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

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

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

[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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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).

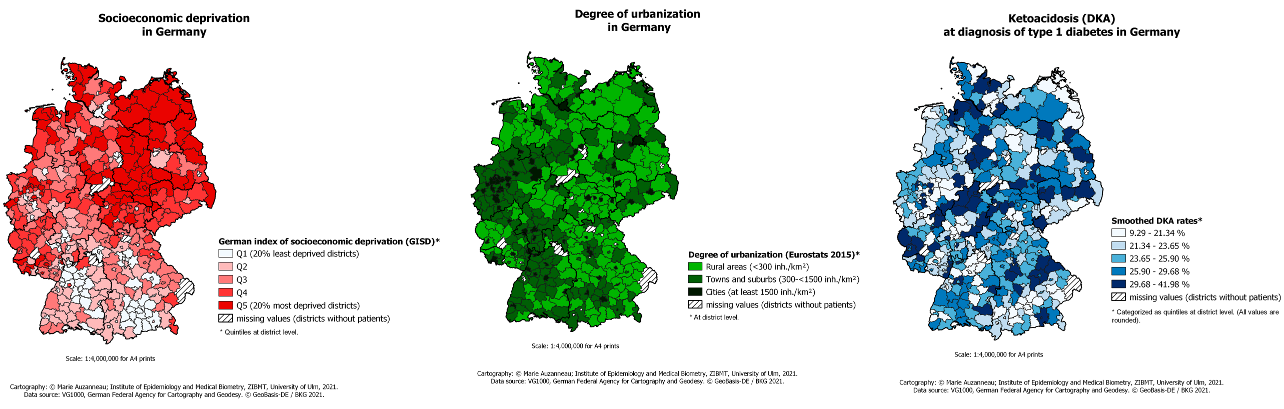

Figure 1—Socioeconomic deprivation, urbanization, and diabetic ketoacidosis (DKA) at diagnosis of type 1 diabetes at the district level in Germany. Socioeconomic deprivation (quintiles), degree of urbanization (three categories), and smoothed rates of DKA at diagnosis adjusted for age-group, sex, and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

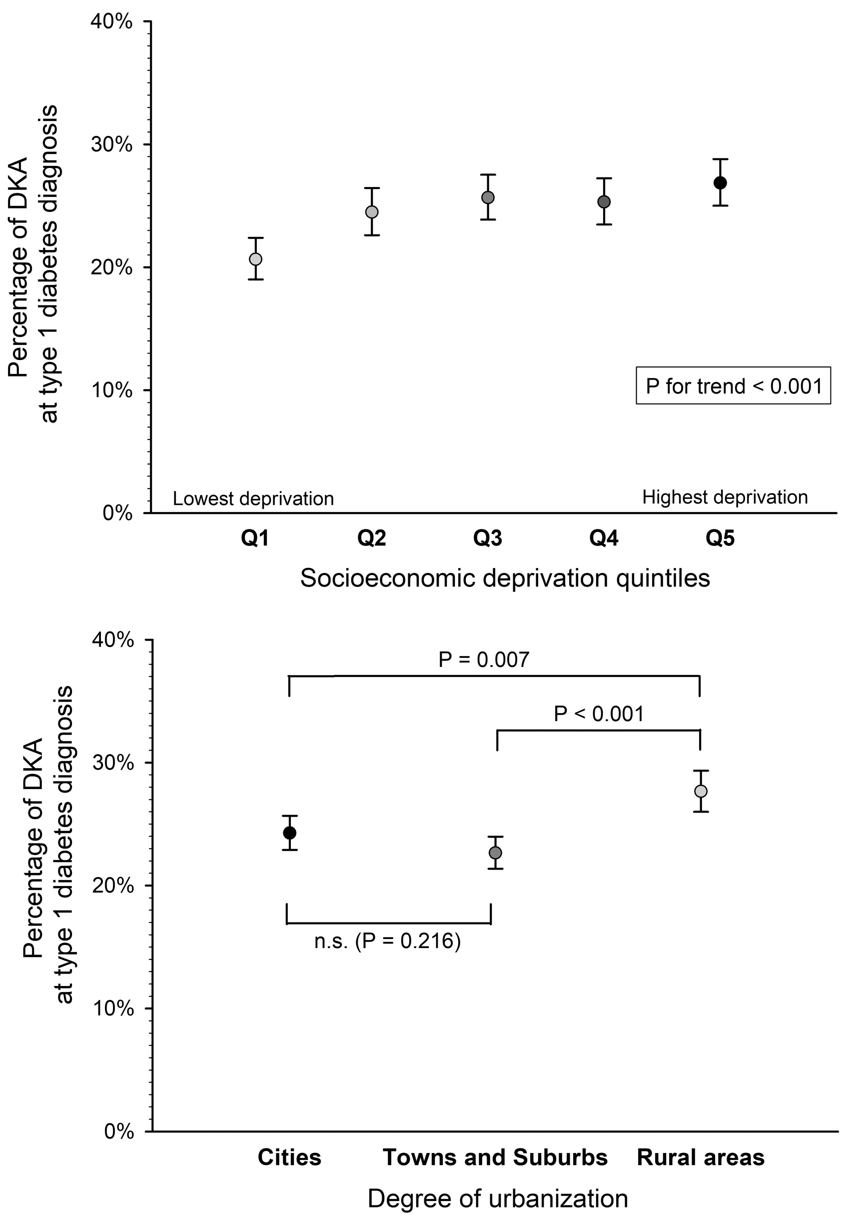

Figure 2—Frequency of DKA at diagnosis by socioeconomic deprivation and urbanization. Percentages of DKA at diagnosis by socioeconomic deprivation quintiles and degree of urbanization are represented using estimates with 95% CIs from logistic regression models, adjusting for sex, age-group, and migration 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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Author Contributions. M.A. created the figures, performed literature research, and wrote the manuscript. M.A. and J.R. performed the statistical analysis. M.A. and W.M. created the maps. M.A. and R.W.H. designed the study. J.R., K.W., C.K., T.H., M.W., J.H., C.S., and K.H. contributed to data collection. All authors reviewed and edited the manuscript. R.W.H. is the coordinator for the DPV Initiative. R.W.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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