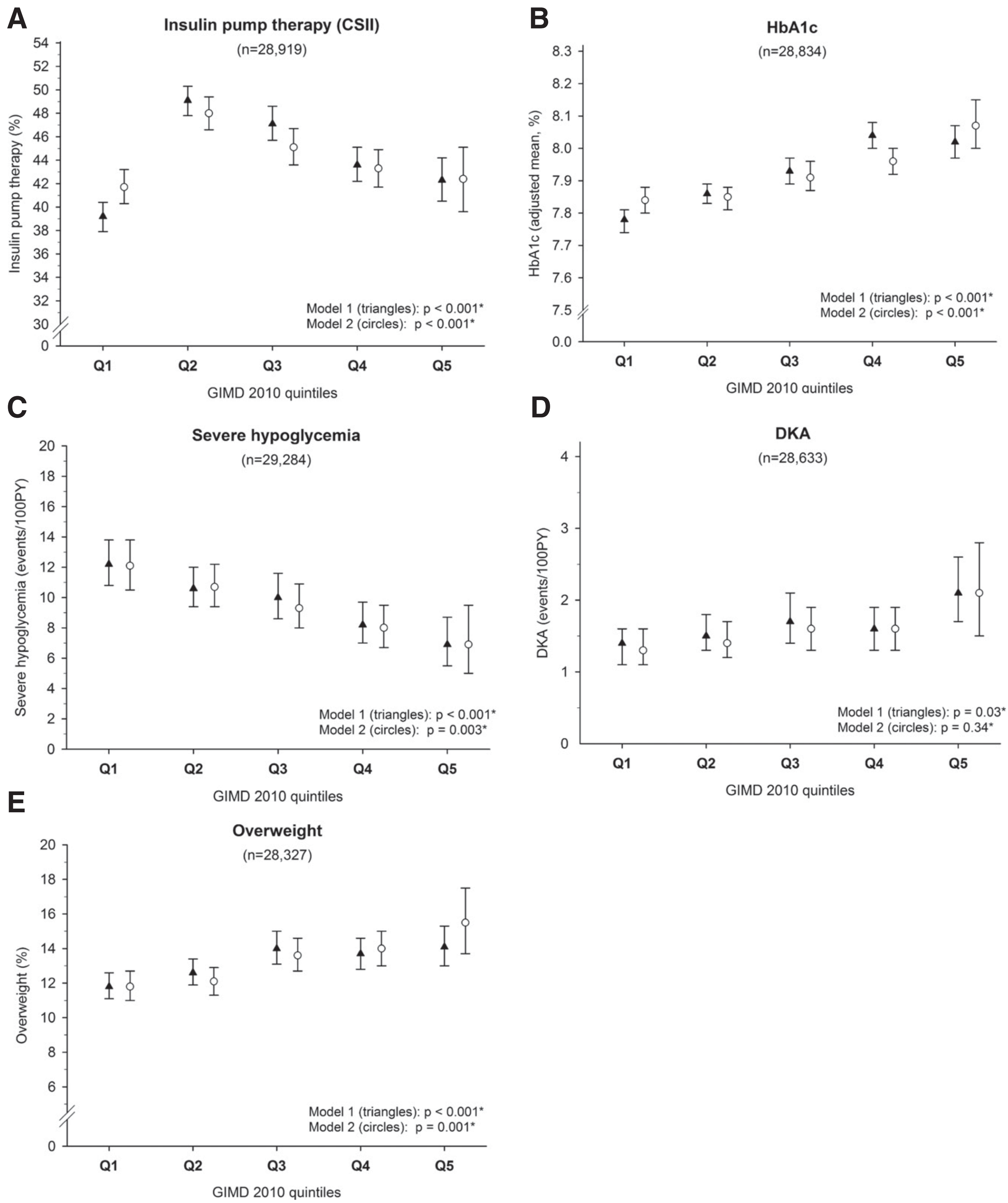

Figure 2—Multiple adjusted mean estimates of indicators of type 1 diabetes care by GIMD 2010 quintiles: CSII (*A*), HbA_{1c} (*B*), severe hypoglycemia (*C*), DKA (*D*), and overweight (*E*). Model 1 (triangles): Adjusted mean estimates (least square means) from regression models (linear, logistic, and Poisson), with GIMD 2010 quintiles as the categorical independent variable, adjusting for sex, age-group, migration, and diabetes duration. Model 2 (circles): Adjusted mean estimates (least square means) from regression models (linear, logistic, and Poisson), with GIMD 2010 quintiles as the categorical independent variable, adjusting for sex, age group, migration, diabetes duration, and federal state. **P* values were adjusted for multiple testing using the FDR-controlling Benjamini-Hochberg procedure (30).

HbA_{1c}, which is related to higher area deprivation in our study. Another hypothesis could be that parents of children with type 1 diabetes living in more deprived areas tend to underreport severe hypoglycemia (minimization of the medical relevance or social desirability bias) compared with parents of children living in less deprived districts. In

Table 2—Multiple adjusted mean estimates (95% CI) of indicators of type 1 diabetes care by GIMD 2010 quintiles

Outcome	*n*	Model	Q1	Q2	Q3	Q4	Q5	*P* value*
Treatment								
CGMS, %	29,284	1	7.3 (6.7–7.9)	5.6 (5.2–6.2)	5.6 (5.1–6.3)	4.8 (4.3–5.4)	4.5 (3.9–5.2)	<0.001
		2	6.3 (5.7–7.0)	5.6 (5.1–6.2)	5.7 (5.1–6.4)	5.3 (4.7–6.0)	3.4 (2.7–4.3)	0.002
Rapid-acting insulin analogs, %	15,719**	1	66.8 (65.3–68.3)	70.4 (68.8–71.9)	66.7 (64.8–68.5)	78.0 (76.5–79.5)	87.8 (86.2–89.2)	<0.001
		2	74.7 (73.1–76.2)	75.9 (74.3–77.4)	70.9 (68.9–72.7)	76.7 (74.9–78.3)	79.0 (75.8–81.8)	<0.001
Long-acting insulin analogs, %	15,719**	1	77.8 (76.5–79.2)	71.5 (69.9–73.0)	75.2 (73.4–76.8)	72.5 (70.8–74.1)	81.2 (79.4–82.9)	<0.001
		2	80.8 (79.4–82.2)	77.3 (75.8–78.8)	80.8 (79.3–82.3)	72.4 (70.5–74.3)	64.3 (60.4–68.0)	<0.001
SMBG, times/day	27,335	1	5.8 (5.7–5.8)	5.7 (5.7–5.8)	5.8 (5.7–5.8)	5.7 (5.7–5.8)	5.6 (5.6–5.7)	0.02
		2	5.7 (5.7–5.8)	5.7 (5.7–5.8)	5.7 (5.7–5.8)	5.8 (5.8–5.9)	5.7 (5.6–5.8)	0.03
Diabetes education program, %	29,284	1	44.2 (43.0–45.4)	46.8 (45.7–48.0)	46.1 (44.8–47.5)	47.7 (46.4–49.0)	51.7 (50.0–53.5)	<0.001
		2	46.0 (44.6–47.4)	48.2 (47.0–49.5)	46.6 (45.1–48.1)	46.6 (45.1–48.1)	46.0 (43.4–48.7)	0.18
Outcome quality								
Severe hypoglycemia with coma, events/100 PYs	29,284	1	1.8 (1.5–2.2)	2.1 (1.8–2.5)	2.5 (2.1–3.0)	2.0 (1.7–2.4)	1.6 (1.3–2.2)	0.06
		2	1.9 (1.6–2.3)	1.9 (1.6–2.3)	2.2 (1.8–2.7)	1.9 (1.5–2.3)	1.8 (1.2–2.6)	0.76
Severe DKA (pH <7.1), events/100 PYs	28,965	1	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.3 (0.2–0.4)	0.2 (0.2–0.4)	0.4 (0.3–0.7)	0.04
		2	0.2 (0.1–0.3)	0.1 (0.1–0.3)	0.2 (0.1–0.5)	0.2 (0.1–0.5)	0.3 (0.1–0.8)	0.48
BMI SDS	28,327	1	0.28 (0.26–0.30)	0.33 (0.31–0.35)	0.35 (0.33–0.37)	0.33 (0.31–0.35)	0.36 (0.33–0.39)	<0.001
		2	0.26 (0.24–0.29)	0.29 (0.27–0.32)	0.33 (0.31–0.36)	0.35 (0.33–0.38)	0.46 (0.41–0.50)	<0.001
Obesity, %	28,327	1	3.2 (2.8–3.6)	3.0 (2.6–3.4)	3.7 (3.2–4.2)	3.6 (3.2–4.2)	3.8 (3.2–4.5)	0.07
		2	3.2 (2.8–3.7)	2.8 (2.5–3.3)	3.6 (3.1–4.2)	3.7 (3.2–4.3)	3.9 (3.0–5.0)	0.10
Number of hospital days/1 PY	29,284	1	3.9 (3.3–4.6)	4.5 (3.9–5.3)	4.5 (3.8–5.4)	4.7 (4.0–5.6)	6.8 (5.7–8.2)	<0.001
		2	4.2 (3.5–5.0)	4.7 (4.0–5.5)	4.5 (3.8–5.5)	4.7 (3.9–5.6)	5.1 (3.8–7.0)	0.85

Model 1: Adjusted mean estimates (least square means) with respective 95% CI derived from logistic regression analysis (for outcomes use of CGMS, use of rapid-acting insulin analogs, use of long-acting insulin analogs, participation in diabetes education program, prevalence of obesity), linear regression analysis (for outcomes SMBG, BMI SDS), or Poisson regression analysis considering overdispersion (for outcomes rate of severe hypoglycemia with coma, rate of severe DKA [pH <7.1], number of hospital days). All regression models were performed with GIMD 2010 quintiles as the categorical independent variable and adjusting for sex, age group, migration background, and diabetes duration. Model 2: Estimates from regression models additionally adjusted for German federal state. **P* value of test of no difference in outcome distribution across GIMD quintiles. *P* values were adjusted for multiple testing using the FDR-controlling Benjamini-Hochberg procedure (30). ** Only patients without CSII.

fact, in contrast to DKA, which requires a visit to the diabetes care center, severe hypoglycemia can be treated by patients or parents themselves and may easily be forgotten until the next medical visit. In accordance with this explanation, no association was observed between area deprivation and severe hypoglycemia with coma, where underreporting is less likely.

In our results, higher area deprivation tended to be associated with higher risk of hospital admission for DKA, and this is consistent with previous findings (34).

Overall, many factors may contribute to the differences in treatment and outcome quality in pediatric patients with type 1 diabetes within Germany. The GIMD 2010 partly reflects East–West inequalities in Germany: districts in less deprived quintiles were mostly located in the western part, whereas districts in the most deprived quintiles were mostly located in the eastern part of the country (Table 1 and Fig. 1*A*). Although the living conditions in former East and West Germany have slowly converged since German reunification (35), economic performance is still lower and the proportion of people affected by poverty and unemployment remains higher in the eastern part of the country (36). The health status of children and adolescents has become more similar, but some important differences in health behavior still remain. In particular, compared with peers living in the western part of the country, more adolescents in the eastern part regularly drink alcohol or smoke, and fewer children are members of a sports club (37). However, our study indicates that half of the analyzed diabetes-related outcomes (use of CSII, CGMS, or insulin analogs; HbA_{1c}; rate of severe hypoglycemia; BMI SDS; and prevalence of overweight) were significantly associated with area deprivation independently of the federal state and, thus, independently of East–West disparities.

The major strength of this study is its very large sample size with patients from a large number of diabetes care centers throughout the country. We used a nationwide diabetes follow-up registry covering more than 85% of the pediatric subjects with type 1 diabetes in Germany, so that the results can be considered as representative of this population. Moreover, detailed information on the patients' demographic and clinical characteristics was available, which allows comprehensive control of potential confounders.

One limitation of this study is that analyses could not consider individual-level SES. In DPV, education level is incompletely documented, and household income is not available. Studies on patients with type 2 diabetes have demonstrated that the effect of area deprivation remains significant after controlling for individual SES (8,19). Maier et al. (19) argue that individual SES and area deprivation may "act through different pathways." For instance, a strong social safety net, as well as dedicated resources through social spending to "stable housing, educational opportunities, nutrition, and transportation," is considered to play a decisive role in enhancing the quality of care, especially for populations with lower income, lower educational level, or minority status (38).

Another weakness is the heterogeneity of German districts: they are administrative units that vary considerably in area and population size (from ~35,000 up to more than 1 million inhabitants). We assume that the analysis could be less sensitive in larger districts than in smaller ones. However, the influence of extreme values in single domains of the GIMD is limited because a ranking transformation was used in the algorithm for the index calculation. Furthermore, because pediatric diabetes health care in Germany is organized at the district level, heterogeneity within districts may play a less important role.

Further shortcomings of this study are that complete data were not available for each patient, and variability in the measurements of clinical characteristics cannot be completely excluded because of the multicenter design. However, we standardized locally measured HbA_{1c} values to the DCCT standard. Furthermore, because of the cross-sectional design, this study does not allow us to draw any causal interpretation. Finally, the nature of the database does not allow in-depth analysis of all possibly important determinants (e.g., individual socioeconomic data), and the nature of the German diabetes care system limits generalizability of the findings.

In conclusion, we showed that in pediatric patients with type 1 diabetes in Germany, area deprivation was significantly associated with many indicators of treatment and outcome quality, independently of the federal state. In particular, our findings suggest that a focus on equal access to diabetes treatment, such as CGMS and CSII, is important because treatment is a directly modifiable factor. Moreover, diabetes technology may improve metabolic control regardless of educational level (39). Consequently, better access to diabetes technology in the most deprived areas may improve the quality of care of pediatric type 1 diabetes, even in high-income countries.

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- co-formulation of the research question
- co-development of the methodology and study design
- data preparation and statistical analysis
- interpretation of the results of the statistical analysis
- creation of the figures
- writing of parts of “research design and methods” and “results” and critical contribution to the manuscript

A Decade of Disparities in Diabetes Technology Use and HbA_{1c} in Pediatric Type 1 Diabetes: A Transatlantic Comparison

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Ananta Addala,[1] Marie Auzanneau,[2,3] Kellee Miller,[4] Werner Maier,[3,5] Nicole Foster,[4] Thomas Kapellen,[6] Ashby Walker,[7] Joachim Rosenbauer,[3,8] David M. Maahs,[1,9] and Reinhard W. Holl[2,3]

OBJECTIVE

As diabetes technology use in youth increases worldwide, inequalities in access may exacerbate disparities in hemoglobin A_{1c} (HbA_{1c}). We hypothesized that an increasing gap in diabetes technology use by socioeconomic status (SES) would be associated with increased HbA_{1c} disparities.

RESEARCH DESIGN AND METHODS

Participants aged <18 years with diabetes duration ≥1 year in the Type 1 Diabetes Exchange (T1DX, U.S., n = 16,457) and Diabetes Prospective Follow-up (DPV, Germany, n = 39,836) registries were categorized into lowest (Q1) to highest (Q5) SES quintiles. Multiple regression analyses compared the relationship of SES quintiles with diabetes technology use and HbA_{1c} from 2010–2012 to 2016–2018.

RESULTS

HbA_{1c} was higher in participants with lower SES (in 2010–2012 and 2016–2018, respectively: 8.0% and 7.8% in Q1 and 7.6% and 7.5% in Q5 for DPV; 9.0% and 9.3% in Q1 and 7.8% and 8.0% in Q5 for T1DX). For DPV, the association between SES and HbA_{1c} did not change between the two time periods, whereas for T1DX, disparities in HbA_{1c} by SES increased significantly (P < 0.001). After adjusting for technology use, results for DPV did not change, whereas the increase in T1DX was no longer significant.

CONCLUSIONS

Although causal conclusions cannot be drawn, diabetes technology use is lowest and HbA_{1c} is highest in those of the lowest SES quintile in the T1DX, and this difference for HbA_{1c} broadened in the past decade. Associations of SES with technology use and HbA_{1c} were weaker in the DPV registry.

Over the past decade, utilization of diabetes technology, such as insulin pumps and continuous glucose monitors (CGMs), for the management of pediatric type 1 diabetes has increased worldwide (1–3). Diabetes technology in the management of pediatric type 1 diabetes is associated with improved hemoglobin A_{1c} (HbA_{1c}) and quality of life and decreased rates of both diabetic ketoacidosis and severe hypoglycemia (2,4–7). Although the Type 1 Diabetes Exchange (T1DX) and Diabetes Prospective Follow-up (Diabetes-Patienten-Verlaufsdokumentation [DPV]) registries have demonstrated increasing adoption of diabetes technology in the past decade (1,2,8), there is a concern of inequities in device use by socioeconomic status (SES) (9–11).

[1]Division of Pediatric Endocrinology, Stanford University, Stanford, CA
[2]University of Ulm, Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm, Germany
[3]German Center for Diabetes Research (DZD), Neuherberg, Germany
[4]Jaeb Center for Health Research, Tampa, FL
[5]Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Health Economics and Health Care Management, Neuherberg, Germany
[6]University of Leipzig, Department of Women and Child Health, Hospital for Children and Adolescents, Leipzig, Germany
[7]Health Equity Initiatives, UF Diabetes Institute, University of Florida, Gainesville, FL
[8]Leibniz Center for Diabetes Research at Heinrich Heine University, Institute for Biometrics and Epidemiology, German Diabetes Center, Düsseldorf, Germany
[9]Stanford Diabetes Research Center, Stanford, CA

Corresponding author: Ananta Addala, aaddala@stanford.edu

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Area deprivation indices, such as the German Index of Multiple Deprivation (GIMD) 2010, have been used as proxy measures when individual SES variables were not available in registries (12,13). Data from Scotland, evaluating all age-groups, and the DPV, evaluating those age <20 years, demonstrated that lower area-level SES was associated with lower rates of insulin pump therapy as well as higher HbA_{1c} and higher rates of diabetic ketoacidosis (14–16). Additionally, the T1DX registry reported both a lower use of diabetes technology and a higher HbA_{1c} for pediatric patients with lower SES and for those of minority status (1,2,17). These data raise the concern that inequitable access to diabetes technology may widen disparities in diabetes outcomes in pediatric patients with type 1 diabetes, especially as data accumulate on improved outcomes with closed-loop and hybrid closed-loop systems (18–20).

In this study, we compare the use of diabetes technology and HbA_{1c} for youth in the T1DX and DPV registries by SES between two time periods: 2010–2012 and 2016–2018. We hypothesized that youth of lower SES, compared with those of higher SES, would have lower rates of diabetes technology use and higher HbA_{1c}. In addition, we hypothesized that disparities of technology use and HbA_{1c} by SES increased over the past decade.

RESEARCH DESIGN AND METHODS

Registries

The T1DX was established in September 2010 and includes 73 U.S.-based pediatric and adult endocrinology clinics that have contributed 18,001 records to the registry as of January 2018. Each participating clinic received approval from its respective institutional review board, and for minors, parent/guardian consent was obtained as well as assent from the minor. Data were collected for inclusion in the registry from the participants' electronic medical records and comprehensive questionnaires completed by participants and/or their parent/guardian, as previously published (1,2,17). Demographic and clinical data collected at each center is anonymized and shared with the Jaeb Center for Health Research for quality assurance and data storage.

As of September 2018, the DPV registry included 538,531 records from 480 diabetes care centers predominantly located in Germany. Each center participating in DPV received approval from its respective institutional review boards. Demographic and clinical data were prospectively collected at each participating center, anonymized, and shared with the University of Ulm for analysis and quality assurance (21), with approval from the Medical Faculty Ethics Committee of the University of Ulm (16). Clinical sites for the DPV and T1DX registries are listed in the Supplementary Material.

Study Population

Participants in the T1DX and DPV registries aged <18 years with type 1 diabetes duration ≥1 year who had data registered in the 2010–2012 period, the 2016–2018 period, or both periods were included in this study for analysis. For DPV, only patients with German residence were included. Participants without information on minority status in the electronic medical record were excluded in T1DX (n = 45). In DPV, participants with information on migration background missing were assumed to have no history of migration. Individuals without information on address or district of residence in the DPV registry (n = 261) and those who did not have sufficient SES documentation in the T1DX registry (n = 1,486) were excluded from the analysis because these variables were required for our analytical models and for categorizing participants into SES quintiles. The final study population comprised 16,457 individuals for T1DX and 39,836 individuals for DPV.

Variables

Clinical Data

For both registries, demographic data, CGM use (defined as all systems that measure interstitial glucose values, e.g., real-time or intermittent CGM), and insulin modality (injections or insulin pump) were captured. Type 1 diabetes diagnosis was established clinically by physicians and by documentation of insulin use as well as age at onset ≥6 months. Adjusting for age and sex, BMI z score was computed according to Cole's least mean squares method using World Health Organization reference tables (22). For DPV and T1DX, HbA_{1c} was standardized to the reference range of the Diabetes Control and Complications Trial (DCCT) (4.05–6.05% [20.7–42.6 mmol/mol]) using the multiple of the mean method to adjust for differences between laboratories (23,24).

SES Quintiles

Insurance type, education level, annual income for T1DX, and the GIMD 2010 for DPV (16) were incorporated to categorize participants (or their districts of residence) into SES quintile–based groups from Q1 (lowest SES) to Q5 (highest SES). Because of data protection concern, a valid measure of individual-level SES was not available for Germany. In DPV, education level is incompletely documented, and household income is not available (16). Information on health insurance is missing in the DPV registry; however, in Germany, all children are covered by health insurance, and the differences between insurances for diabetes technology reimbursement are minimal or absent (16). The GIMD is a validated measure of area deprivation for Germany (16) that is based on the methodology of Noble et al. (25). This methodology is based on the >40 years of experience of indices to measure deprivation at a local level in the U.K. (25). The GIMD methodology has been previously described (16,26). The German index for the reference year 2010 (GIMD 2010) includes aggregated data for the 412 districts of Germany in seven deprivation domains, each weighted differently: income (25%), employment (25%), education (15%), municipal/district revenue (15%), social capital (10%), environment (5%), and security (5%) (16,26). The districts were categorized into deprivation quintiles according to the GIMD 2010. For the DPV registry, patients were assigned to districts using the five-digit postal code of their residence. For the 132 records that had missing postal codes, we used the postal code of the diabetes clinic where patients receive treatment.

For the T1DX registry, we calculated a composite SES score composed of three individual variables that were equally weighted: education level (highest of either parent), insurance type, and annual income. Education level was coded from 1 to 6 (professional/doctoral degree = 1; master's degree = 2; bachelor's degree = 3; associate's degree = 4; high school diploma = 5; less than high school diploma = 6). Insurance was coded as 1 (private), 3 (public), and 6 (no insurance). Annual income was coded from

1 to 6 (≥\$100,000 = 1; <\$100,000 to \$75,000 = 2; <\$75,000 to \$50,000 = 3; <\$50,000 to \$35,000 = 4; <\$35,000 to \$25,000 = 5; <\$25,000 = 6). If one of the three domains was not documented (n = 4,208), it was replaced by the mean of the domain; if two or more domains were missing, the records were excluded (n = 1,486 patients).

Minority Status

For the DPV registry, minority status is defined as youth with personal or any parental history of being born outside of Germany. For the T1DX registry, minority status was defined as any participant race/ethnicity other than non-Hispanic white. These definitions are consistent with prior joint publications (1,16,21).

Statistical Analysis

For each time period in DPV, we aggregated participant's data from the most recent year as median (BMI, HbA_{1c}) or maximum (age, diabetes duration). Pump and CGM use were defined as at least one pump use or CGM use documented in the last treatment year. In T1DX, we used participant data from the last visit in each time period. Age was categorized into three groups (1 to <6, 6 to <12, and 12 to <18 years) and diabetes duration into three groups (1 to <2, 2 to <5, and ≥5 years). All analyses were conducted for each registry separately because different methodologies were used to assess SES. We analyzed the effect of SES on the three outcomes (pump use, CGM use, and HbA_{1c}) within each time period and compared these effects between time periods.

We performed logistic (for pump and CGM use) and linear (for HbA_{1c}) multiple regression with SES, time period, and an interaction of SES and time period. First, we modeled SES as a categorical variable to obtain mean estimates (least mean squares) for each outcome by SES quintiles and time period. Next, we modeled SES as an ordinal variable to compare the slopes of the regression lines (effect of SES) for each outcome in each time period and to test whether associations between SES and outcomes within and between the two time periods were significantly different. All models were adjusted for sex, age-group, diabetes duration group, minority status, and interaction of minority status with SES. We repeated these analyses for HbA_{1c}, with an additional adjustment for pump and CGM use in the regression model. Considering the size of the study population, the level of significance of two-sided tests was set at $P < 0.01$. Statistical analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Study Population

Demographic data and clinical characteristics of participants are listed in Table 1 by registry in both 2010–2012 and 2016–2018. Diabetes technology use and HbA_{1c} by components of the SES and by minority are presented for DPV (area-level income and education) (Supplementary Table 1*A*) and T1DX (income, education, and insurance) (Supplementary Table 1*B*).

Primary Outcomes

Insulin Pump Use

Insulin pump use increased in the DPV and T1DX registries from 2010–2012 to 2016–2018. When examined by SES quintiles in the DPV registry, insulin pump use in 2010–2012 increased from 53.8% in Q1 and 53.0% in Q2 to 57.0% in Q4 and then decreased to 49.1% in Q5 (slope −0.028, P = 0.02). The pattern was similar in 2016–2018, with an increase from 65.5% in Q1 to 71.5% in Q4 and a decrease to 63.2% in Q5 (slope −0.009, P = 0.41) (Fig. 1*A*). In the T1DX registry, insulin pump use in 2010–2012 was 28.6% for Q1 and 70.3% for Q5 (slope 0.462, $P < 0.001$), whereas in 2016–2018, it was 36.5% for Q1 and 75.8% for Q5 (slope 0.446, $P < 0.001$) (Fig. 1*B*).

CGM Use

CGM use increased in the DPV and T1DX registries from 2010–2012 to 2016–2018. When examined by SES quintiles in the DPV registry, CGM use in 2010–2012 was 5.7% for Q1 and 3.8% for Q5 (slope −0.053, P = 0.04), whereas in 2016–2018, it was 48.5% for Q1 and 57.1% for Q5 (slope 0.068, $P < 0.001$) (Fig. 1*C*). In the T1DX population, CGM use in 2010–2012 was 2.9% for Q1 and 11.0% for Q5 (slope 0.381, $P < 0.001$), whereas in 2016–2018, it was 15.0% for Q1 and 52.3% for Q5 (slope 0.460, $P < 0.001$) (Fig. 1*D*).

HbA_{1c}

HbA_{1c} was lower in the DPV registry at both time periods compared with the T1DX registry. The most deprived quintile had the highest HbA_{1c} in both registries and both time periods. For the DPV registry, mean HbA_{1c} in 2010–2012 was 8.0% for Q1 and 7.6% for Q5 (slope −0.093, $P < 0.001$). In 2016–2018, HbA_{1c} decreased to 7.8% in Q1 and 7.5% in Q5 (slope −0.078, $P < 0.001$) (Fig. 1*E*). In the T1DX registry, mean HbA_{1c} in 2010–2012 was 9.0% for Q1 and 7.8% for Q5 (slope −0.301, $P < 0.001$). In 2016–2018, HbA_{1c} was 9.3% for Q1 and 8.0% for Q5 (slope −0.354, $P < 0.001$) (Fig. 1*F*).

HbA_{1c} by SES was additionally adjusted for pump and CGM use in a regression model. In DPV, the adjusted mean HbA_{1c} in 2010–2012 was 7.9% for Q1 and 7.5% for Q5 (slope −0.094, $P < 0.001$). In 2016–2018, the adjusted mean HbA_{1c} was 7.8% for Q1 and 7.5% for Q5 (slope −0.074, $P < 0.001$) (Fig. 1*G*). In T1DX, adjusted mean HbA_{1c} in 2010–2012 was 8.7% for Q1 and 7.7% for Q5 (slope −0.255, $P < 0.001$). In 2016–2018, adjusted HbA_{1c} was 9.1% for Q1 and 8.1% for Q5 (slope −0.276, $P < 0.001$) (Fig. 1*H*).

Comparison of the Effect of SES on Device Use and HbA_{1c} Between 2010–2012 and 2016–2018

We compared the effect of SES between the two time periods for each outcome (Fig. 2). Changes in insulin pump use by SES between the two time periods were not statistically significant in either registry. The association between lower SES quintiles and lower CGM use was more pronounced in the 2016–2018 time period for DPV ($P < 0.001$), and change was not significant for T1DX (P = 0.038). Associations between HbA_{1c} and SES were not statistically different between the two time periods for DPV, and adjusting for pump and CGM use did not modify the results. For T1DX, although HbA_{1c} increased in all SES quintiles, the HbA_{1c} increased more in those of lower SES quintiles between the two time periods (P = 0.0005). When adjusting for pump use and CGM use, the increased effect was still observed but was no longer significant.

CONCLUSIONS

In this international comparison of 56,293 youth with type 1 diabetes, differences exist in diabetes technology use and HbA_{1c} between the U.S. and Germany by SES quintiles. As previously reported (2), HbA_{1c} in the youth <18 years of age in the T1DX increased from 2010–2012 to 2016–2018. Reasons for this are

Table 1—Participant characteristics

	DPV			T1DX		
	2010–2012	2016–2018	*P* value	2010–2012	2016–2018	*P* value
Male sex	52.2 (23,167)	52.4 (26,670)	0.5654	51.2 (10,463)	51.6 (9,979)	0.5975
Age (years)			<0.0001			<0.0001
Mean ± SD	12.9 ± 3.7	13.1 ± 3.7		11.8 ± 3.6	13.0 ± 3.5	
n	23,167	26,670		10,463	9,979	
Diabetes duration (years)			<0.0001			<0.0001
Mean ± SD	5.5 ± 3.6	6.7 ± 3.7		5.1 ± 3.5	7.3 ± 3.5	
n	23,167	26,670		10,463	9,979	
Minority status†	19.1 (23,167)	23.9 (26,670)	<0.0001	20.9 (10,463)	22.3 (9,979)	0.0194
BMI *z* score			0.7498			0.0012
Mean ± SD	0.67 ± 0.9	0.67 ± 1.03		0.89 ± 1.04	0.93 ± 1.11	
n	22,917	26,543		10,315	9,838	
HbA_{1c}						
%			<0.0001			<0.0001
Mean ± SD	8.0 ± 1.4	7.9 ± 1.4		8.5 ± 1.5	8.9 ± 1.7	
n	22,872	26,400		10,409	9,601	
mmol/mol			<0.0001			<0.0001
Mean ± SD	63.9 ± 15.7	62.9 ± 15.3		69.3 ± 15.8	74.0 ± 19.0	
n	22,872	26,400		10,409	9,601	
HbA_{1c} <7.5%*	41.2 (22,872)	43.5 (26,400)	<0.0001	22.1 (10,409)	17.3 (9,601)	<0.0001
Pump use	43.9 (23,166)	56.6 (26,667)	<0.0001	57.3 (10,419)	64.9 (9,803)	<0.0001
CGM use	4.0 (23,167)	48.7 (26,670)	<0.0001	5.9 (10,409)	30.1 (9,665)	<0.0001

Data are % (*n*) unless otherwise indicated. †Defined as birthplace outside of Germany for the patient or for one or both parents in DPV and as not belonging to the non-Hispanic white group in T1DX. *Recommended HbA_{1c} target by the American Diabetes Association and International Society of Pediatric and Adolescent Diabetes during the study period.

uncertain, likely multifactorial, and require additional investigation. In this analysis, we demonstrate a strong association between HbA_{1c} and SES, both cross-sectionally and across the two time periods: the increase in HbA_{1c} was greatest in those with lower SES. Both registries demonstrate higher HbA_{1c} in youth from the lowest SES quintiles, although the magnitude of difference is greater in T1DX. In the T1DX, we report lower rates of insulin pump and CGM use in those of the lowest SES quintiles. For the DPV registry, a linear association was not observed between pump use and SES quintiles; CGM use was modestly lower in those of lowest SES in the second time period. Although a disparity between the lowest and highest SES quintiles exists with regard to HbA_{1c} in both registries, the disparity in the T1DX is greater than in the DPV, and the disparity in HbA_{1c} has widened between the two time periods in the T1DX. For the DPV registry, the CGM use gap by SES increased between 2010–2012 and 2016–2018, but this increase was not observed in insulin pump use or HbA_{1c}.

Analysis of CGM use further highlights this SES disparity when comparing CGM use by SES in 2010–2012 to 2016–2018. For T1DX, Q5 saw an increase of 41 percentage points in use between these two time points, whereas Q1 only increased use by 12 percentage points. In contrast, in the DPV registry, both Q1 and Q5 had a comparable increase in use (43 and 53 percentage points, respectively). The increase in HbA_{1c} for T1DX was no longer significant after adjustment for technology use.

These data raise important considerations for the care being provided for youth with type 1 diabetes. Despite the numerous barriers that have been documented in the delivery of care to those of lower SES (27–30), the findings from the DPV registry demonstrate more comparable HbA_{1c} outcomes for youth with type 1 diabetes across the SES spectrum. Given that this is the first report comparing device use and HbA_{1c} by SES quintiles in these two registries, the causal factors for the differences among the SES quintiles in mean HbA_{1c} and device use rates between the two countries require further investigation. Data from T1DX demonstrate an association with CGM use and HbA_{1c}, irrespective of insulin delivery (insulin pump or multiple daily injection), and CGM may be a mediator in the relationship between SES and HbA_{1c} (11).

As previously hypothesized, differences in child-rearing practices (24), access to and cost of device use (24), individual type 1 diabetes management practices (31), education (31), expectation (32) specific to devices use, maternal education level (33), and patient and provider factors (34) may also contribute to the observed difference between the two registries. Cost of insulin is higher in the U.S. than other countries, and this cost continues to increase (35,36). Additionally, out-of-pocket costs associated with some private insurance plans in the U.S. make diabetes technology access cost prohibitive, despite having insurance coverage, and the differential access to care among private payers warrants further studies. Difference in access to physicians, health care expenditure, and payer structures may also contribute to the different outcomes in each country (37). Studies in the U.S. and Europe have demonstrated disparate care and poorer outcomes across medical conditions for people of lower SES or lower education level (27,30,38).

These data have strengths and limitations. The DPV registry is population based and inclusive of >85% youth living with type 1 diabetes in Germany (16),

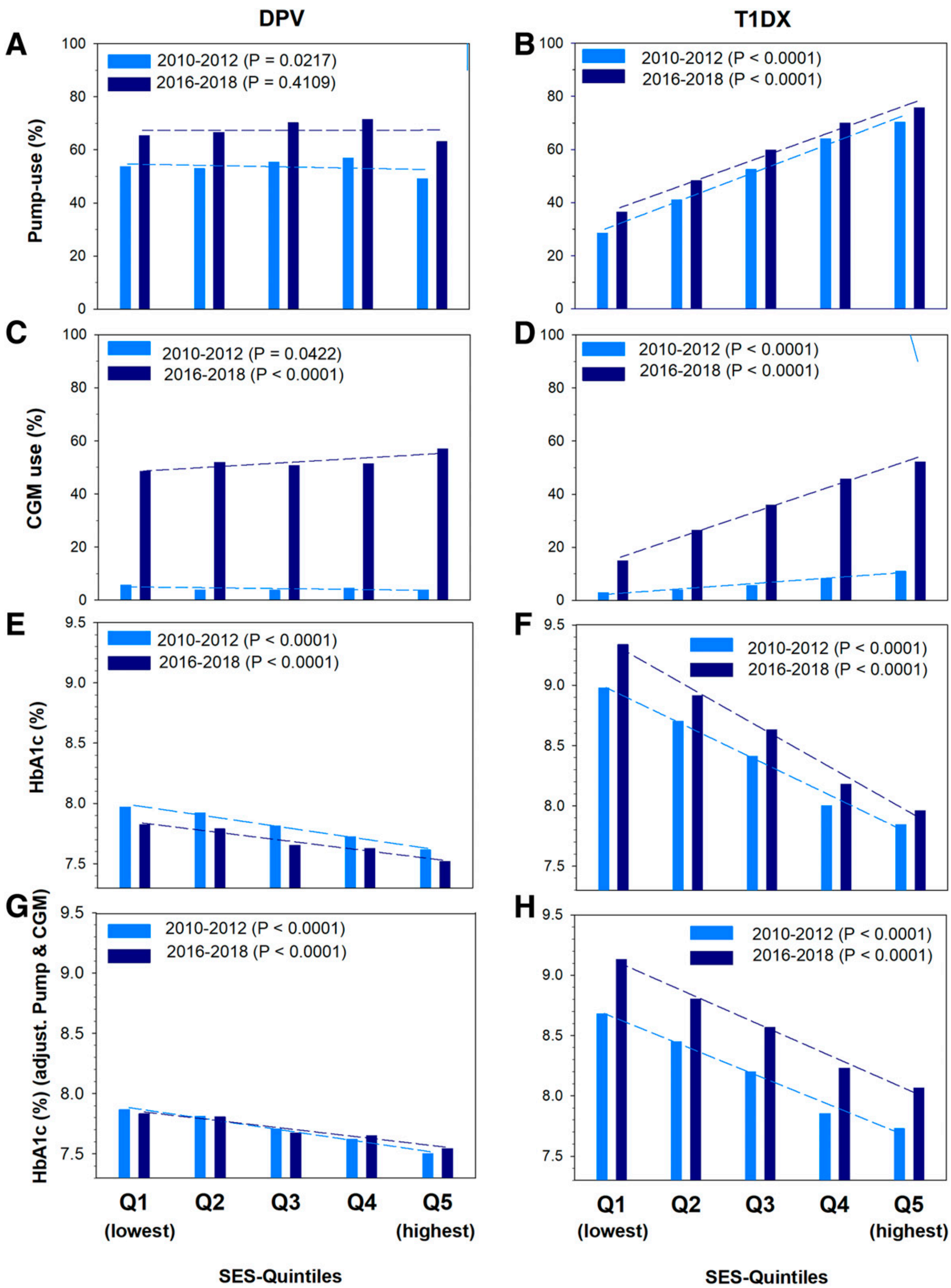

Figure 1—Pump use, CGM use, and HbA_{1c} by SES in the DPV and T1DX registries in 2010–2012 and 2016–2018. *A*–*F*: Mean estimates by SES quintiles and time period from logistic (pump use, CGM use) and linear (HbA_{1c}) regression models adjusted for sex, age, diabetes duration, SES, time period, minority status, SES-by-time period interaction, and SES-by-minority status interaction. *G* and *H*: Mean estimates with the regression model additionally adjusted for pump and CGM use. Dashed lines are connecting mean estimates for pump and CGM use or regression lines for HbA_{1c} from models including SES as an ordinal term. From these models, *P* values for trend are given for the association with SES within each time period. Q1 is the lowest and Q5 is the highest SES quintile.

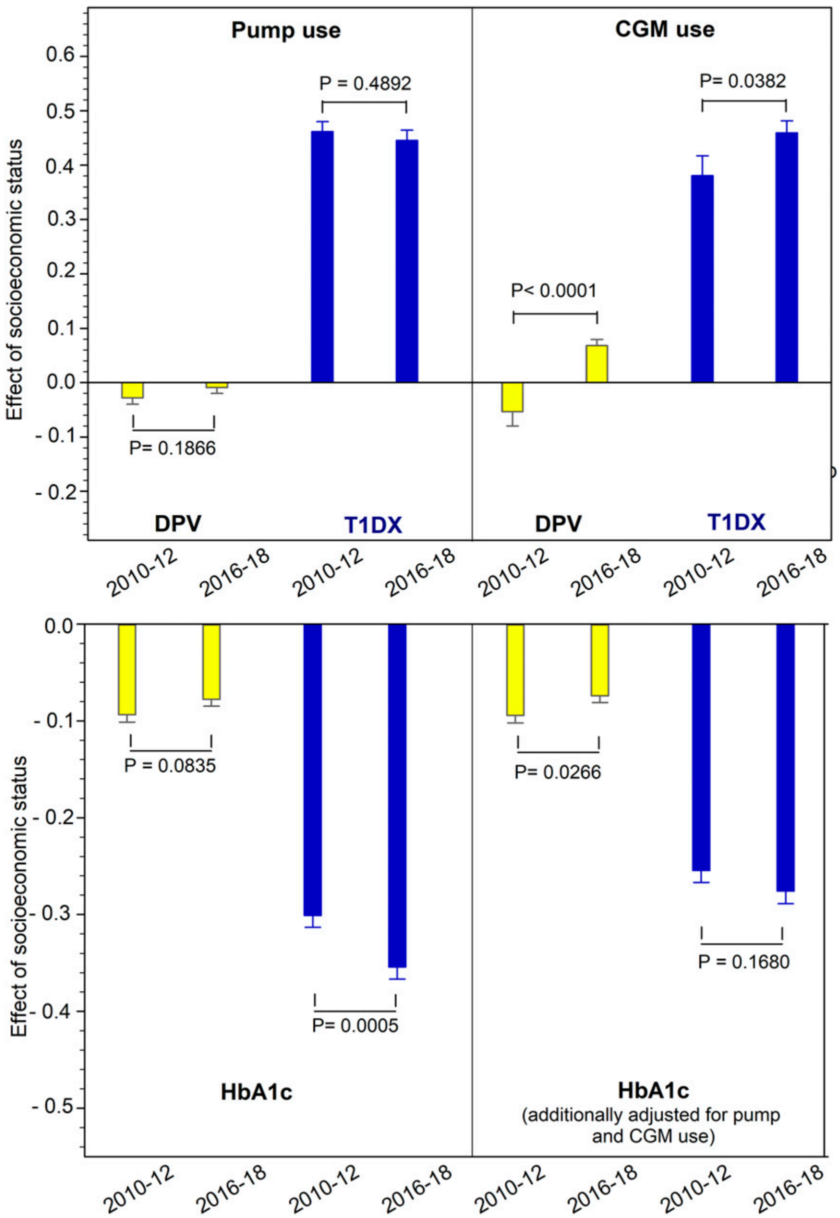

Figure 2—Effect of SES on insulin pump use, CGM use, and HbA_{1c}. Effects of SES are slopes with 95% CIs of the regression lines for the dependent variables derived from multiple regression models including sex, age, diabetes duration, SES, time period, minority status, SES-by-time period interaction, and SES-by-minority status interaction, with SES modeled as an ordinal term. A positive value in insulin pump use and CGM use indicates higher use in quintiles of higher SES. A negative value in HbA_{1c} indicates higher HbA_{1c} in quintiles of lower SES. *P* values are given for the difference in effects of SES between the two time periods.

whereas the T1DX registry is not population representative but, rather, the largest registry sample of youth with type 1 diabetes in the U.S. (29). Because of constraints in data collection for each registry (and consistent with prior joint publications [1–3]), demographic variables were processed differently (aggregate of patient values in DPV vs. most recent visit in T1DX), and minority status was defined differently (not non-Hispanic white for T1DX vs. first- or second-generation migration for DPV) because of differences between minority and majority population on the respective continents. Furthermore, variables that may confound or affect the relationship between SES and outcomes, such as nutritional intake and approval for diabetes technology by payers, were not available, including differences between countries. Variables that are associated with both SES and diabetes outcomes warrant further studies. Additionally, SES quintiles for T1DX are calculated from individual-level variables, whereas the DPV registry used the GIMD, an area-based measure, as proxy for individual-level SES; therefore, analyses for DPV and T1DX were performed separately. However, area deprivation indices are frequently used as a surrogate for individual-level SES (12,13), a number of prior publications has demonstrated the validity of the GIMD (16,39), and individual-level data were not available in Germany because of data protection concerns. Data on diabetes technology use and HbA_{1c} by each individual component of the T1DX SES quintile score (annual income, parental education, and insurance type) were consistent with findings related to our calculated SES quintiles (Supplementary Table 1*B*). However, we cannot exclude that the differences observed in the effect of social disparity between the two countries are partly due to the different methodologies used to measure SES.

Overall, because of the observational, cross-sectional design of the study, a causal relationship between SES and HbA_{1c} or diabetes technology use cannot be established. Moreover, the association of SES with outcomes is much more complex than simply access to diabetes technology. Other contributors related to SES include barriers to high-quality health care, health beliefs, health behaviors (physical activity, nutrition, diabetes regimen adherence), and possible health care provider bias. In particular, we cannot exclude possible confounding with regard to who receives CGM: It is possible that providers offer CGM or pump therapy more often to youth of lower SES who have a lower HbA_{1c} than youth from lower SES who have a higher HbA_{1c}. Nevertheless, this is the largest study to date evaluating diabetes technology use and HbA_{1c} by SES and is the first to make international comparisons.

These data are real-world observations on the associations of diabetes technology use and HbA_{1c} by SES. Although causal conclusions cannot be drawn from these data, they indicate that the use of diabetes technology is lowest and HbA_{1c} is highest in those of the lowest SES quintile in the U.S., and this difference for HbA_{1c} has broadened in the past decade. Even though there is an association of HbA_{1c} and CGM with SES quintiles in the DPV registry, the widening gap of device use and HbA_{1c}

seen in the T1DX is not as pronounced in the DPV. As advances are made in diabetes management, including the use of closed-loop and hybrid closed-loop systems (18–20), these data from the U.S. raise the concern that youth with type 1 diabetes from lower SES quintiles will be at a systematic disadvantage to achieve optimal diabetes outcomes. Further studies are needed to investigate the reasons for increasing HbA_{1c} despite increasing technology use in the U.S.

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- preparation of the data and statistical analysis
- interpretation of the results of the statistical analysis
- creation of the maps and figures
- literature research
- writing of the manuscript
- revision of the manuscript according to comments and suggestions of the co-authors
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Heterogeneity of Access to Diabetes Technology Depending on Area Deprivation and Demographics Between 2016 and 2019 in Germany

Marie Auzanneau, MPH[1,2], Joachim Rosenbauer, MD[2,3], Werner Maier, PhD[2,4], Simone von Sengbusch, MD[5], Johannes Hamann, MD[6], Thomas Kapellen, MD[7], Guido Freckmann, MD[8], Silke Schmidt, MD[9], Eggert Lilienthal, MD[10], and Reinhard W. Holl, MD, PhD[1,2] on behalf of the DPV Initiative

Abstract

Background: Despite increasing use of technology in type 1 diabetes, persistent ethnic and socio-economic disparities have been reported. We analyzed how the use of insulin pump therapy and continuous glucose monitoring (CGM) evolved over the years in Germany depending on demographics and area deprivation.

Method: We investigated the use of insulin pump and CGM between 2016 and 2019 in 37,798 patients with type 1 diabetes aged < 26 years from the German Prospective Follow-up Registry (DPV). Associations with federal state, area-deprivation quintile (German Index of Multiple Deprivation 2010 on district level), gender, and migration background were investigated over time using multiple logistic regression.

Results: Between 2016 and 2019, the regional distribution of insulin pump use did not change substantially and the association with area deprivation remained non-linear and statistically non-significant. The effect of area deprivation on CGM use decreased continuously and disappeared in 2019 (OR [95%-CI] Q1 vs Q5: 1.85 [1.63-2.10] in 2016; 0.97 [0.88-1.08] in 2019). The effect of migration background on the use of either technology decreased over the years but remained significant in 2019. Girls had constantly higher odds of using an insulin pump than boys (OR: 1.25 [1.18-1.31] in 2019), whereas no gender difference was identified for CGM use.

Conclusions: Although disparities decreased in Germany, access to diabetes technology still depends on migration background in 2019, and gender differences in pump use persist. As technological advances are made, further research is needed to understand the reasons for these persistent disparities.

Keywords
CGM, deprivation, insulin pump, migration, type 1 diabetes

Introduction

Despite considerable advances in the management of type 1 diabetes, achievement of optimal metabolic control remains challenging, especially for adolescents and young adults.[1,2] Nevertheless, both efficacy and safety of diabetes technology improve continuously. Insulin pumps and continuous glucose monitoring systems (CGM), which are now widely used in many high-income countries,[2-5] are associated with better glycemic control and have the potential to reduce the risk of acute complications.[2,6] Furthermore, evidence on improved glycemic outcomes obtained with automated insulin delivery systems is accumulating.[7-9] In 2018, the first hybrid closed-loop system has been approved for children aged 7 years or older in Europe and in the U.S.[7]

However, it remains illusory to believe that every child enjoys an equal access to these devices. Despite improved reimbursement for established diabetes technology, important disparities based on socio-economic factors[4,10] or on migration background[2,11-14] have been reported. Moreover, there is a concern that further advances in diabetes technology widen these disparities and increase the systematic disadvantage of children in more deprived situations.[4,15] Nevertheless, considering the sharp increase in CGM and insulin pump use over the last years in Germany, it remains uncertain how exactly these disparities have evolved in more recent years.

We used real-world data from a representative registry to analyze how the use of these devices evolved in children, adolescents and young adults with type 1 diabetes between 2016 and 2019 in Germany. More particularly, we investigated whether the influence of area-based (federal states, district-based deprivation) and demographic factors (gender, migration background) on this technology use changed over time.

Methods

For this population-based study, we used data from the multicenter Diabetes Prospective Follow-up (DPV) Initiative based at the University of Ulm, Germany. Since 1995, all participating diabetes care centers, mainly located in Germany and Austria, prospectively document clinical and demographic data of patients with any type of diabetes into the standardized DPV database.[16] Semi-annually, the collected data are transmitted in pseudonymous form to the University of Ulm, which aggregates the data for central analysis and quality assurance, after plausibility checks and corrections. The Ethics Committee of the Medical Faculty of the University of Ulm (vote number 202/09), as well as the local review boards of participating centers, approved both data collection and analysis of anonymized data from the DPV registry.

Patients with type 1 diabetes living in Germany, aged <26 years, and with visits documented between 2016 and 2019 were eligible for this study. Further inclusion criteria were: documentation of insulin treatment, age $\geq$ 6 months at diagnosis, and diabetes duration $\geq$3 months. Individuals without available or assignable 5-digit postal code of residence ($n=393$) were excluded from the analysis as this information was required to categorize participants into area deprivation quintiles.

Demographic and Socioeconomic Variables

According to prior publications from the DPV registry,[4,10] migration background was defined as place of birth outside Germany for the patient or at least for one parent. Patients without information on migration background ($n=6,150$) were assumed to have no history of migration. Additionally, patients with migration background were categorized into 2 groups depending on the patient's place of birth: "first-generation immigrant" (patient born outside Germany) and "second-generation immigrant" (patient born in Germany with at least one parent born outside Germany). For 1.2% of the patients with migration background, this information was missing.

Area deprivation[17] was assessed at district level using the German Index of Multiple Deprivation for the reference year 2010 (GIMD 2010).[4,18,19] As described previously,[10] the GIMD includes 7 deprivation domains differently weighted: income (25%), employment (25%), education (15%), municipal/district revenue (15%), social capital (10%), environment (5%), and security (5%). Districts were categorized into area deprivation quintiles from Q1 (lowest area deprivation quintile) to Q5 (highest area deprivation quintile). Patients were assigned to districts and consequently to GIMD quintiles using the 5-digit postal code of their residence.

Clinical Variables

Body Mass Index (BMI) was calculated as kg/m^2. For children and adolescents less than 18 years of age, BMI values were transformed to standard deviation scores (SDS or z score) adjusting for age and gender, using national pediatric reference data[20] by applying the LMS method.[21] For young adults aged 18 years or older, we used BMI values. HbA1c was mathematically standardized to the reference range of

[1]Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Baden-Württemberg, Germany
[2]German Center for Diabetes Research (DZD), Neuherberg, Germany
[3]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, North Rhine-Westphalia, Germany
[4]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Bayern, Germany
[5]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Endocrinology and Diabetes, University of Lübeck, Lübeck, Schleswig-Holstein, Germany
[6]Department of Pediatrics, St. Marien Hospital Landshut, Landshut, Germany
[7]Department of Women and Child Health, Hospital for Children and Adolescents, University of Leipzig, Leipzig, Sachsen, Germany
[8]Institut für Diabetes-Technologie, Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Baden-Württemberg, Ulm, Germany
[9]Department of Paediatrics and Adolescent Medicine, Klinikum Dritter Orden, Munich, Bavaria, Germany
[10]Department of Pediatrics, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Nordrhein-Westfalen, Germany

Corresponding Author:
Marie Auzanneau, MPH, Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Albert-Einstein-Allee 41, Ulm, Baden-Württemberg D-89081, Germany.
Email: marie.auzanneau@uni-ulm.de

the Diabetes Control and Complications Trial (DCCT) (4.05-6.05% [20.7-42.6 mmol/mol]) using the multiple of the mean method to adjust for differences between laboratories.[22]

Use of Diabetes Technology

Insulin pumps were increasingly used and refunded in Germany in the early 2000s.[3] The statutory health insurance (covering approximately 90% of the pediatric patients) refunds insulin pump therapy in pediatric patients with type 1 diabetes on a case-by-case-basis. Indication criteria are numerous, in particular: insufficient glycemic control with intensified conventional insulin therapy, severe hypoglycemia, dawn phenomenon, preschool age, pregnancy, needle phobia, or participation in competitive sports.[23] Application for reimbursement must contain an explanatory statement of the indication, a detailed documentation of the therapy and glycemic outcomes of the last 3 months, and certify that the patient will receive adequate pump education. Approval of the health insurance is first given for a probation period, and if glycemic values improves, final approval is given. Regional medical services of the health insurance funds often take part in decision-making, with more or less restrictive positions.

Real-time glucose monitoring (rtCGM) is refunded since September 2016 in Germany by the statutory health insurance for patients with insufficient glycemic control and/or severe hypoglycemia.[23] Since July 2019, the second generation of intermittent scanning glucose monitoring (iscCGM) with alarm function can be reimbursed as well. Application process is similar to those for insulin pump therapy, but a probation period is not required.

For the 10% of children with private insurance, reimbursement of diabetes technology depends of contract specifications.

In the present analysis, use of insulin pump and use continuous glucose monitoring (CGM) were defined as any use of these technologies documented at least once per year. For many patients in our study population (between 31% and 46% depending on the year), the type of CGM (iscCGM or rtCGM) was not documented and we therefore decided to perform the analysis for all types of CGM without distinction.

Statistical Analysis

Data were aggregated per patient and year as median (age, diabetes duration, HbA1c, BMI SDS, and BMI) or maximum (pump use, CGM use). Age was categorized into 3 groups: 0.5-<11 years, 11-<16 years and 16-<26 years. Diabetes duration was categorized into the following groups: 0.25-<2 years, 2-<5 years and ≥5 years.

Unadjusted patient characteristics were presented, as median with interquartile range (IQR) or proportion, for continuous or categorical variables, respectively. Wilcoxon tests (continuous variables) and X^2 tests (categorical variables) were used to compare demographic and clinical characteristics between years, adjusting for multiple comparisons according to the Holm-Bonferroni stepdown procedure.

We represented the regional distribution of the use of pump or CGM in 2016 und 2019 in Germany, using tertile-based choropleth maps. For that purpose, we performed logistic regression models adjusting for gender, age group, diabetes duration group, and migration background, to estimate the use of pump of CGM for each of the 16 federal states of Germany. Then, the adjusted estimates were assigned to 3 categories: low, middle or high use.

In a second step, we performed logistic regression models to assess the association of the 3 independent variables (area deprivation, migration background, and gender) with pump or CGM use by year (interaction terms: area deprivation*year, migration background*year or gender*year), adjusting for area deprivation, migration background, gender, age group, diabetes duration group, and an interaction between migration background and area deprivation. To take the dependence of the data within regions into consideration, we used sandwich variance estimators. Results of regression analyses are presented as adjusted estimates of pump or CGM use with their respective 95% confidence intervals (95% CI) for each independent variable category, as well as odds ratios (OR) for the use of pump or CGM for female vs male, individuals without vs with migration background, and those with area deprivation quintile Q1 vs Q5. *P*-values for trend were calculated to test the overall logit-linear trend of the independent variables (area deprivation modelled as ordinal variables) in each year. Additionally, we tested if these associations were significantly different between years (trend-test for the total period).

A 2-side *P*-value <.05 was considered statistically significant. Statistical analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC).

Results

The final study population of overall 37,798 youths with type 1 diabetes for the period 2016-2019 is described stratified by year in Table 1 (unadjusted results). From 2016 to 2019, the use of insulin pump increased from 51.7% to 57.6%, and the use of CGM from 17.9% to 70.3% (Table 1).

Evolution by Federal State (Figure 1)

Between 2016 and 2019, the regional distribution of the use of insulin pumps did not change substantially, with the lowest use in Baden-Württemberg (from 2016 to 2019: 40.9%-47.1%) and Bavaria (43.6%-51.7%), and the highest use in Schleswig-Holstein (62.0%-63.9%), Brandenburg (61.0%-65.7%), and Lower-Saxony (59.3%-67.8%). The relatively strongest increase, from 41.5% to 51.8%, was observed in

Table 1. Characteristics of the Study Population, Stratified by Year.

	2016 (n = 25,442)	2017 (n = 25,807)	2018 (n = 26,218)	2019 (n = 26,628)	P-values[b]
Girls, n (%)	12,060 (47.4)	12,233 (47.4)	12,349 (47.1)	12,568 (47.2)	n.s. (1.00)
Age, years (median, IQR)	13.7 (10.2-16.4)	13.7 (10.2-16.5)	13.7 (10.2-16.5)	13.7 (10.3-16.5)	n.s. (1.00)
Diabetes duration, years (median, IQR)	4.6 (2.1-8.1)	4.6 (2.1-8.1)	4.7 (2.1-8.1)	4.7 (2.1-8.1)	n.s. (1.00)
Migration background[a], n (%)	5,750 (22.6)	6,065 (23.5)	6,266 (23.9)	6,471 (24.3)	.0002
- First generation	1,018 (4.0)	1,161 (4.5)	1,258 (4.8)	1,358 (5.1)	<.0001
- Second generation	4,630 (18.2)	4,826 (18.7)	4,903 (18.7)	5,059 (19.0)	n.s. (.75)
BMI SDS (median, IQR) for patients aged <18 years	0.33 (−0.23–0.92)	0.35 (−0.22–0.94)	0.35 (−0.22–0.94)	0.39 (−0.19–0.99)	<.0001
BMI (median, IQR) for patients aged ≥18 years	23.7 (21.6-26.3)	23.7 (21.6-26.6)	23.7 (21.6-26.2)	23.8 (21.6-26.4)	n.s. (1.00)
HbA1c, % (median, IQR)	7.58 (6.87-8.38)	7.65 (6.97-8.48)	7.52 (6.83-8.33)	7.52 (6.83-8.31)	<.0001
Use of insulin pump, n (%)	13,154 (51.7)	13,910 (53.9)	14,708 (56.1)	15,338 (57.6)	<.0001
Use of CGM, n (%)	4,554 (17.9)	10,839 (42.0)	15,573 (59.4)	18,719 (70.3)	<.0001

Unadjusted data.

BMI SDS, standard deviation score of Body Mass Index (kg/m^2); IQR, interquartile range.

[a]Migration background is defined as birth of the patient himself outside Germany (first-generation immigrant) or at least one of his parents (second-generation immigrant). Documentation of the place of birth was missing for 0.8-1.8% of the patients with migration history.

[b]Comparison between years using Wilcoxon test for continuous variables and X^2 test for variables with binomial distribution, adjusted for multiple comparisons according to the Holm-Bonferroni stepdown procedure. $P < .05$ (two-sided) was considered statistically significant.

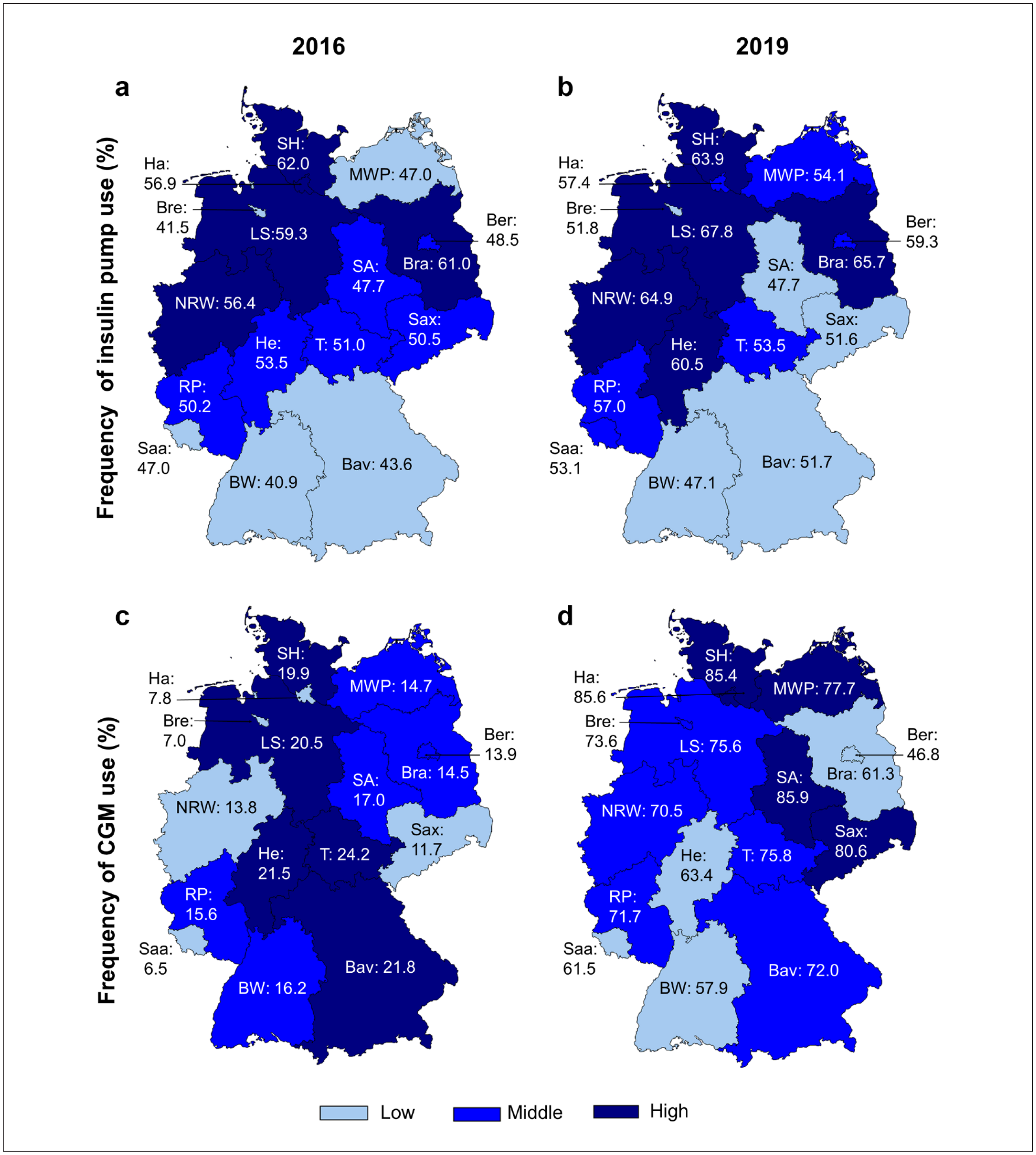

Figure 1. Use of diabetes technology by federal state in 2016 and 2019. *Legend*: Tertile-based choropleth map representing the regional distribution of the use of insulin pump in 2016 (a), in 2019 (b), as well as of CGM in 2016 (c) and 2019 (d), using estimates from logistic regression models, adjusting for gender, age group, diabetes duration, and migration background, for each of the 16 federal states of Germany.

Bav, Bavaria; Ber, Berlin; Bra, Brandenburg; Bre, Bremen; BW, Baden-Württemberg; Ha, Hamburg; He, Hesse; LS, Lower Saxony; MWP, Mecklenburg-Western Pomerania; NRW, North Rhine-Westphalia; RP, Rhineland-Palatinate; SA, Saxony-Anhalt; Saa, Saarland;
Sax, Saxony; SH, Schleswig-Holstein; T, Thuringia.

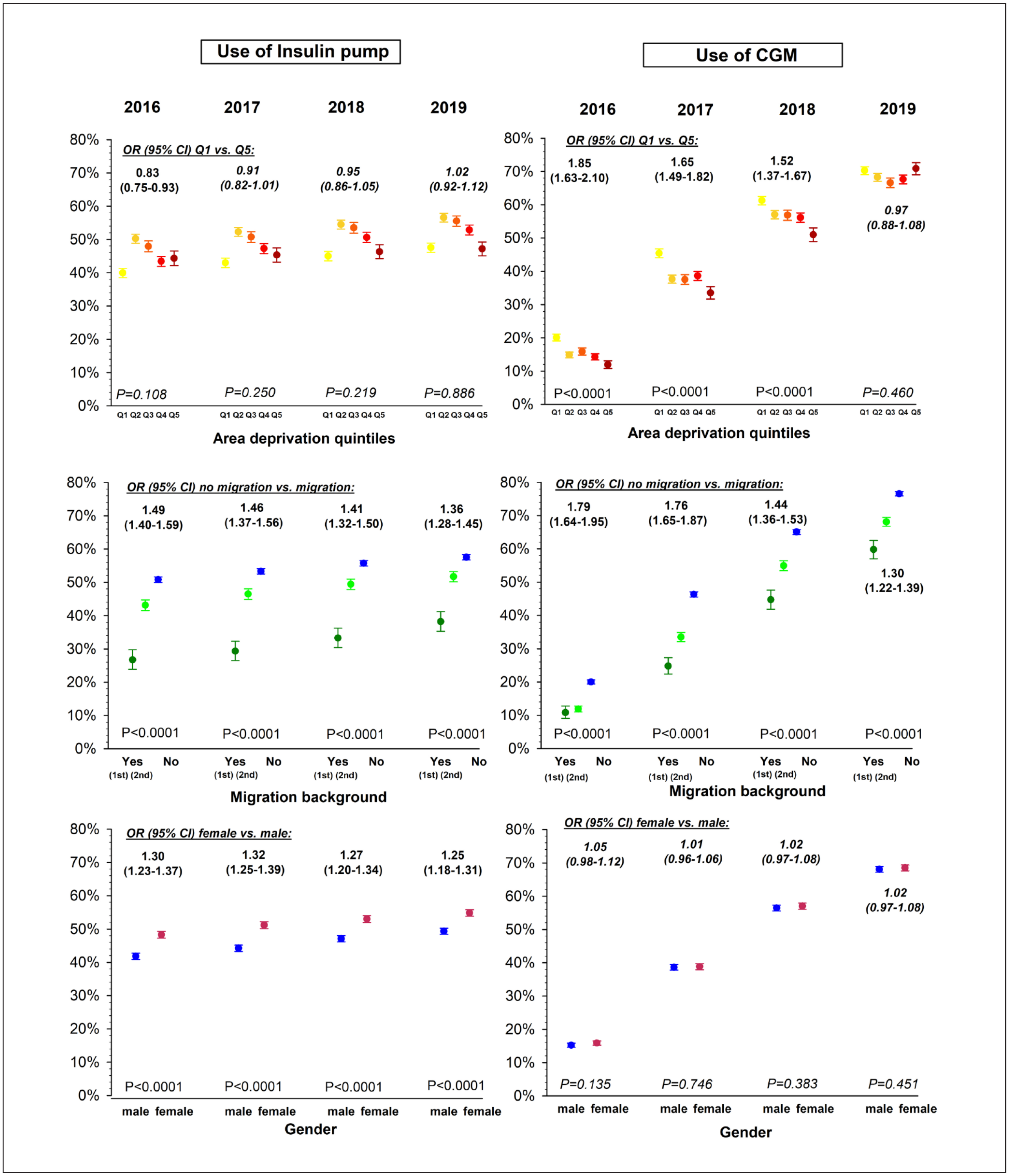

Figure 2. Use of diabetes technology by year and by area deprivation, migration background, and gender. *Legend*: Use of insulin pump and CGM in percentage by year and area deprivation, migration background, or gender interaction are represented using estimates with 95% CI from logistic regression models, adjusting for area deprivation, migration background, gender, age group, diabetes duration, and migration background - area deprivation interaction. Q1 is the least deprived quintile (yellow) and Q5 is the most deprived quintile (dark red). Migration background is defined as birth of the patient himself outside Germany (1st: first generation, dark green) or at least one of his parents (2nd: second generation, light green). *P*-values for trend are given for the effect of gender, migration background, or area deprivation (modelled as an ordinal term) by year. Non-significant *P*-values are indicated in italics.

Bremen, and the weakest in Saxony-Anhalt, were the use of insulin pump remained nearly stable around 47.7%.

In the same time period, the regional distribution of the use of CGM changed substantially. In 2016, the lowest use was reported in Saarland, Bremen, and Hamburg (6.5%, 7.0%, and 7.8% respectively) and the highest in Thuringia (24.2%). By contrast in 2019, the lowest use was observed in Berlin (46.8%) and the highest use in Schleswig-Holstein, Hamburg, and Saxony-Anhalt (85.4, 85.6, and 85.9% respectively). The increase in CGM use was weakest in Berlin (+33 percentage points) and strongest in Hamburg (+78 percentage points), as well as in Saxony-Anhalt and Saxony (both: +69 percentage points).

Evolution Depending on Area Deprivation (Figure 2)

The effect of area deprivation on the use of insulin pumps followed each year a similar non-linear pattern. Between 2016 und 2018, pump use remained lowest in the lowest area deprivation quintile Q1 (39.9% in 2016 and 45.0% in 2018) whereas in 2019, the lowest use was both in Q1 (47.6%) and Q5 (47.2%), compared to other quintiles (Q2: 56.6%, Q3: 55.5%, Q4: 52.9%). Nevertheless, a decrease of insulin pump use with higher deprivation, between area deprivation quintile Q2 and Q5, could be observed throughout the observation period.

Between 2016 and 2018, patients living in districts of the lowest deprivation quintile Q1 had significant higher odds of using a CGM compared to those living in districts of the highest deprivation quintile Q5, but over the years, the effect of area deprivation decreased continuously (OR [95%-CI] Q1 vs Q5: 1.85 [1.63-2.10] in 2016 to 1.52 [1.37-1.67] in 2018, P-value for interaction area deprivation*year $<.001$), and eventually disappeared in 2019 (0.97 [0.88-1.08], P-value for trend = 0.460).

Evolution Depending on Migration Background (Figure 2)

Between 2016 and 2019, the odds of using an insulin pump was constantly and significantly higher in patients without migration background compared to those with a history of migration (OR [95%-CI]: from 1.49 [1.40-1.59] in 2016 to 1.36 [1.28-1.45] in 2019, all $P < .001$). A trend towards a weaker effect on migration background on pump use could be observed, but did not reach statistical significance (P-value for interaction migration*year = .169).

Similarly, the odds of using a CGM was significantly higher in patients without migration background over the whole study period. Nevertheless, the effect on former immigration on the use of CGM decreased significantly over the years (OR [95%-CI]: from 1.79 [1.64-1.95] in 2016 to 1.30 [1.22-1.39] in 2019, P-value for interaction migration*year $< .001$).

Taking into consideration the generation of immigration, second-generation immigrants had a significant higher use of insulin pump and CGM than first-generation immigrants (except for CGM in 2016), but still had a lower use than patients without migration background (all $P < .001$).

Evolution Depending on Gender (Figure 2)

During the whole observation period, the odds of using an insulin pump was higher in girls than in boys (OR [95%-CI]: 1.25 [1.18-1.31] in 2019, $P < .001$). The effect of gender on the use of insulin pump did not change significantly over the years (P-value for interaction gender*year = 0.415). By contrast, the odds of using a CGM remains similar in girls and boys, throughout the observed years.

Discussion

In this population-based study, we analyzed the evolution of the use of insulin pump and CGM in Germany between 2016 and 2019, focusing on their regional distribution, as well as on the influence of regional socio-economic and demographic factors.

The regional distribution of the use of insulin pumps did not change substantially since an initial analysis for the years 2012-2013,[24] which reported the lowest use of insulin pump in Southern Germany and the highest use in Northern-Western Germany. The pattern of the association with area deprivation partly reflects these regional disparities: the lowest use was found nearly every year in districts of the least deprived quintile Q1 which predominate in Southern Germany, that is, Bavaria (where 57% of the districts are Q1 vs <1% of the districts Q5) and Baden-Württemberg (44% of the districts Q1 vs <1% of the districts Q5). Regional disparities, like the lower use of insulin pumps in Southern Germany, result from complex interactions between several factors. Among other things, local preferences (patients and/or physicians) as well as less or more restrictive positions of the regional medical services of the health insurance funds can play a role. Nevertheless, apart from the lower use in Q1, insulin pumps tend to be less frequently used with higher deprivation (from quintile Q2 to Q5), following the same pattern described in previous publications.[4,10] Lower health literacy skills and more particularly lower parental perceived self-efficacy associated with lower socioeconomic status, may lead to a lower use of diabetes technology in more deprived regions.[12,25,26] Besides, the necessity to apply for reimbursement and the uncertainty of approval by health insurance may discourage some families in most deprived socioeconomic situations.[10,12] Overall, the persistent non-linear association between pump use and area deprivation indicates that several covariates with partly opposite effects are interacting.

Our results on CGM use reflect more dynamic changes in the regional distribution during the study period. Over the years, the effect of area deprivation decreased and eventually disappeared in 2019. In accordance with this finding, we observed in the study period a strong increase in the use of CGM in the most deprived areas. In Saxony-Anhalt, where the highest use in Germany was reported in 2019, 94% of the districts are classified in the highest area deprivation quintile Q5. In Mecklenburg-Western Pomerania, Saxony, and Thuringia, where districts of quintile Q5 are also predominant, the use of CGM increased also strongly between 2016 and 2019. In Germany, rtCGM are reimbursed by statutory health insurance since 2016, and iscCGM with alarm-function since 2019. At first, and in the same manner as for the insulin pump, the necessity to apply individually for reimbursement as well as the apparent higher complexity of using diabetes technology in everyday life may have constituted an obstacle for some families in more deprived regions. However, these barriers seem to have diminished gradually over time. One plausible explanation is that approval for reimbursement of CGM has become easier to obtain over the years. In particular, reimbursement in 2019 of the second generation of iscCGM systems, which are particularly popular in youth (marketing and delivery directly to the consumer, easy use, no calibration required), may have contribute to increase the use of these devices especially in the most deprived regions.

This study revealed that migration background affects the access to diabetes technology in Germany independently of area deprivation. Lower use of insulin pump in patients from ethnic minority groups has often been described, not only in Germany,[3,12] but also in Austria, England, Wales[27] or New-Zealand.[28] In the U.S., persistent and strong racial disparities in diabetes technology use, independent of socio-economic status, have been described until recently.[2,13,14,27,29] Overall, complex discriminatory reasons[15,30-32] cannot be excluded. Besides, language barriers certainly limit access of many migrant families to diabetes technology in Germany.[12,30] Sufficient German language skills are required not only to apply for reimbursement, but also for pump education, which is predominantly given in an inpatient setting, and for pump management in everyday life. Children from parents who migrated into Germany (second-generation immigrants) used diabetes technology more often than first-generation immigrants, however their technology uptake was lower compared to patients without a migration background. Indeed, second-generation immigrants may experience less language and cultural barriers. Nevertheless, even if the children are born in Germany, one or both parents born outside of Germany may still have difficulties with the language and health care system in Germany. This may limit the access to technology especially for younger children, for whom the parents are still playing the main role in the therapy.

Regarding access to CGM, a previous report found no significant difference depending on migration background in Germany,[3] but the results were not adjusted, contrary to those of the present study. Barriers to CGM use in patients with migration background may be similar to those described above for pump use. Nevertheless, our findings indicate that the effect of a history of migration on the access to CGM decreased over the years in Germany. However, while the effect of area deprivation on access to CGM disappeared in 2019, the effect of a migration history remained significant.

In accordance with numerous reports,[3,27,28,33] we found a higher use of insulin pump in female versus male patients, consistent over the study period. In Germany, this gender difference has only been observed in children aged 10 and older, and was more pronounced in those aged above 15 years.[3] Despite higher psychological barriers to technology use and higher concern of wearing a pump in public,[34] many indications, like poorer metabolic control,[35] variable insulin requirement during the menstrual cycle, or possibility of pregnancy,[23] contribute to a higher use of insulin pump in female adolescents and young adults compared to male of the same age. By contrast, as reported in other studies,[3,33,34] CGM use did not depend on gender, whatever the year.

One major strength of the present study is the large size of the study population with more than 37,000 patients with type 1 diabetes, from a national prospective diabetes registry capturing more than 85% pediatric patients with type 1 diabetes in Germany.[10] Moreover, we used robust statistical methodology to investigate how the effect of demographic and socio-economic factors changed over the years, adjusting for several confounder, including the interaction between migration background and area deprivation. Thus, our study confirms that a history of migration and socio-economic factors like area deprivation affect diabetes treatment of pediatric patients independently.[4,11] One limitation of our study is the lack of information on health insurance type in the DPV-Registry, due to data protection reasons. However, nearly all children and adolescents are covered by health insurance in Germany (about 90% statutory and 10% private health insurance) and differences between insurance types have only minimal consequences on the access to diabetes technology in the pediatric population. In addition, since education level and household income are incompletely documented in DPV, information on individual socio-economic status was not available. However, indices of area deprivation have been frequently used in epidemiological research, either as surrogate for individual socio-economic status[4] or much more to take an "area effect" into consideration, with its multiple dimensions.[10,17-19,36]

Conclusions

Over the last years in Germany, the effect of area deprivation on the use of CGM disappeared, and the effect of migration decreased continuously. By contrast, the effect of area deprivation and migration on the use of insulin pump did not change significantly. The decrease of ethnic and socio-economic disparities in CGM use contrasts with the situation observed in other countries with similar rates of CGM-use, like the U.S.,[2,4,13,29] and is therefore encouraging. Nevertheless, disparities based on migration background, independent of area deprivation, still impede providing every child an equal access to diabetes technology. As safety and efficacy of hybrid closed-loop and closed-loop systems will further increase,[7-9] our findings raise the concern that inequitable access to diabetes technology will continue to systematically disadvantage children living in more deprived regions and/or with a history of migration.[15] Certainly, efforts are required to consider solutions to overcome the language barriers. Moreover, further research is needed to deepen our understanding of the reasons for these persistent disparities.

Author Contribution

M.A. and R.W.H. designed the study. M.A. analyzed the study data, created the figures, and wrote the manuscript. J.R., W.M., S.v.S., J.H., T.K., G.F., S.S., E.L., and R.W.H. contributed to the discussion, reviewed, and approved the manuscript.

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Abbreviations

BMI, body mass index; CI, confidence interval; DPV, German diabetes prospective follow-up registry; IQR, interquartile range; LMS method, method using lambda-mu-sigma parameters;

SDS: standard deviation score.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.v.S. reports beeing consultant for Abbott, Lilly, Medtronic and NovoNordisk and received lecture fees from Abbott, Berlin-Chemie, Dexcom, Hexal, Infectopharm, Lilly, Medtronic and NovoNordisk. The other authors declare no competing financial interest.

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Ethical approval

The Ethics Committee of the Medical Faculty of the University of Ulm (vote number 202/09), as well as the local review boards of participating centers, approved both data collection and analysis of anonymized data from the DPV database.

ORCID iDs

Marie Auzanneau https://orcid.org/0000-0002-5906-6579
Guido Freckmann https://orcid.org/0000-0002-0406-9529

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Own contribution:
I was the first and corresponding author of this publication and contributed to the following parts:

- co-formulation of the research question
- co-development of the methodology and study design
- preparation of the data and statistical analysis
- interpretation of the results of the statistical analysis
- creation of the maps and figures
- literature research
- writing of the manuscript
- revision of the manuscript according to comments and suggestions of the co-authors
- submission of the manuscript to the journal
- revision of the manuscript after peer review

Frequency of Ketoacidosis at Diagnosis of Pediatric Type 1 Diabetes Associated With Socioeconomic Deprivation and Urbanization: Results From the German Multicenter DPV Registry

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Marie Auzanneau,[1,2] Joachim Rosenbauer,[2,3] Katharina Warncke,[4] Werner Maier,[2,5] Clemens Kamrath,[6] Thomas Hofmann,[7] Michael Wurm,[8] Johanna Hammersen,[9] Carmen Schröder,[10] Kathrin Hake,[11] and Reinhard W. Holl,[1,2] on behalf of the DPV Initiative

[1]Zentralinstitut für Biomedizinische Technik (ZIBMT), Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany
[2]German Center for Diabetes Research (DZD), Neuherberg, Germany
[3]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany
[4]Department of Pediatrics, Kinderklinik München Schwabing, Technical University of Munich School of Medicine, Munich, Germany
[5]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München–German Research Center for Environmental Health, Neuherberg, Germany
[6]Center of Child and Adolescent Medicine, Justus Liebig University, Giessen, Germany
[7]Pediatric Practice of the Medical Center Arnsberg, Hochsauerland Clinic, Arnsberg, Germany
[8]St. Hedwig Clinic for Pediatric and Adolescent Medicine, Regensburg University, Hospital of the Order of St. John of God, Regensburg, Germany
[9]Department of Pediatrics, University Hospital Erlangen, Erlangen, Germany
[10]Division of Endocrinology and Diabetes, Department of Pediatrics, University of Greifswald, Greifswald, Germany
[11]Children's Hospital, Müritzklinikum Waren, Waren, Germany

Corresponding author: Marie Auzanneau, marie.auzanneau@uni-ulm.de

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OBJECTIVE

To investigate whether socioeconomic deprivation and urbanization are associated with the frequency of diabetic ketoacidosis (DKA) at diagnosis of pediatric type 1 diabetes.

RESEARCH DESIGN AND METHODS

Children and adolescents aged ≤18 years, living in Germany, with newly diagnosed type 1 diabetes documented between 2016 and 2019 in the Diabetes Prospective Follow-up Registry (DPV; Diabetes-Patienten-Verlaufsdokumentation), were assigned to a quintile of regional socioeconomic deprivation (German Index of Socioeconomic Deprivation) and to a degree of urbanization (Eurostat) by using their residence postal code. With multiple logistic regression models, we investigated whether the frequency of DKA at diagnosis was associated with socioeconomic deprivation or urbanization and whether associations differed by age-group, sex, or migration status.

RESULTS

In 10,598 children and adolescents with newly diagnosed type 1 diabetes, the frequency of DKA was lowest in the least deprived regions (Q1: 20.6% [95% CI 19.0–22.4], and increased with growing socioeconomic deprivation to 26.9% [25.0–28.8] in the most deprived regions [Q5]; *P* for trend <0.001). In rural areas, the frequency of DKA at diagnosis was significantly higher than in towns and suburbs (intermediate areas) or in cities (27.6% [95% CI 26.0–29.3] vs. 22.7% [21.4–24.0], *P* < 0.001, or vs. 24.3% [22.9–25.7], *P* = 0.007, respectively). The results did not significantly differ by age-group, sex, or migration background or after additional adjustment for socioeconomic deprivation or urbanization.

CONCLUSIONS

This study provides evidence that prevention of DKA at diagnosis by means of awareness campaigns and screening for presymptomatic type 1 diabetes should particularly target socioeconomically disadvantaged regions and rural areas.

Diabetic ketoacidosis (DKA) at the time of diagnosis of pediatric type 1 diabetes is an acute, potentially life-threatening complication associated with detrimental long-term consequences, such as poorer metabolic control (1,2) and impaired neurocognitive function (3). A systematic review reported a considerable geographic variation of its frequency, ranging from 13 to 80% worldwide (4). Even in countries with developed health care systems, this complication is relatively common: according to a comparison among 13 countries, the standardized prevalence of DKA at diagnosis in the years 2006–2016 ranged from 20% in Sweden to 44% in Luxembourg (5). A particular cause of concern is the increase of the prevalence observed in recent years in many high-income countries, as in Sweden (6), Italy (7), or the U.S. (8). Also in Germany, where studies reported a prevalence varying between 20% (9) and 27% (5), depending on age and observation period, an increase has been noted in the past few years (9). Lastly, in the context of the coronavirus disease 2019 pandemic, the prevalence of this complication increased even further (10).

Nevertheless, current medical evidence suggests that DKA at diagnosis may often be preventable (11). A frequent cause is a delayed treatment of the disease at onset (6,12), because the symptoms of type 1 diabetes have been overlooked or misdiagnosed (13,14) or because the urgency of the situation has not been recognized (6). To date, strong evidence indicates that some individual factors are associated with an increased risk of DKA at diagnosis (15). In particular, higher DKA risk is associated with younger age (5,11,15,16), lower parental education (11,17), ethnic minority group (5,11,15,16), or lower access to medical care for socioeconomic reasons (11,15,16). By contrast, only a few contextual or area-based factors have been investigated. Studies have shown, for instance, that a high type 1 diabetes incidence (11) or a high "Index of Human Development" (18) at the country level has a protective effect. However, variations within countries, and especially within high-income countries, have hardly been explored (17). In order to understand the reasons for the high regional variation of DKA at diagnosis and the increase in the prevalence observed in many high-income countries in recent years, further research is urgent.

We therefore aimed to investigate whether contextual factors within a high-income country (socioeconomic deprivation, degree of urbanization) influence the prevalence of DKA at the time of diagnosis in a representative population of children and adolescents with type 1 diabetes. We also explored whether the influence of both factors varied by sex, age-groups, or migration background.

RESEARCH DESIGN AND METHODS

Study Population

The data source for this study was the multicenter Diabetes Prospective Follow-up Registry (DPV; Diabetes-Patienten-Verlaufsdokumentation), covering >90% of the pediatric population with type 1 diabetes in Germany (19). As of September 2020, 459 diabetes centers located in Germany have been prospectively documenting treatment and outcome data of 640,132 patients with any type of diabetes in the standardized DPV electronic health record. The analysis of anonymized data from the DPV registry was approved by the Medical Faculty Ethics Committee of the University of Ulm, Germany. Data collection is approved by local review boards.

Only visits in diabetes care centers within a time interval of 7 days before or after the date of a type 1 diagnosis between 2016 and 2019 were included in the analysis. In the DPV database, the definition of type 1 diabetes is based on a physician's diagnosis according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (20). At all centers participating in the registry, physicians specialized in diabetes are available. Further inclusion criteria were age between 6 months and 18 years and residence in Germany in this time interval of diagnosis. DPV patients living in Austria, Switzerland, or Luxemburg at the time of diagnosis were excluded as deprivation and urbanization indices were not available for those countries.

Demographic and Clinical Variables

Age at diagnosis was categorized into five groups: 0.5 to <5 years, 5 to <9 years, 9 to <12 years, 12 to <15 years, and 15 to ≤18 years. Migration background was defined as place of birth outside Germany for the patient or at least for one parent.

DKA at diagnosis of type 1 diabetes was defined, as recommended in the ISPAD guidelines (15), as either pH <7.3 or bicarbonate <15 mmol/L or "DKA" documented as the reason for hospitalization. Absence of all three parameters was considered as no DKA. To avoid an underestimation of the DKA rates, 527 patients treated in 46 diabetes centers that never document pH values (mainly inpatient rehabilitation units) were excluded from the analysis. In addition, we tested a more sensitive definition of DKA (bicarbonate <18 mmol/L instead of 15 mmol/L), as described by Von Oettingen et al. (21). Since all associations were similar despite increased DKA frequency, we chose to maintain the initial cutoff, as defined by the ISPAD, because it offers the best positive predictive value (21). To adjust for differences between laboratories, HbA_{1c} values were mathematically standardized to the reference range of the Diabetes Control and Complications Trial (4.05–6.05% [20.7–42.6 mmol/mol]) using the multiple of the mean method (22).

Contextual Variables

Districts in Germany were categorized into socioeconomic deprivation quintiles, from Q1 (lowest deprivation) to Q5 (highest deprivation), by using the German Index of Socioeconomic Deprivation of the year 2012 ($GISD_{2012}$) (23). The GISD is open to be used for research at the data repository of the German GESIS Leibniz-Institute for the Social Sciences (https://doi.org/10.7802/1460). The $GISD_{2012}$ encompasses regional data on education, occupation, and income, the three dimensions of the socioeconomic status as it is usually defined in social epidemiology. The methodology used to develop this index has been described in detail previously (23). In the current study, patients were assigned to districts and consequently to $GISD_{2012}$ quintiles using the five-digit postal code of their residence.

Postal codes were also used to assign each patient to a degree of urbanization. Three degrees of urbanization were defined, based on the population density of local administrative units as provided by Eurostat (24): "cities" (densely populated area with at least 50% of the population living in a urban center with ≥1,500 inhabitants/ km^2, and a minimum of 50,000 inhabitants collectively), "rural areas" (thinly populated areas with at least 50% of the population living in areas with <300 inhabitants/km^2, and

<5,000 inhabitants collectively), and all other areas (intermediate density areas) called “towns and suburbs.”

The analysis excluded 168 individuals without a five-digit postal code of residence, who could not be categorized into socioeconomic deprivation quintiles or related to a degree of urbanization.

Statistical Analysis

Data documented within 7 days before or after the date of diagnosis were aggregated for repeated visits per patient as median, minimum (pH, bicarbonate), or maximum (DKA at diagnosis). Unadjusted patient characteristics are presented as median with the interquartile range (IQR) for continuous variables or as proportion for variables with binomial distribution. Wilcoxon tests and χ^2 tests, adjusted for multiple comparisons according to the Holm-Bonferroni step-down procedure, were respectively used to compare these characteristics between socioeconomic deprivation quintiles.

We used the free and open source Geographic Information System QGIS (version 3.16.0-Hannover) with districts shapefiles from the Federal Agency for Cartography and Geodesy (GeoBasis-DE/BKG 2021) to create choropleth maps representing the regional distribution of the socioeconomic deprivation (quintiles), the urbanization (median degree), and DKA at diagnosis (smoothed DKA rates categorized into quintiles) at district level. Smoothed DKA rates were estimated (shrinkage estimator) using logistic regression models with district as random effect, adjusted for migration background, sex, and age-group of the whole study population.

We investigated the association between the independent variables (quintiles of socioeconomic deprivation modeled as an ordinal variable; degree of urbanization) and the frequency of DKA at diagnosis using logistic regression models with a sandwich estimator to take the potential dependency of the data within each district into account. In a sensitivity analysis, we repeated this analysis additionally considering the districts as a random effect. *P* values were calculated to test the logit-linear trend of the frequency of DKA at diagnosis by socioeconomic deprivation quintiles (modeled as an ordinal variable), as well as the difference of the frequency of DKA at diagnosis between two degrees

Table 1—Characteristics of the study population

	Overall (N = 10,598)	By quintiles of socioeconomic deprivation: Q1 (lowest deprivation) (n = 2,209)	Q2 (n = 1,940)	Q3 (n = 2,233)	Q4 (n = 2,093)	Q5 (highest deprivation) (n = 2,123)	P values*
Girls	4,759 (44.9)	965 (43.7)	856 (44.1)	1,041 (46.6)	948 (45.3)	947 (44.6)	0.35
Age, years	9.7 (6.0–13.0)	9.6 (5.8–13.0)	10.0 (6.0–13.0)	9.9 (6.3–13.2)	9.8 (6.1–13.1)	9.6 (5.8–12.7)	0.18
Migration background	2,692 (25.4)	634 (28.7)	528 (27.2)	627 (28.1)	442 (21.1)	463 (21.8)	<0.001
HbA_{1c}, %	11.02 (9.59–12.73)	10.81 (9.39–12.60)	11.13 (9.72–12.83)	11.01 (9.51–12.82)	11.22 (9.63–12.87)	11.01 (9.63–12.63)	<0.001
HbA_{1c}, mmol/mol	97 (81–115)	95 (79–114)	98 (83–116)	97 (80–116)	99 (81–117)	97 (81–114)	
DKA							
All (pH<7.3 or bicarb <15 mmol/L)	2,639 (24.9)	471 (21.3)	481 (24.8)	581 (26.0)	530 (25.3)	571 (26.9)	<0.001
Severe (pH<7.1 or bicarb <5 mmol/L)	901 (8.5)	161 (7.3)	155 (8.0)	205 (9.2)	167 (8.0)	206 (9.7)	0.09
Degree of urbanization							
Cities	3,783 (35.7)	1,058 (47.9)	537 (27.7)	498 (22.3)	770 (36.8)	917 (43.2)	<0.001
Towns and suburbs	3,964 (37.4)	828 (37.5)	982 (50.6)	1,045 (46.8)	659 (31.5)	450 (21.2)	<0.001
Rural areas	2,851 (26.9)	323 (14.6)	421 (21.7)	690 (30.9)	664 (31.7)	756 (35.6)	<0.001

Unadjusted data. Data are presented as *n* (%) or median (IQR). Migration background is defined as birth of the patient or at least one of the parents outside of Germany. *Comparison between socioeconomic deprivation quintiles using the Wilcoxon test for continuous variables and χ^2 test for variables with binomial distribution, adjusted for multiple comparisons according to the Holm-Bonferroni step-down procedure. $P < 0.05$ (two-sided) was considered statistically significant.

of urbanization (adjusting for multiple comparisons according to the Tukey-Kramer procedure). To investigate whether the effects of either independent variable ($GISD_{2012}$ or urbanization) differed by age-group, sex, or migration background, we included interaction terms of GISD or urbanization with these demographic variables in the logistic models.

Results of regression analyses are presented as adjusted estimates with their respective 95% CIs. A *P* value <0.05 (two-sided) was considered statistically significant. Statistical analysis was performed using SAS 9.4, built TS1M7 software (SAS Institute, Cary, NC).

RESULTS

A total of 10,598 children and adolescents with type 1 diabetes living in 387 of the 402 German districts and treated in 199 diabetes centers met the inclusion criteria. The unadjusted DKA prevalence was 24.9% (Table 1). Age (median 9.7 [IQR 6.0–13.0] years) and sex (girls 45%) did not differ significantly by socioeconomic deprivation quintiles (Table 1, unadjusted results). The proportion of children with a migration background was significantly higher in the least deprived regions compared with those most deprived (27–29% in Q1–Q3 vs. 21–22% in Q4–Q5, $P < 0.001$) (Table 1). Patients living in rural areas were more frequently living in the most deprived districts (36% in Q5 vs. 15% in Q1, $P < 0.001$), whereas those living in towns and suburbs were more frequently living in less deprived areas (38–51% in Q1–Q3 vs. 21–32% in Q4–Q5, $P < 0.001$) (Table 1). For children living in cities, the association with socioeconomic deprivation was not linear (Table 1).

A simple visual comparison of the maps representing the regional distribution of the socioeconomic deprivation and of the degree of urbanization on the one hand, and of the rates of DKA at diagnosis, on the other hand, does not demonstrate any clear association between these variables at district level (Fig. 1). However, the regression models revealed that the percentage of DKA at diagnosis significantly increased with higher socioeconomic deprivation (from 20.6% [95% CI 19.0–22.4] in the least deprived districts [Q1] to 26.9% [25.0–28.8%] in the most deprived districts [Q5], *P* for trend <0.001) (Fig. 2). The association of the frequency of DKA with socioeconomic deprivation did not differ significantly by age-groups (interaction term $GISD_{2012}$*age-groups: *P* for trend $= 0.863$), by sex (interaction term $GISD_{2012}$*sex: *P* for trend $= 0.915$), or by migration background (interaction term $GISD_{2012}$*migration background: *P* for trend $= 0.265$).

Depending on the degree of urbanization, the percentage of DKA at diagnosis was significantly higher in rural areas than in towns and suburbs or in cities (27.6% [95% CI 26.0–29.3] vs. 22.7% [21.4–24.0], $P < 0.001$, or vs. 24.3% [22.9–25.7], $P = 0.007$, respectively) (Fig. 2). The association of DKA frequency with urbanization did not differ significantly by age-groups (interaction term urbanization*age-groups: $P = 0.216$), by sex (interaction term urbanization*sex: $P = 0.168$), or by migration background (interaction term urbanization*migration background: $P = 0.772$).

Both the associations of the frequency of DKA with urbanization and with socioeconomic deprivation remained significant after additionally adjusting for the other variable. Moreover, results did not differ after considering the districts as random intercept in the regression models (sensitivity analysis).

CONCLUSIONS

In this representative population-based study, we investigated the association of two contextual factors with the frequency of DKA in >10,000 children and adolescents at type 1 diabetes diagnosis between 2016 and 2019 in Germany. Overall, we found a DKA prevalence of ∼25%, which is higher than the prevalence reported in Sweden, Denmark, or Norway (5,6), but lower than the rates found in the last years in the U.S. or in Italy (5,8).

In our results, the prevalence of DKA at diagnosis was higher in regions with higher socioeconomic deprivation, independently of age-groups, sex, or migration status. There is evidence that individual socioeconomic factors are associated with the risk of DKA at the diagnosis of childhood diabetes. In particular, studies from the U.S. have shown that not only lack of insurance but also public versus private insurance was associated with an increased risk of DKA at diagnosis in children with type 1 diabetes (16,25). However, these findings are unlikely transferable to Germany, where nearly all children are covered by health insurance (∼90% statutory and 10% private insurance), without notable differences between the types of insurance in the access to diabetes care (26).

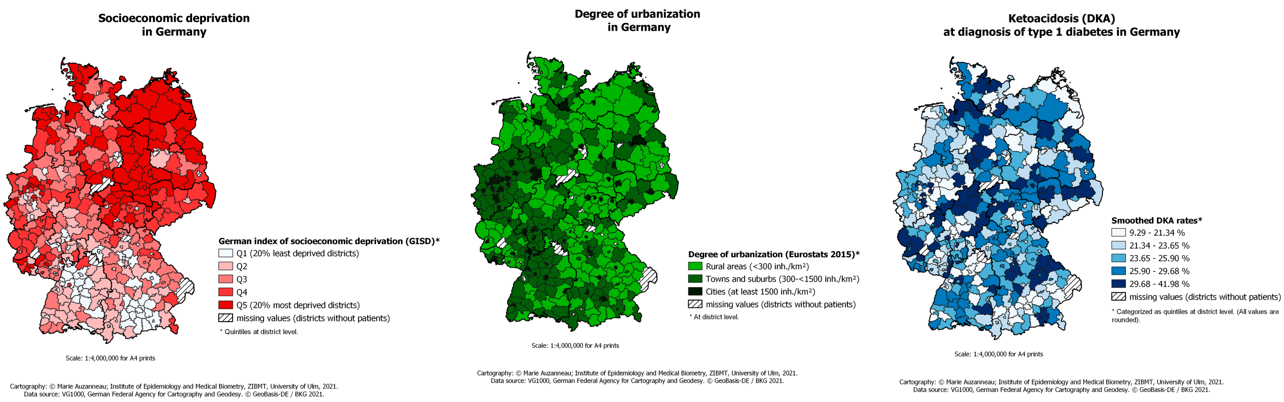

Figure 1—Socioeconomic deprivation, urbanization, and diabetic ketoacidosis (DKA) at diagnosis of type 1 diabetes at the district level in Germany. Socioeconomic deprivation (quintiles), degree of urbanization (three categories), and smoothed rates of DKA at diagnosis adjusted for age-group, sex, and migration background (quintiles) represented at the district level in Germany using choropleth maps.

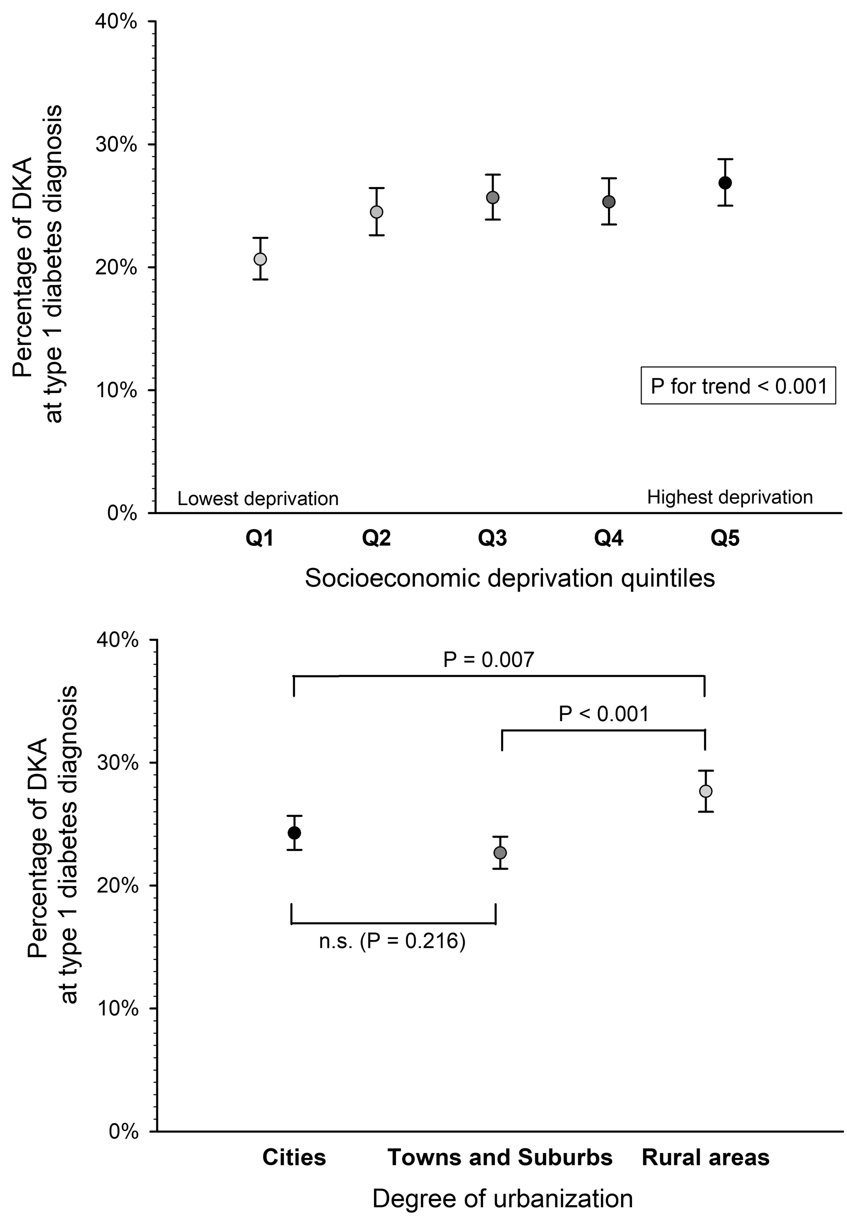

Figure 2—Frequency of DKA at diagnosis by socioeconomic deprivation and urbanization. Percentages of DKA at diagnosis by socioeconomic deprivation quintiles and degree of urbanization are represented using estimates with 95% CIs from logistic regression models, adjusting for sex, age-group, and migration background. Q1 is the least and Q5 is the most deprived quintile. *P* value for trend is given for the association with socioeconomic deprivation modeled as an ordinal term. *P* values adjusted for multiple comparisons according to the Tukey-Kramer procedure are given for the comparison between degrees of urbanization modeled as categorical terms.

Concerning income, which is one of the three dimensions of the socioeconomic deprivation index used in the current study, previous analyses have demonstrated that the frequency of DKA at diagnosis increases with a higher degree of poverty, either measured individually (11) or collectively (13,25). Since nearly all children in Germany are covered by health insurance, income itself is not expected to limit the access to general pediatric care in this country. However, lower income is related with lower levels of parental education and occupation (the two other dimensions of the socioeconomic deprivation), which have been related to an increased risk of DKA at diagnosis too (11,17). As shown and discussed in previous studies, health literacy, which is associated with better health outcomes, is lower in families with lower education (27,28). Moreover, families with a lower degree of occupation may less frequently have a strong social network to exchange important information or to provide help that facilitates an early diagnosis (17). Thus, it is possible that caregivers in socioeconomically disadvantaged regions overlook the symptoms of type 1 diabetes in their child more frequently or, due to a lack of social support, wait longer before consulting a health care provider (6,13). On the other hand, we cannot exclude that in regions with higher socioeconomic deprivation, general practitioners or pediatricians more frequently delay referral to pediatric emergency wards in the presence of DKA, either because they are less aware of the symptoms of type 1 diabetes (e.g., they diagnose a viral infection) (6,13,14), or because they ignore current guidelines (e.g., they arrange for a fasting glucose test instead of an immediate random glucose test) (12,15). We may also consider that working conditions in these areas may be more difficult. Moreover, communication problems with families with lower education can complicate the record of the medical history and contribute to delay diagnosis.

In our analysis, rural areas were also associated with a higher frequency of DKA at diagnosis, even after adjusting for socioeconomic deprivation. In a recent analysis from Germany, the authors found no differences in DKA rates between urban and nonurban hospitals (29). However, in this study, the "nonurban" group merged the two categories "towns and suburbs" and "rural areas," where the lowest and the highest DKA rates were found in the present analysis. Thus, the differences between subgroups have most likely been obliterated. In Australia, the higher frequency of DKA in rural regions has been related to a reduced access to health care, insulin therapy, or glucose testing equipment (30). However, population density in Germany is much higher than in Australia (238 vs. 3 people/km^2 in 2020) (31) and distances are smaller (9). Moreover, there is some evidence that the risk of DKA at diagnosis is not associated with a longer distance to hospital in this country (9,29). Since parents may first consult a private medical practice before going to a hospital, primary care might play a more important role than inpatient care to reduce delayed diagnosis and the risk of DKA; in particular, a lower density of pediatricians in rural areas (more relevant than general practitioners who have less experience in pediatrics) could be associated with an increased frequency of DKA.

Further analyses should take physician density by specialty into account to enhance our understanding of these results.

A recent review and meta-analysis has shown that awareness campaigns are effective to reduce the frequency of DKA at diagnosis of pediatric type 1 diabetes if they are targeted toward key populations and if they select well-defined geographic areas (32). According to the present findings, it seems to be crucial to develop prevention strategies, such as screening for presymptomatic stages of type 1 diabetes (33), and awareness campaigns (especially in kindergarten and schools, as well as for pediatricians and general practitioners) in socioeconomically disadvantaged regions and rural areas. In particular, campaigns should inform that in case of symptoms such as thirst, polyuria/nocturia, tiredness, weight loss, nausea, tachypnea, or abdominal pain, a random glucose test is sufficient to diagnose type 1 diabetes and that children and adolescents with suspected or confirmed DKA need to be immediately referred to a pediatric hospital equipped to provide emergency care, and subsequently, as soon as possible, to a center with expertise in pediatric diabetology. Besides, screening of islet autoantibodies to identify type 1 diabetes in an early presymptomatic stage not only aims to reduce the prevalence of DKA but also enables the development of potential immunotherapies to delay or even prevent diabetes (34,35).

A strength of this analysis is the use of a large multicenter registry highly representative for pediatric diabetes in our country (36). Our results were robust, even after adjusting for several confounders, such as age, sex, and migration background, or after testing for interaction between deprivation and urbanization. We deliberately focused on area-based factors, because individual risk factors for DKA at diagnosis have previously been thoroughly investigated and because the whole context (patient and health care system) needs to be taken into consideration to organize targeted public health measures where they are most needed. This analysis has implications for the general population and for primary care (i.e., pediatricians, general practitioners, and emergency medicine), much more than for diabetologists who contribute after a diagnosis of diabetes is suspected.

A possible limitation is the heterogeneity of the districts, which vary from $\sim$35,000 up to $>$1 million inhabitants. Indices based on smaller areas may have enhanced the precision of our findings. However, pediatric diabetes care is organized at the district level in Germany, and thus, heterogeneity within districts may only have a limited impact on our results.

In conclusion, this study identified risk factors for the development of DKA at diagnosis of type 1 diabetes at a regional level. Education campaigns or screening strategies that address these factors and target socioeconomically disadvantaged regions and rural areas may thereby reduce DKA rates more efficiently than uniform strategies.

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Curriculum vitae

Name	Marie Sophie Auzanneau
Year and place of birth	1974 in Libourne, France

Principal work experience

03/2017 to present	Research associate at the Ulm University, Institute of Epidemiology and Medical Biometry, Ulm, Germany
2003 -2008	Head of the communication, Editor-in-Chief, at the French Heamophilia Society, Paris, France

Grants and awards

03-10/2022	Financial support Nr. 027/162/P/Med from the Financial support programmes for female researchers, Office Gender Equality, Ulm University
02/2020	Financial support (third party fund) from the German Diabetes Association 2020 for the project: “Hospitalization with or without diabetes in Germany. Analysis based on the DRG-statistics“

Education/academic qualification

02/2019 to present	PhD student *Ulm University, Institute of Epidemiology and Medical Biometry, Ulm, Germany*
06/2017	PhD course Diabetes Epidemiology *Danish Diabetes Academy, University of Southern Denmark/ University of Copenhagen/ Aarhus University*
2014-2016	Master of Public Health (MPH), final grade: 1.86 (good) *Institute for Medical Informatics, Biometry and Epidemiology (IBE) at the Ludwig-Maximilians-Universität (LMU), Munich, Germany*

1996-1998	Master of Political Science, final grade: good *Université Montesquieu-Bordeaux IV and* *Institut d'Etudes Politiques (IEP), Bordeaux, France*
1993-1996	Bachelor in Law and French-German law certificate *Université Montesquieu-Bordeaux IV, Bordeaux, France, and Humboldt-Universität zu Berlin, Berlin, Germany (Erasmus-Program)*
1992	Baccalauréat C (French university entrance qualification with focus on mathematics/physics) *Lycee Max Linder, Libourne, France*

Publications

Publications of the thesis

Auzanneau M, Rosenbauer J, Warncke K, Maier W, Kamrath C, Hofmann T, Wurm M, Hammersen J, Schröder C, Hake K, Holl RW. Frequency of ketoacidosis at diagnosis of pediatric type 1 diabetes associated with socioeconomic deprivation and urbanization: Results from the German multicenter DPV registry. Diabetes Care 2022 Aug 1;45(8):1807-1813. doi: 10.2337/dc21-2227. PMID: 35727029. [IF: 19.112]

- *Editorial selection on cover*
- *Accompanying Commentary:* Social Deprivation and Urbanization Levels Influence DKA Rates in Germany. In This Issue of Diabetes Care, By Max Bingham

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Initiative, *shared last authorship*. Area deprivation and regional disparities in treatment and outcome quality of 29,284 pediatric patients with type 1 diabetes in Germany: a cross-sectional multicenter DPV analysis. Diabetes Care 2018; 41 (12): 2517-2525. doi: 10.2337/dc18-0724 [IF: 15.270]

Additional publications

Van den Boom L, Auzanneau M, Woelfle J, Sindichakis M, Herbst A, Meraner D, Hake K, Klinkert C, Gohlke B, Holl RW. Use of continuous glucose monitoring in pump therapy (SAP) or automated insulin delivery (AID) in different age groups (0.5 to <26 years) with type 1 diabetes from 2018-2021: Analysis of the German/Austrian/Swiss/Luxemburg DPV registry. In press, accepted on 19.1.2023. J Diabetes Sci Technol. [IF: 3.123]

Eckert A J, Fritsche A, Icks A, Siegel E, Kilian R, Karges W, Rosenbauer J, Auzanneau M, Holl RW. Common procedures and conditions leading to inpatient hospital admissions in adults with and without diabetes from 2015 to 2019 in Germany: a comparison of frequency, length of hospital stay and complications. In press, accepted on 10.1.2023. Wiener klinische Wochenschrift. [IF: 2.275]

Bratina N, Auzanneau M, Birkebaek N, de Beaufort C, Cherubini V, Craig ME, Dabelea D, Dovc K, Hofer SE, Holl RW, Jensen ET, Mul D, Nagl K, Robinson H, Schierloh U, Svensson J, Tiberi V, Veeze HJ, Warner JT, Donaghue KC; Australasian Diabetes Data Network (ADDN) Study Group, the Prospective Diabetes Follow-up Registry (DPV) initiative, Danish National Diabetes Registry (DanDiabKids), National Pediatric Diabetes Audit (NPDA), Region Marche Registry for Diabetes, Diabeter Diabetes Database, Slovenian Childhood Diabetes Registry, SEARCH for Diabetes in Youth Study. Differences in retinopathy prevalence and associated risk factors across 11 countries in three continents: A cross-sectional study of 156,090 children and adolescents with type 1 diabetes. Pediatr Diabetes. 2022 Sep 13. doi: 10.1111/pedi.13416. Epub ahead of print. PMID: 36097824. [IF: 3.409]

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Auzanneau M, Bohn B, Schiel R, Stachow R, Koch S, Hermann T, Holl RW. Inpatient rehabilitation for children and adolescents with diabetes in Germany between 2006 and 2013. Descriptive study based on data from the German Statutory Pension Insurance Scheme. Exp Clin Endocrinol Diabetes 2020 May;128(5):325-331. doi: 10.1055/a-0741-6801. Epub 2018 Oct 2. [IF: 2.058]

Conference contributions

Oral presentations

Auzanneau M. Socioeconomic disparities in access to CGM for adults with diabetes. Results from the DPV registry. ATTD 2023. Berlin, 22-25. Februar 2023

Auzanneau M. Soziale Ungleichheit in der Diabetestherapie. Herbsttagung der Diabetes Gesellschaft in Kooperation mit der Deutschen Gesellschaft für Angiologie – Gesellschaft für Gefäßmedizin e.V. 2022, Wiesbaden. 24- 26. November 2022

Auzanneau M, Schwettmann L, Polier M, Bokelmann J, Askenas M, Haberland H, Rütschle H, Müller-Roßberg E, Holl RW. Diabetestechnologie in der Pädiatrie: Wo stehen wir in Deutschland? Daten des DPV-Registers zum Einfluss demographischer und sozioökonomischer Faktoren auf den Zugang zu SUP und AID in 2021. Gemeinsamen Jahrestagung der Arbeitsgemeinschaft Pädiatrische Diabetologie (AGPD) e.V. und der Deutschen Gesellschaft für Kinderendokrinologie und -diabetologie (DGKED) e.V., JA-PED 2022. Lübeck, 10-12. November 2022

Auzanneau M, Holl RW. CGM-Verwendung bei Erwachsenen mit Typ-2-DM: spielt der soziale Hintergrund eine Rolle? DPV-Anwendertreffen 2022. Online, 28. Oktober 2022

Auzanneau M, Holl RW. AID bei Typ-1-DM: wer verwendet diese Therapieform? DPV Anwendertreffen 2022. Online, 30. September 2022

Auzanneau M, for the DPV initiative. Socioeconomic barriers and disparities to diabetes technology: Experience in Germany. ATTD 2022. Barcelona, Spain, 27-30 April 2022

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Auzanneau M, Rosenbauer J, Maier W, von Sengbusch S., Hamann J, Kapellen T, Freckmann G, Schmidt S, Lilienthal E, Holl RW. Sozialräumliche Einflüsse auf den Zugang zu Diabetestechnologie in Deutschland von 2016 bis 2019: eine DPV-Analyse. DDG Diabetes Kongress 2021. Online, 13. Mai 2021

Auzanneau M, Holl RW. Haben alle Patienten denselben Zugang zu CGM? DPV Anwendertreffen 2020. Online, 27. November 2020

Auzanneau M, Rosenbauer J, Icks A, Karges B, Neu A, Ziegler R, Marg W, Kapellen T, Holterhus PM, Holl RW. Stationäre Versorgung von Kindern mit Diabetes in Deutschland: Analyse von drei verschiedenen Datenquellen. 14. Jahrestagung der DGEpi. Ulm, 11-13. September 2019

Auzanneau M, Karges B, Neu A, Kapellen T, Wudy SA, Grasemann C, Krauch G, Gerstl EM, Däublin G, Holl RW für die DPV Initiative. Stationäre Behandlungsdauer bei Pumpentherapie vs. Injektionstherapie bei 47.160 pädiatrischen Patienten mit Typ 1 Diabetes in Deutschland. Gemeinsame Jahrestagung der Arbeitsgemeinschaft für Pädiatrische Diabetologie e.V. (AGPD) und der Deutschen Gesellschaft für Kinderendokrinologie und –diabetologie e.V. (DGKED) - JA-PED 2018. Weimar, 23.-25. November 2018. (Veröffentlicht in: Monatsschrift Kinderheilkunde 11 (2018) 1054 (FV-24)). *Kooperationsprojekt der Nationalen Diabetes-Surveillance am Robert Koch-Institut*

Auzanneau M, Lanzinger S, Bohn B, Lange K, Boeckmann A, Bartus B, von Sengbusch S, Schenk B, Grasemann C, Rosenbauer J, Maier W für die DPV Initiative. Versorgung von 29.284 Kindern und Jugendlichen mit Typ 1 Diabetes in Deutschland: Einfluss der regionalen Deprivation und der Bundesländer. DDG Diabetes Kongress 2018. Berlin, 10. Mai 2018

Auzanneau M, Bohn B, Holl RW. Kind mit Diabetes im Krankenhaus: was können wir aus verschiedenen Datenquellen lernen? DPV Anwendertreffen 2018. Mainz, 20. April 2018

Auzanneau M, Lanzinger S, Kroschwald P, Kuhnle-Krahl U, Holterhus PM, Placzek K, Hamann J, Bachran R, Bohn B, Rosenbauer J, Maier W für die DPV Initiative. Einfluss regionaler Deprivation auf die Versorgung von 29.284 pädiatrischen Patienten mit Typ-1-Diabetes in Deutschland. JA-PED 2017. Freiburg, 17.-19. November 2017

M. Auzanneau, S. Lanzinger, B. Bohn, J. Rosenbauer, W. Maier, R. W. Holl. Deprivation und regionale Unterschiede: Pumpentherapie und Stoffwechseleinstellung. DPV-Anwendertreffen 2017. Mainz, 12. Mai 2017

W. Maier, S. Lanzinger, M. Auzanneau, B. Bohn, J. Rosenbauer, R.W. Holl. Einfluss regionaler Deprivation auf Stoffwechseleinstellung und Pumpentherapie bei pädiatrischen Patienten mit Typ-1-Diabetes. 12. Jahrestagung der Deutschen Gesellschaft für Epidemiologie (DGEpi). Lübeck, 5-8. Sep. 2017. (Veröffentlicht in: Das Gesundheitswesen. 2017; 79 (8/9): S. 723-724). *Kooperationsprojekt der Nationalen Diabetes-Surveillance am Robert Koch-Institut*

Poster presentations

Auzanneau M, Galler A, Renner C, Praedicow K, Haberland H, Mirza J, Kieninger D, Steigleder-Schweiger C, Laubner K, Holl RW. Gewichtsveränderung bei Patienten mit Typ-1-Diabetes vor und während der COVID-Pandemie: Individuelle Zu- und Abnahme bei Erwachsenen und Kindern anhand der Daten des DPV-Registers. DDG Diabetes Kongress 2022. Berlin, 25-28. Mai 2022

Auzanneau M, Fritsche A, Icks A, Mueller-Stierlin A, Lanzinger S, Holl RW. Stationäre Krankenhausaufnahmen mit und ohne Diabetes: Langzeittrends und erstes COVID-Jahr (DRG-Statistik). DDG Diabetes Kongress 2022. Berlin, 25-28. Mai 2022

Auzanneau M, Maier W, Rosenbauer J, Jacoby U, Kieninger-Baum D, Grasemann C, Sindichakis M, Holterhus PM, Holl RW. Regionale Deprivation ist mit Therapieergebnissen des pädiatrischen Typ-1-Diabetes assoziiert: Analyse nach Deprivationsdomänen und Geschlechtsvergleich. 14. Jahrestagung der DGEpi. Ulm, 11-13. September 2019

Auzanneau M, Maier W, Rosenbauer J, Holterhus PM, Hahn E, Haberland H, Moser S, Holl RW für die DPV Initiative. Regionale Deprivation und Versorgung von 30.512 Kindern und Jugendlichen mit Typ-1-Diabetes in Deutschland: Vergleich von zwei Deprivationsindizes. DDG Diabetes Kongress 2019. Berlin, 31. Mai 2019

Auzanneau M, Lanzinger S, Kroschwald P, Kuhnle-Krahl U, Holterhus PM, Placzek K, Hamann J, Bachran R, Bohn B, Maier W on behalf of the DPV Initiative. The impact of area deprivation on treatment and outcome quality of 29,284 pediatric patients with type 1 diabetes in Germany – results from the German DPV registry. European Congress of Epidemiology. Lyon, France, 4-6. Juli 2018