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REVIEW

The Challenges of Identifying Environmental Determinants of Type 1 Diabetes: In Search of the Holy Grail

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Abstract: Type 1 diabetes is the result of autoimmune-mediated destruction and inflammation of the insulin-producing β-cells of the pancreas. The excess morbidity and mortality from its complications coupled with its increasing incidence emphasize the importance to better understand the etiology of this condition. It has a strong genetic component, but a genetic predisposition is not the sole contributor to disease development as only 30% to 50% of identical twins both develop the disease. In addition, there are multiple lines of evidence to support that environmental factors contribute to the pathogenesis of type 1 diabetes. Environmental risk factors that have been proposed include infections, dietary factors, air pollution, vaccines, location of residence, childhood obesity, family environment and stress. Researchers have conducted many observational studies to identify and characterize these potential environmental factors, but findings have been inconsistent or inconclusive. Many studies have had inherent methodological issues in recruitment, participation, defining cases and exposures, and/or data analysis which may limit the interpretability of findings. Identifying and addressing these limitations may allow for greatly needed advances in our understanding of type 1 diabetes. As such, the purpose of this article is to review and discuss the limitations of observational studies that aim to determine environmental risk factors for type 1 diabetes and propose recommendations to overcome them.

Keywords: type 1 diabetes, risk factors, epidemiology

Introduction

Type 1 diabetes is the result of autoimmune-mediated destruction and inflammation of the insulin-producing β-cells of the pancreas.[1] It has a strong genetic component, and over the last several decades, multiple loci have been identified in its pathogenesis.[1] But genetic predisposition is not the sole contributor to disease development as only 30% to 50% of identical twins both develop the disease and the incidence of type 1 diabetes has been increasing worldwide by 3% to 5% per year, which is far too quickly if genetic factors were only at play.[1–8]

Multiple lines of evidence support the role of environmental risk factors in the pathogenesis of type 1 diabetes including (1) migration studies showing increased incidence in groups who have moved from areas of low incidence to high incidence[9,10]; (2) shift to earlier onset of disease[11]; (3) increased incidence in all age groups[4];and (4) greatest increase in rate of incidence is observed in previously low-incidence countries.[3,5] Despite this compelling evidence that environmental factors are likely at play, identifying specific factors has been challenging with findings to date being inconsistent or inconclusive.[12]

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Many environmental factors have been postulated in the pathogenesis of type 1 diabetes (Table 1).[12] Viruses have been implicated as an environmental trigger of type 1 diabetes; however, in many cases, the temporal relationship between viruses and type 1 diabetes is unclear.[13–17] Common childhood vaccinations have also been questioned in the etiology of type 1 diabetes; however, well-conducted studies have negated the relationship.[18,19] Dietary factors, like gluten, nitrate, and nitrite intake, have been associated with increased risk of type 1 diabetes; however, studies describe inconsistent results.[20–22] Results from cohort studies suggest that exclusive breastfeeding may have a small protective effect in early infancy, potentially when introducing cereal grains to the infant diet, but evidence is inconclusive.[23,24] Childhood obesity has also been linked to increasing rates of type 1 diabetes, with promising mechanisms proposed, but further studies are required in this area.[25] The increase in type 1 diabetes, as well as other immunologic disorders, may be due to the reduced or lack of exposure to agents that previously children were more exposed to mediated factors such as improved sanitation and hygiene.[26] Researchers refer to this as the "hygiene hypothesis", which suggests that the developing immune system requires stimulation from environmental factors for maturation of immune defenses.[27] Surrogate markers of this hypothesis have been assessed, including gut flora/permeability, rural versus urban residence, and birth order or number of siblings.[12] Finally, the gut microbiome may play an important role in the pathogenesis of islet autoimmunity (leading to type 1 diabetes) with research in this area still underway.[28]

Table 1 Environmental Factors and Type 1 Diabetes[12,93]

Viruses and infections
Enteroviruses[13]
Cytomegalovirus[14]
Mumps[15]
Rubella[15]
Rotavirus[16]
Dietary factors
Breastfeeding[24]
Cow's milk[78,94]
Vitamin D[51]
Nitrates, nitrites, and *N*-nitroso compounds[20,22]
Gluten and fibre[95–97]
Solid foods and cereals[98]
Polyunsaturated fatty acids[99]
Pollutants
Air pollution[100,101]
Toxins[93,102,103]
Chemical compounds[93,102]
Gut microbiome[28]
Urban versus rural residence[104]
Family density[105]
Overload and accelerator hypotheses
Birthweight[104,106]
Childhood growth[107]
Perinatal and psychological stresses[108]
Childhood obesity/overweight[25]
Post-translational modification and neoautoantigens[109,110]

Observational studies pose several challenges, and biases may be introduced in design or analyses, leading to heterogeneity in the literature.[29] The purpose of this article is to review and discuss the methodological issues present in observational studies and outline how they pose challenges in determining environmental risk factors for type 1 diabetes.

Study Participation and Recruitment

There are two main approaches for enrolling participants into observational studies for type 1 diabetes. They include (1) direct recruitment and (2) administrative databases with advantages and disadvantages for each method.

Direct Recruitment

Observational studies that investigate the causes of type 1 diabetes often recruit patients directly from diabetes centres or clinics to participate in research.[30–32] The advantages of this approach include efficiency in the recruitment of participants, detailed information on disease status, detailed clinical information, information on multiple environmental exposures, and the opportunity to follow patients prospectively. Unfortunately, recruiting patients directly can result in selection bias in that non-attendees of clinics are not included in studies. Non-attendees of diabetes clinics have been shown to differ from those that do attend the clinic in their sociodemographic characteristics such as age, sex, and socioeconomic status, resulting in an unrepresentative sample population.[33] While it may be possible to identify potential participants in individual academic centres, few larger national networks of children and adolescents with incident type 1

diabetes exist, so enrolling large cohorts of participants in this manner can be challenging. The Environmental Determinants of Diabetes in the Young (TEDDY) study has done an exemplary job of recruitment by addressing some of these issues.[34] The primary goal of TEDDY, a prospective cohort study, is to determine the environmental causes of type 1 diabetes. Participants are recruited from the general population, at birth, and researchers follow them prospectively throughout childhood or until the development of either islet autoimmunity or type 1 diabetes.[34]

Administrative Databases

Administrative databases have several advantages including population-based sampling, information on multiple exposures, efficiency in recruitment of large sample sizes, and the ability to be linked with other databases be it clinical, laboratory, or other administrative databases. Administrative databases often have independent data recording, which not only minimizes non-response, selection, and recall biases but can also provide both cross-sectional and longitudinal information about prevalence and incidence rates of diabetes at a population level. Several databases and electronic medical records have been used in type 1 diabetes research including the Swedish National Diabetes Register,[35] the Danish Adult Diabetes Database,[36] the Scottish Care Information–Diabetes Collaboration (SCI-DC) database[37] and The Health Improvement Network (THIN).[38] Disadvantages of databases include that they are limited to the variables collected, the way the variables are collected (ie data may be collected by category rather than as a continuous variable), lacking in rich clinical detail, and expensive to create, maintain, and manage. Furthermore, studies that use large diabetes databases are often a secondary analysis of data collected for other purposes. This may lead to issues with data quality (eg missing or nonsense data), crude or surrogate measures of important predictors, and misclassification biases. Confounding may be more difficult to address if important covariate information is not available.[39] Together, although direct recruitment from clinical settings or from databases has advantages, there are also some disadvantages in doing so as outlined above.

Selection of Cases and Controls

Observational studies often draw inferences from comparing cases and controls. However, the procedures used to select cases and controls in observational studies for type 1 diabetes have the potential to introduce biases (Table 2).

Selection Bias

In case–control studies, selection bias occurs when the selection of cases differs from the selection of controls. For example, recruitment of people with type 1 diabetes may occur at speciality diabetes centres through posters in reception areas, direct invitation to participate (eg at clinic appointments), or via registration in an electronic medical record. In contrast, controls may be selected through population registries. Selection bias may occur as cases and controls are selected from two different source populations where cases are recruited from clinics and controls are recruited from the community. For example, in a matched case–control study investigating the risk of atrial fibrillation in people with type 1 diabetes, cases were recruited from a pool of individuals in a diabetes

Table 2 Study Limitations to Consider in Epidemiologic Studies[41]

Study Limitation	Description of Study Limitation
Selection bias	Differential selection of cases and/or controls by exposure or disease status.
Response bias	Recruited participants (e.g. cases and/or controls) differ from non-participants by exposure status.
Prevalence–incidence bias	Prevalent cases may represent a subset of incident cases (i.e. survivors, milder disease, etc.).
Misclassification bias	Error in the classification of an outcome or exposure.
Recall bias	Error in the recollection of an exposure.
Time-varying covariates	Exposures that across time can vary based on time since exposure.
Confounding	The distortion of an exposure-disease relationship due to the association of another factor (or factors) with the exposure and the subsequent influence this has on the outcome.
Missing data	Unmeasured or missing data or information.
Multiple comparisons error	Chance associations from analyzing multiple exposures or factors.
Gene–environment interactions	Heterogeneity across disease phenotypes due to interactions between genes and environmental exposures.

database, while controls (matched by age, sex, and country of residence) were selected from a pool of healthy individuals in the general population.[40] When cases are selected from diabetes clinics, the selection may not be representative of the actual population. First, those with type 1 diabetes, particularly adults, do not necessarily receive centralized care. Instead, they may receive care from a variety of care providers, including general practitioners or family physicians, internists, and endocrinologists so they may not attend diabetes clinics. Second, patients with severe presentations of type 1 diabetes (ie severe diabetic ketoacidosis (DKA)) may die prior to attending the clinic. Finally, community controls may be misclassified or early in their disease course. All these factors require consideration to minimize selection bias in observational studies.

Response Bias

Response bias occurs when the exposure occurs differently in participants of a study than it does in non-participants.[41] Non-responders are known to differ from responders in a number of sociodemographic characteristics and health-related behaviours like age, sex, socioeconomic status, and smoking, all of which have been postulated to be related to type 1 diabetes onset.[42–44] Non-response often occurs in a higher proportion of controls than cases, and many studies do not take this into account. For example, an inverse relationship between socioeconomic status and non-response has been observed.[44] Some studies have demonstrated that type 1 diabetes risk is associated with indicators of higher socioeconomic status.[44,45] Similarly, smoking, alcohol consumption, and drug use all appear to be higher in non-responders.[43,46] In a case–control study, maternal smoking was observed to be protective of type 1 diabetes risk.[47] These findings may need to be interpreted with caution, as statistically significant associations may have been influenced by a non-response bias driving the observed significant associations.[47,48] Investigators using observational studies to determine environmental causes of type 1 diabetes could minimize response bias by recruiting participants from the general population to help ensure socioeconomic and behavioural diversity.

Prevalence–Incidence Bias

Prevalence–incidence bias may occur in observational studies, particularly in case–control studies where selection of participants occurs after onset of the condition. Prevalent cases of a condition only represent a subset of individuals from the source population. Some groups may not be appropriately represented, like those who are rural-residing, migrated, or those who have died.[49] Associations found in prevalence studies may be a reflection of markers of survival or disease progression rather than actual risk factors of a disease.[50] Failure to take these unique population factors into account could skew the resulting data.

Prevalent cases may be a more attractive option for investigators because these cases enhance study feasibility (eg study recruitment), but inferences made from the study of prevalent cases only may lead to inaccurate conclusions. For example, in a systematic review and meta-analysis of 23 studies of children, adolescents, and adults, prevalent cases of individuals with type 1 diabetes had lower levels of serum 25-OH vitamin D compared to age- and sex-matched controls.[51] However, in a study of participants with incident type 1 diabetes, prevalent type 1 diabetes, and healthy controls, serum 25-OH vitamin D levels were low among all groups, and reduced levels were not specifically associated with type 1 diabetes.[52] Following cohorts of study participants prospectively is one of the best ways to minimize the biases often found in prevalence studies.

Misclassification Bias

Misclassification bias results from the errors in classification of the outcome or exposure. Challenges arise using clinical and administrative databases for the study of type 1 diabetes, because surveillance systems may not distinguish diabetes by type.[53] Some investigators have used a combination of features for case ascertainment of type 1 diabetes including age, prescription history (eg insulin use), and/or body mass index, but the validity of these criteria has not been determined.[54,55] Others have used a genetic risk score to identify cases of type 1 diabetes, but the score has only been validated in people of white European descent, limiting its applicability.[56,57] Researchers using clinical or administrative databases to define cases of type 1 diabetes need to carefully select criteria that are valid for the population they are studying, then confirm that the information contained in the database(s) is accurate.

Selection and Definition of Exposure Information

The procedures used to select and define exposure information in observational studies are also subject to introducing several biases (Table 2).

Misclassification Bias

Misclassification (or information) bias occurs with inaccurate classification of the exposure. This bias may be introduced when using databases to ascertain exposure information. For example, studies of infections as an environmental risk factor for type 1 diabetes have been inconsistent and this may be due to misclassification bias.[58–60] In one study, no association was observed between early infections in life and subsequent risk of type 1 diabetes.[60] The authors used a primary care database to collect general practitioner visits for infections and prescriptions for antibiotics. However, infections were likely underestimated as parents may not consult their general practitioner for every infection, particularly milder presentations, and antibiotics are not clinically indicated for many viral infections.[60] Studies using more inclusive criteria, such as serologic markers for enterovirus infection, have demonstrated a significant association with type-1-diabetes-related autoimmunity.[13] Misclassification bias could be minimized by collecting data directly instead of extracting secondary data from databases.

Recall Bias

Recall bias is a systematic difference in the recollection of exposure information among cases and controls. A number of characteristics have been shown to influence recall, including age, education, socioeconomic status, and the time interval since exposure.[61] Several environmental factors for type 1 diabetes have been assessed using survey data that relies on recall, like maternal characteristics and practices, breastfeeding, childhood factors, and dietary habits.[62–67] Recall of dietary habits is especially challenging, as participants cannot always recall their dietary intake accurately.[68] Many breastfeeding studies have retrospective designs that require recollection of exposure history from several years prior.[69] Mothers of children with type 1 diabetes are more apt to recall times when they deviated from breastfeeding recommendations.[69] People may be more likely to recall their exposure information if they are more motivated to discover important links for their condition.[70]

Time-Varying Covariates and Diagnostic Bias

The timing of exposure is another challenge in studying the environmental factors associated with type 1 diabetes. The latency period between time of exposure and type 1 diabetes onset is unknown. Several timelines have been proposed, including a linear process, relapse and remitting process, or a dose threshold (of an environmental agent) but proposed timelines remain hypothetical.[71] Using a feature of the Bradford Hill criteria known as "temporality", an exposure must occur prior to the outcome; however, the timing, dose, and or/threshold is not known for many environmental factors in type 1 diabetes.[72] There is certainty of the timing of some exposures as they are known to have occurred prior to disease onset such as maternal infections in pregnancy and breastfeeding during infancy. It is less clear with other factors that may influence type 1 diabetes risk in a time-dependent fashion. For example, vitamin D levels are known to vary with sun exposure, activity, season, diet, supplementation, and clothing, but some studies of vitamin D have used a single serum sample in their analyses.[73] Similarly, studies of other environmental factors have not collected exposures as time-varying covariates. Instead, the studies applied repeated-measures analysis.[74]

In addition, in case–control studies, the exposure window is often overlooked, and cases and controls have different exposure windows by design. Many studies will match cases with type 1 diabetes to healthy controls on age and sex instead of an index date (eg date of diagnosis). In type 1 diabetes cases, the exposure window ends at disease onset, while controls are given a longer exposure window.[75,76] As such, exposures may be over-represented, which dilutes possible exposure-disease associations. For example, in a case–control study of several environmental risk factors, controls were siblings of children with type 1 diabetes. If there was more than one sibling, the control child would be the one with age closest to the index child. Because controls may have been older, they would have had a longer exposure window at the time of questionnaire administration.[76] This bias can be overcome by assigning an index date of a matched case and not including exposure history after that date. For example, a study on the relationship between serum vitamin D and development of insulin-dependent diabetes matched cases with controls based on five factors, including age, sex, and blood serum collection date for the study.[77] Adding the collection date as an index may have allowed for a more precise estimation of participant exposure windows.

Analytical Methods

Multiple issues may arise in the analytical stage of observational studies for environmental factors related to type 1 diabetes onset (Table 2).

Confounding Data

Isolating the independent effect of any given factor to observe its association with type 1 diabetes is challenging because of potential confounding. Systematic reviews and meta-analyses often fail to control for important confounders. For instance, a systematic review and meta-analysis concluded that breastfeeding for more than 3 months was associated with approximately a 30% risk reduction of type 1 diabetes in those that were breastfed.[78] A subsequent meta-analysis using individual participant data found a smaller protective benefit for type 1 diabetes, possibly because the data allowed for adjustment of potential confounders. Those that were exclusively breastfed for greater than 2 weeks were at decreased risk of developing type 1 diabetes (odds ratio 0.75, 95% CI, 0.64 to 0.88) but the protection was attenuated in those breastfed exclusively for greater than 3 months (odds ratio 0.87, 95% CI, 0.75 to 1.00).[24] Modern cohort studies investigating the environmental determinants of type 1 diabetes address this concern by collecting a variety of data, including child and maternal dietary factors, body mass index, exposure to infectious agents, and psychosocial factors.[34,66,79] Other procedures may be used to control for confounding including matching, restriction and multivariable analysis.

Missing Data

In studies using data collected from clinical and administrative databases, investigators are limited to the data elements collected, so the investigators may not be able to collect information on important factors that may influence type 1 diabetes risk.[39] For example, data to determine an individual's socioeconomic status may not be readily available, so investigators may use proxy measures to approximate exposure at the level of the individual.[80,81] Such proxy measures may be subject to ecological fallacy, where data about an individual are extrapolated from group data, but is not accurate for the individual (ie an individual's income is derived from neighbourhood income estimates, but the individual is unemployed, thus leading to ecological fallacy). Similarly, partial missing observations of data elements pose an issue as data may be missing in a biased manner.[82] For example, illicit drug users may leave survey questions blank as their true responses are perceived as less socially desirable.[70] Some approaches have been suggested to deal with missing data such as (1) using additional data sources; (2) omitting data element with missing data; (3) omitting participants with missing data; (4) using proxy measures; and/or, (5) estimation of missing value.[82] None of these alternatives have the strength of a complete data set.

Multiple Comparison Error

Studies that assess multiple risk factors in one study are often underpowered due to small sample sizes, use of lengthy questionnaires, and application of multivariable analyses without an a priori exposure of interest. Multiple comparison errors can occur when statistically significant findings result from chance alone (ie 5% alpha error rate). For example, in one study of environmental risk factors, the authors aimed to assess the influence of over 70 environmental risk factors on 68 participants with type 1 diabetes.[76] In this case, multivariable regression analyses were applied without consideration of overfitting models. Further, the precision of risk estimates is limited. This is reflected by wide confidence intervals and, subsequently, potential loss of statistical significance.

Gene–Environment Interactions

The onset of type 1 diabetes is likely the result of interplay among various gene and environmental factors that make the study of interactions more complicated. The higher-risk alleles of type 1 diabetes vary among and between populations.[83] Furthermore, Petrone et al have demonstrated *HLA DRB1* and *DQB1* genes influence the age of onset of type 1 diabetes as well as the degree of beta-cell destruction at diagnosis.[84] Few studies have accounted for genetic heterogeneity of their underlying study population like in the prospective birth cohort study of Finnish children where researchers observed an interaction between a polymorphism in the *PTPN22* gene and infant feeding.[85] A *PTPN22* allele was associated with autoantibodies and clinical type 1 diabetes among children exposed to cow's milk before the age of 6 months, but not in among children exposed later. Many studies have not included genetic heterogeneity, which may account for diluted results. Similarly, the distribution of environmental factors may also vary among populations (eg dietary preferences, family sizes, types of infectious agents, etc.), so more work is required to gain further understanding of the gene–environment interactions.

Recommendations

Consider the following when evaluating environmental risk factors for type 1 diabetes.

Prospective Studies

Well-designed prospective cohort studies are important to evaluate environmental risk factors and further advance our understanding of type 1 diabetes.

- Defining and collecting environmental factors prospectively allows researchers to collect robust data that is targeted to type 1 diabetes.
- These studies allow investigators to address and eliminate many biases discussed above by defining environmental factors a priori, collecting information prospectively, and performing appropriate analyses.
- Collecting information prospectively minimizes recall and exposure biases as it allows researchers to rely less on participant recall and limit the time since exposure.

Preliminary results are available from several promising prospective cohort studies that adhere to many of these recommendations.[31,86–92] Many of these studies, which follow large cohorts of healthy individuals to a new diagnosis of type 1 diabetes, are well positioned to determine the environmental factors associated with type 1 diabetes development because they are not subject to the methodological pitfalls of many other observational studies described.

Case–Control Studies

If a case–control study design is used to evaluate environmental determinants of type 1 diabetes, factors to consider are:

- Collecting cases and controls from the same pool of participants.
- If collecting data from a database, the use of a combination of features for case ascertainment is suggested.
- Studies using databases are vulnerable to misclassification bias, particularly if the method of classification has not been validated for the study population and/or the source data have not been reviewed for accuracy.
- If selecting cases from diabetes clinics, be aware that they may systematically differ from those that would be found in the general population (eg those with severe presentations may not attend or die prior to attending).
- Once cases are selected, match them to controls using an index date to represent exposure windows as accurately as possible, and consider that community controls may also be misclassified or early in their disease course.

Analyses

Performing appropriate analyses is also key to a well-designed observational study.

- It is important to be aware of potential confounders and collect data on them so that they can be controlled for.
- Whenever possible, try to work with a complete dataset so that missing data does not need to be accounted for in a different way.
- As more evidence on gene–environment interactions becomes available, researchers will also need to account for genetic heterogeneity of their underlying study population.

Conclusion

Environmental factors play a role in the development of type 1 diabetes, but identifying strong preventive or risk factors have been challenging. Observational studies to identify environmental risk factors for developing type 1 diabetes may have inherent issues in study recruitment and participation; defining cases and exposures; and data analysis. Such issues may limit the interpretability of findings. Investigators looking to conduct research in this area can take steps to identify and address the limitations inherent in observational research. Well-designed studies may allow for greatly needed advances in our understanding of type 1 diabetes.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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