Épidémiologie du diabète de type 1 : incidence mondiale et ses déterminants

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Two angels were born during this thesis:

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To Andrea and in the memory of my beloved brother Rodrigüito

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Paula Andrea Diaz-Valencia

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Summary

Background

Type 1 Diabetes (T1D) is one of the most common metabolic diseases in childhood Soltesz (298). There is a general agreement that the incidence of T1D has been increasing in children since the 1950's. By 1998, using existing data on 37 studies (from 27 countries), the increase of worldwide incidence of T1D was on average 3.0% per year (Confidence Interval (CI) 95% 2.6-3.3) and it was predicted that it will be 40% higher in 2010 (231) in children aged 0-14 years. The causes of this increase are still under study; this thesis updates the current knowledge on the global incidence of T1D and taking advantage of the increasing availability of public databases examines the correlation between incidence and country characteristics.

Methods

A comprehensive systematic literature search of published articles on the incidence of T1D worldwide was conducted to study global variations of the incidence within countries. Were included in the study references whose main subjects were epidemiological studies with reports of T1D incidence from population-based data/registers, and reporting incidence by year and age at diagnosis. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group recommendations (213). The registration number in PROSPERO (International Prospective Register of Systematic Reviews) is: CRD42012002369[1].

The initial goal of this thesis was to study the correlation between environmental variables available in public databases with the country incidence of T1D. Seventy-seven independent factors were searched in public databases of the World Health Organization (WHO), the United Nations (UN) and the World Bank (WB) websites and arranged in four domains *Climate and environment, Demography, Economy,* and *Health Conditions*.

[1] Available on http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369

Correlations and multiple linear regressions between indicators from these domains and incidence of T1D retrieved during the systematic review were then performed. The percentage of variance explained by environmental variables was assessed by 10-fold cross validation.

We also carried out a similar analysis of the genetic component of T1D. The frequency of major HLA (Human Leukocyte Antigens) susceptible and protective haplotypes, corresponding to 21 HLA DR/DQ alleles (DR/DQ are subunits of antigens in humans), as reported by the *Type 1 Diabetes Genetics Consortium Families* (2008) (89) was explored. The *Allele Frequency Net* at the http://www.allelefrequencies.net/ (115) website was used to retrieve information on allele frequencies of worldwide populations. The principal statistical methods used were correlations and linear regression models.

Finally, to better understand the dynamic trends of T1D among all the retrieved information on T1D incidence, we used the Age-Period-Cohort (APC) approaches in this thesis.

For statistical and graphic analyses the R software (version 3.0.1) (255), and for data visualization the Tableau software (262) were used.

Key findings

Through the literature review, 265 selected references that contained epidemiological data about incidence cases of T1D among individuals aged 0-14 years, and 70 references of T1D incidence in those aged over 15 years, published between 1975 and 2014, were collected. Information was available on 86 of the 194 WHO countries and four "territories". The incidence of T1D is highly variable between countries and regions worldwide in both children and adults. In the group of children (0-14 years) it varied from 0.08/100.000 persons/year in Papua New Guinea (230) to 62.42/100.000 persons/year in Finland (128); in the group of young adults (15-19 years), the lowest incidence of T1D was reported in Mauritius, (1.1/100.000 persons/year) (332), and the highest in Estonia (39.9/100.000 persons/year) (157) and in the 70-79 year age group, the lowest incidence was reported in Navarra, Spain (0.8/100.000 persons/year) (97) and the highest in Kronoberg, Sweden (55/100.000 persons/year) (320). Despite the fact that few studies on epidemiology of T1D in adults are available compared to those on children T1D, we were able to show that the

geographical variations of T1D incidence in adults paralleled those reported in children. Also, as opposed to what is known in children, we found that the incidence was in most studies larger in males than in females.

Independently of the initial level of incidence, an incidence increase was observed in all continents from 1960 to 2010: Asia (incidence slope = 0.11 per 100.000 per year), Africa (incidence slope = 0.13 per 100.000 per year) and Latin America and the Caribbean (incidence slope = 0.13 per 100.000 per year) show the smallest increases, Europe (incidence 0.22 per 100.000 per year) presents an intermediate increase, and North America (incidence slope = 0.45 per 100.000 per year) and Oceania (incidence slope = 0.53 per 100.000 per year) the largest.

Finally, after having built a 6824 line x 59 column tidy database (**Appendix A: Database I**), in which we assembled all the incidences by age class and period of the studies from tables, texts and or figures in the 265 articles identified in the systematic review (223 included in the analyses), we extracted data to analyzed information from 2,327,604,529 person-years at risk from 192,741 cases using APC models. A strong cohort effect was observed; in addition the model shows an apparent period effect that decreases after 1987. Also as expected, the incidence of T1D increases with age. These variations are in part explained by the interaction between environmental factors and genetic components of the populations.

For the environmental component, the highest incidences of T1D were noted in the more urbanized, wealthy and cool countries in the world, and with a higher body mass index (BMI) in males. In contrast, exposition to UV radiations showed a significant negative correlation with T1D. Using Stepwise Multiple Linear Regressions (MLR) models the most significant environmental predictors of the country-to-country variation of T1D incidence were UV radiation, number of mobile cellular subscriptions in the country, health expenditure per capita, hepatitis B immunization and mean BMI.

For the genetic component, we then correlated the frequency of HLA alleles retrieved in the *Allele Frequency Net* with the incidence of T1D found through our systematic review. High heterogeneity of susceptible and protector haplotypes for T1D within populations was found. Seven significant correlations were noted. Using Stepwise MLR models, significant

variables were the susceptible alleles: DRB1*04:01 (p-value = 0.0001) and DRB1*08:01 (p-value = 0.0032).

Conclusions and implications

During this thesis, using a comprehensive systematic review of the literature, we quantified the country-to-country variation in T1D incidence worldwide in children and adults, and show that a large part of this incidence could be accounted by the variability of environmental factors within the countries.

This thesis was initially motivated by the increase in T1D incidence. Here we could quantify this increase and show that it was even larger than had been predicted in an earlier study (231).

This thesis was also based on the will to take advantage of the increasing availability of public databases providing informing on the country-to-country variation of environmental and genetic factors. For the moment much data are missing, some of them are low quality, in particular in low-income countries, where information on T1D incidence is still lacking. However, we are confident that in the near future high quality information on T1D incidence will be available, as well as genetic and environmental factors that will allow deepening of the approach used here, and will unravel new clues on the gene-environment causality of T1D.

Résumé

Introduction

Le diabète de type 1 (DT1) est une des maladies métaboliques les plus répandues chez les enfants (298). Les recherches s'accordent pour dire qu'il y a une augmentation de l'incidence du DT1 chez les enfants depuis 1950. En 1998, en utilisant les données sur 37 études (de 27 pays), l'augmentation de l'incidence mondiale du DT1 a été calculée à 3,0% en moyenne (intervalle de confiance (IC) 95% 2,6 à 3,3), et il a été prédit qu'elle serait de 40% en 2010 (231) chez les enfants âgés de 0 à 14 ans. Les causes de cette augmentation ne sont pas encore déterminées; cette thèse met à jour les connaissances actuelles sur l'incidence mondiale du DT1, en profitant de la disponibilité croissante des bases de données publiques et en examinant la corrélation entre l'incidence et les caractéristiques des pays.

Méthodes

Revue systématique de la littérature

Une recherche exhaustive et systématique des articles publiés sur l'incidence du DT1 dans le monde a été effectuée pour étudier les variations globales de cette incidence dans les divers pays. Ont été inclus dans cette étude, les articles épidémiologiques qui rapportent l'incidence de DT1 dans la population générale, et qui rapportent l'incidence par âge et par année au moment du diagnostic. Nous avons suivi les recommandations de PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (213). Le numéro d'inscription à PROSPERO (International Prospective Register of Systematic Reviews) est: CRD42012002369[2].

Nous avons développé une méthode comportant sept étapes pour obtenir une équation de recherche bibliographique, dans laquelle les 92 articles précédemment récupérés ont été trouvés (voir **Annexe B)**, mais en ajoutant de nouvelles références qui sont identifiées ici

[2] Disponible sur http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369

comme «requête # 9». En résumé, les sept étapes utilisées pour obtenir la recherche finale sont:

- ***Étape 1***. L'analyse du terme MeSH (Medical Subject Headings) présent dans les 92 articles sélectionnés et inclus dans la base de données.
- ***Étape 2***. Une nouvelle recherche dans MeSH Recherche avancée de PubMed en tenant compte les principaux termes MeSH trouvées dans l'étape 1.
- ***Étape 3***. La vérification du terme MeSH pour repérer les références non pertinentes, de manière à mieux repérer les termes MeSH les plus communs et les plus pertinents.
- ***Étape 4***. Etablir une nouvelle équation de recherche comme dans l'étape 1 avec les termes MeSH les plus communs trouvées dans les articles pertinents en utilisant le constructeur NOT pour exclure les articles non pertinents.
- ***Étape 5***. Comparer les références retrouvées dans les différentes (nouvelles) recherches. Par exemple, si nous avons deux recherches, la recherche A et la recherche B, en utilisant une stratégie telle que les diagrammes de Venn (A∪B, A∩B), les références retrouvées dans les recherches seront explorées comme suit: la recherche A NOT la recherche B et la recherche B NOT la recherche A. Les 60 premières références de chaque recherche seront examinées: la recherche A, la recherche B, la recherche A NOT la recherche B, et la recherche B NOT la recherche A, en analysant les termes MeSH inclus afin de déterminer si elles sont pertinentes. Une fois que les termes MeSH ont été sélectionnés de façon plus précise, on a répété les étapes 3-5 dans la recherche sélectionnée jusqu'à ce que moins de 50% (25/60) des articles examinés ont été désignés pertinents. Dans cette stratégie, nous avons identifié les recherches pour lesquelles un numéro spécifique peut être attribué en fonction de la formulation de la recherche, par exemple : «requête # 0», ..., «requête # 9».
- ***Étape 6***. Examiner les résultats de la requête sélectionnée pour vérifier que toutes les 92 références de base de données sont inclues.
- ***Étape 7***. Répéter les étapes 2-7 jusqu'à ce qu'une majorité de 92 articles soient inclus.

Les équations de recherche ont été mises à jour périodiquement, la ayant été mise à jour en Novembre 2014. Les détails des sept étapes proposées sont présentés dans **l'Annexe C**.

Extraction des données

Les données brutes ont été extraites des articles, et introduites manuellement dans une grille de collection de données, « **Annexe A**: **base de données I** », en utilisant le logiciel Microsoft Excel. Les données de l'incidence ont été prélevées des études individuelles comme elles ont été signalées dans les publications dans les textes, les tables ou les graphiques; un logiciel a été utilisé pour extraire les données d'origine (x, y) à partir des images (1). La **Table 1** présente les principales catégories de l'extraction des données inclues dans la base de données principale (**Annexe A**: **base de données I**).

Table 1: Information extraite des documents et inclue dans la base de données

Informations sur l'étude	Informations sur l'incidence
Nombre d'identifications de la référence	Incidence moyenne par pays / zone
Nom du premier auteur	L'âge du début et la période au cours de laquelle le DT1 a fait son apparition
Date de publication (reçu / accepté / publié)	Incidence par genre: masculin, féminin et les deux ensemble.
Région du monde / pays / domaine d'étude	Augmentation annuelle de l'incidence
Période du début de l'étude / date de fin	Nombre de cas incidents
Durée de l'étude	Population à risque pendant la période
Tranche d'âge couverte par l'étude	Critères diagnostic de DT1
Source d'information des données de la population	**informations Complémentaires**
Conception de l'étude: historique, prospective ou les deux	Indicateur sur la gestion du diabète en 2010 (OMS)
Les analyses statistiques utilisées dans l'étude	Signaler si l'information a été standardisée
Pourcentage de détermination	Sources de l'information extraite (table, texte ou figure)

Objectifs de la revue systématique

Étudier les informations publiées sur l'incidence du DT1 au niveau mondial depuis 1950.

Objectifs spécifiques

- Décrire l'incidence mondiale du DT1 au niveau de chaque pays.
- Décrire l'épidémiologie du DT1 chez les enfants et les adultes au niveau mondial.

- Étudier la co-variation, au niveau des pays, de l'incidence du DT1 avec les déterminants environnementaux et génétiques disponibles dans les bases de données publiques.
- Analyser si la tendance mondiale actuelle de l'incidence du DT1 est compatible avec un effet de période ou de cohorte de naissance.

Statistiques

Les tendances d'incidence ont été corrélées avec des facteurs environnementaux et génétiques, et modélisées en utilisant une approche APC.

Pour les analyses statistiques et graphiques le logiciel R (version 3.0.1) a été utilisé (255), et pour la visualisation des données le logiciel Tableau (262).

Déterminants environnementaux analysés

L'objectif initial de cette thèse était d'étudier la corrélation entre les variables environnementales disponibles dans les bases de données publiques, et l'incidence du DT1 selon les pays. Pour corréler les variables environnementales à l'incidence du DT1, présentées dans le **chapitre 3**, des facteurs indépendants ont été recherchés dans les bases de données publiques de l'Organisation Mondiale de la Santé (OMS), l'Organisation des Nations Unies (ONU) et la Banque Mondiale (WB), et disposés dans quatre domaines : *Climat et environnement, Démographie, Economie,* et *Etat de* Santé. Nous avons examiné tous les indicateurs présentant une relation plausible avec le DT1 et ceux qui précédemment on été rapportés dans la littérature comme corrélés avec le DT1, et pour lesquels il y avait moins de 5% de valeurs manquantes. Ceci a donné 77 indicateurs. Des corrélations et des régressions linéaires multiples parmi les indicateurs récupérés, lors de la revue systématique de ces domaines ont ensuite été réalisées. Le pourcentage de la variance expliquée par des variables environnementales a été évalué par la méthode de 10 fois la validation croisée.

Analyse des déterminants génétiques

Nous avons également réalisé une analyse similaire à celle décrite ci-dessus concernant les variables environnementales, pour les composantes génétiques du DT1 présentés au **chapitre 6**. Pour les analyses génétiques, la fréquence des haplotypes de HLA (Human Leukocyte Antigens) qui confèrent la susceptibilité à, ou la protection contre le DT1, correspondant à 21 HLA allèles DR/DQ (DR/DQ sont des sous-unités d'antigènes chez les humains), rapportés par le *Type 1 Familles génétiques du Consortium diabète* (2008) a été exploré (89). L'*Allele Frequency Net* à http://www.allelefrequencies.net/ (115) a été utilisé pour récupérer des informations sur les fréquences des allèles dans les populations à travers le monde. Les principales méthodes statistiques utilisées étaient des corrélations et des modèles de régression linéaire.

Analyses des tendances de l'incidence mondiale du DT1

Enfin, afin de mieux comprendre les tendances dynamiques du DT1 avec toutes les informations récupérées sur l'incidence du DT1, nous avons utilisé l'APC présenté dans le **chapitre 5.**

Principaux résultats

Informations recueillies lors de la revue systématique

Grâce à la revue de la littérature publiée entre 1975 et 2014, 265 références ont été sélectionnées, qui contenaient les données épidémiologiques sur les cas d'incidences de DT1 chez les individus âgés de 0-14 ans. Chez les personnes de plus de 15 ans, 70 références ont été sélectionnées.

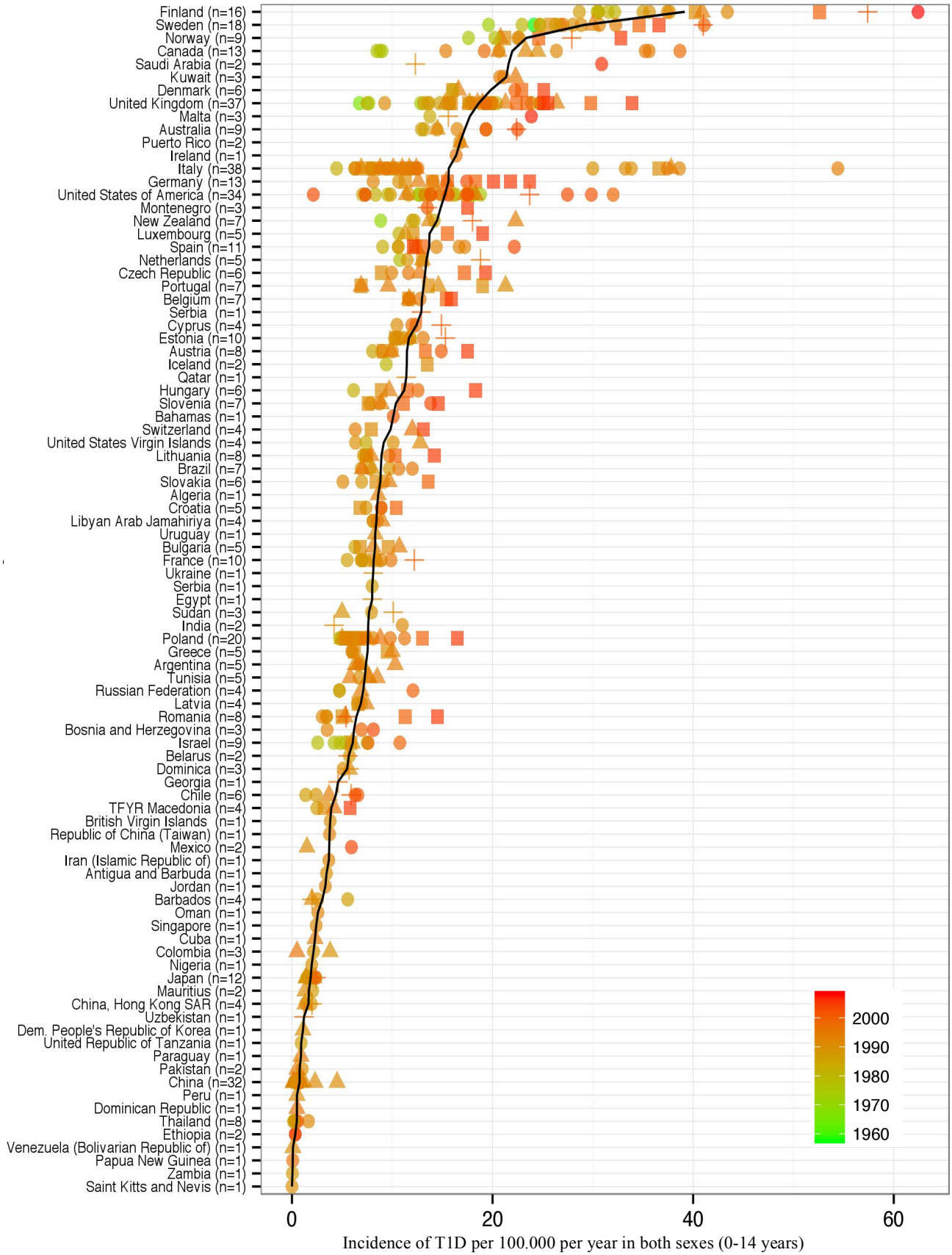
Parmi les enfants âgés de 0 à 14 ans, cette revue systématique a récupéré 237 documents de PubMed et GoogleScholar, couvrant 86 pays et quatre «territoires», et 28

documents supplémentaires, des résumés et des informations mises à jour pour la IDF (International Diabetes Federation) dans l'Atlas de la IDF (300) ont été joints. De ces 265 références, nous avons extrait 527 ensembles de données. Parmi ces 527 ensembles de données, 298 étaient des études individuelles, et 201 étaient des études de collaboration internationale (114 de l'étude Diamond en 2006 (318), 44 de l'étude EURODIAB en 2000 (90), 21 de l'étude EURODIAB en 2009 (242), 22 de l'étude EURODIAB en 2012 (243)), et 28 de l'Atlas de l'IDF (300) ; **Figure 1.**

Parmi les jeunes de plus de 15 ans, 70 articles rapportant l'incidence du DT1 dans le pays, et un article concernant deux pays ont été récupérés dans cette revue, résultant en un total de 71 études portant sur 35 pays, et 24 des 71 études étaient à l'échelle nationale. 43 documents ont fourni des informations sur l'incidence du DT1 dans la classe d'âge 15-29 ans, 26 dans la classe d'âge 30-59 ans et 6 chez les personnes de plus de 60 ans.

Tendances de l'incidence mondiale du DT1

L'incidence du DT1 est très variable selon les pays et les régions du monde pour les enfants et les adultes. Dans le groupe d'enfants de 0-14 ans, l'incidence varie de 0,08 / 100.000 personnes / an en Papouasie-Nouvelle-Guinée (230) à 62,42 / 100.000 personnes / an en Finlande (128). Dans le groupe de jeunes de 15-19 ans, la plus faible incidence du DT1 a été signalée dans l'île Maurice, (1,1 / 100.000 personnes / an) (332), et la plus élevée en Estonie (39,9 / 100.000 personnes / an) (157) et dans le groupe d'âge de 70-79 ans, le taux le plus faible a été signalé en Navarre, Espagne (0,8 / 100.000 personnes / an) (97) et le plus élevé à Kronoberg, Suède (55 / 100.000 personnes / an) (320); **Figure 1**.



(n =) nombre de l'ensemble de données récupérées par pays. Symboles géométriques: les triangles indiquent l'ensemble des données de l'étude Diamond (n = 114) (318), les carrés indiquent les bases de données de EURODIAB (n = 87) (90, 242, 243), les signes "+" indiquent les données de la IDF (n = 28) (241, 300) et les cercles sont des autres publications que nous avons récupérée (n = 298); ils sont colorés pour visualiser la tendance de l'incidence (vert: 1958 à rouge: 2009). La ligne noire représente l'incidence moyenne du DT1 de chaque pays. Pour la liste détaillée des études et ensemble des données voir **Base de données II.**

Figure 1: Variation de l'incidence du DT1 dans 90 pays

Indépendamment de l'incidence initiale, une tendance à l'augmentation de l'incidence dans tous les continents entre 1960 et 2010 a été observée: l'Asie (pente d'incidence = 0,11 pour 100.000 personés par an), l'Afrique (pente d'incidence = 0,13 pour 100.000 par an) et l'Amérique latine et les Caraïbes (pente d'incidence = 0,13 pour 100.000 par an) ont montré les plus faibles hausses, l'Europe (pente d'incidence de 0,22 pour 100.000 par an) a présenté une augmentation intermédiaire, et l'Amérique du Nord (pente d'incidence = 0,45 pour 100.000 par an) et l'Océanie (pente d'incidence = 0,53 pour 100.000 par an) la plus grande augmentation d'incidence.

Incidence du DT1 chez les jeunes et les adultes

Peu d'études sur l'épidémiologie du DT1 chez les adultes sont disponibles par rapport à celles sur les enfants atteints de DT1. Cependant, même avec la quantité limitée de données disponibles, nous avons pu montrer que les variations géographiques de l'incidence du DT1 chez les adultes suivent une voie parallèle à celles rapportées chez les enfants. Une corrélation géographique importante, mesurée par le coefficient de corrélation de Spearman, a été trouvée entre l'incidence du DT1 chez les enfants de 0-14 ans et chez les adultes dans les classes d'âge 15-19 ans, 20-24 ans, 25-29 ans, 30-34 ans et globalement dans l'ensemble du groupe de 15 à 60 (r = 0,75; p -valeur: 5,7 $X10^{-10}$). Dans 23 des 35 pays (66%) (55 de 71 études), l'incidence du DT1 était plus élevée dans la tranche d'âge de 0 à 14 ans par rapport aux 15 à 19 ans. Contrairement à ce qui est connu chez les enfants, l'incidence était généralement plus élevée chez les hommes que chez les femmes. Le rapport moyen hommes-femmes chez les adultes utilisé dans notre revue était 1,47 (IC à 95% pour la moyenne de 1,33 à 1,60; SD = 0,49; n = 54; p = <0,0001).

Tendances de l'incidence du DT1 en utilisant un modèle Age-Période-Cohorte

Après avoir construit un base de données comportant 6824 lignes x 59 colonnes, dans laquelle nous avons recueilli toutes les incidences par classe d'âge et la période des études, Ces données ont été prélevées de tables, textes et/ou des figures contenus dans les 265 articles identifiés par la revue systématique. Nous avons extrait des données à analyser (223 articles sélectionnés) en utilisant des modèles APC, des informations équivalentes à 2,327,604,529 années-personnes à risque et de 192,741 cas de DT1 ont été analysés. Avec le

modèle APC un fort effet de cohorte a été observé; le modèle indique également un effet période probable qui diminue après 1987. Finalement, comme prévu, l'incidence du DT1 augmente avec l'âge. Ces variations s'expliquent en partie par l'interaction entre les facteurs environnementaux et les composants génétiques des populations.

L'ensemble des données réunies dans le modèle APC provenaient de pays européens (*n* = 2007), suivie par l'Amérique du Nord (*n* = 527) et l'Asie (*n* = 499). La période de 1989 à 1993 fut celle comportant le plus grand nombre d'ensembles de données (*n* = 844), suivie de 1984 à 1988 (*n* = 643) et de 1994 à 1998 (*n* = 550); **Figure 2.**

Age (years) / Last year of the five-year period	1938	1943	1948	1953	1958	1963	1968	1973	1978	1983	1988	1993	1998	2003	2008	2013	Total
0 _ 4	2	5	5	6	15	32	35	48	77	121	215	281	183	111	43	7	1186
5 _ 9	2	5	5	6	6	22	38	61	78	123	216	283	185	115	43	7	1195
10 _14	2	5	5	6	6	7	28	60	77	121	212	280	182	112	43	7	1153
Total	6	15	15	18	27	61	101	169	232	365	643	844	550	338	129	21	3534

Le gradient du vert au rouge représente le nombre d'ensemble de données trouvé par classe d'âge et vert foncé <10 au rouge> 20. L'âge est la moyenne pour chaque classe d'âge (0-4, 5-9, 10-14), chaque période correspondant à cinq années calendrier.

Figure 2: Répartition de l'information (bases de données) utilisée dans le modèle APC

Déterminants environnementaux de l'incidence du DT1

Pour la composante environnementale, les incidences les plus élevées de DT1 ont été trouvées dans les pays plus urbanisés, riches et froids dans le monde, et avec un indice de masse corporelle (IMC) élevé chez les hommes. En revanche, l'exposition aux radiations UV a montré une corrélation négative significative avec le DT1. L'utilisation de modèles de régression linéaire multiple (MLR) *Stepwise* effectués dans les quatre domaines explorés indiquent que les pourcentages de variance expliqués par les indicateurs étaient respectivement de 35% pour le *Climat et l'environnement*, 33% pour la *Démographie*, 45% de pour l'*Economie* et 46% pour les *Conditions de Santé*, et 51% dans le *Modèle Final (*41% après 10 fois la validation croisée), où toutes les variables sélectionnées ont été examinées. Les facteurs prédictifs environnementaux les plus importants de la variation de l'incidence du DT1 pays à pays étaient: rayonnement UV, nombre d'abonnements au cellulaire mobile dans le pays, les dépenses de santé par habitant, vaccination contre l'hépatite B et l'IMC moyen.

Les déterminants génétiques de l'incidence du DT1

Pour les composants génétiques, nous avons corrélé la fréquence des allèles HLA récupérés sur l'*Allele Frequency Net,* avec l'incidence du DT1 par pays trouvé grâce à notre revue systématique. Une grande hétérogénéité des haplotypes susceptibles ou protecteurs face au DT1 au sein des populations a été trouvée. Sept corrélations significatives ont été détectées parmi les 21 allèles testés (12 conférant une susceptibilité et 9 une protection face au DT1). Après la MLR *Stepwise* les variables significatives étaient les allèles sensibles: DRB1*04:01 ($p = 0,0001$) et DRB1*08:01 ($p = 0,0032$). Dans le modèle le pourcentage brut ajusté de la variance expliquant (R^2) était du 61%, et 30% après 10 fois la validation croisée. Seul l'allèle de protection DQB1*06:02 présentait une corrélation positive significative avec la répartition géographique de l'incidence du DT1.

Conclusions et implications

Au cours de cette thèse, grâce à l'aide d'une revue systématique et exhaustive de la littérature, nous avons quantifié la variation pays par pays de l'incidence du DT1 dans le monde chez les enfants et les adultes, nous montrons qu'une grande partie de cette incidence pourrait s'expliquer par la variabilité de facteurs environnementaux dans les pays.

L'information de l'incidence du DT1 chez les enfants a été trouvée dans 265 références couvrant 90 pays; l'information sur le DT1 chez les adultes n'est disponible que dans 35 pays, et seule une petite proportion ($n = 14$) des 71 études ont utilisé la détection d'auto-anticorps et / ou le dosage spécifique du C-peptide (34) comme critères de diagnostic du DT1 chez les adultes.

Malgré le peu d'information sur le DT1 chez les adultes, nous avons trouvé une forte corrélation géographique des incidences chez les adultes et les enfants. Cette corrélation peut s'expliquer par le fait que les adultes atteints de DT1 partagent les allèles de gènes connus comme étant associés au DT1 juvénile, (49, 322), et / ou certaines causes environnementales prédisposant au DT1 (81).

Entre les déterminants génétiques de DT1 présentés au **chapitre 6**, où nous avons exploré certains haplotypes HLA face au DT1, dans le Complexe Majeur d'Histocompatibilité (CMH), qui joue un rôle crucial dans la pathogenèse du DT1 (182). Nous avons constaté que certains haplotypes de protection dans une population peuvent conférer une sensibilité dans d'autres populations. Le deuxième constat est que, parmi tous les allèles étudiés, DRB1 * 04:01 et DRB1 * 08:01 étaient des prédicteurs significatifs de l'incidence du DT1 dans l'ensemble des 56 pays pour lesquels nous pourrions corréler des allèles HLA. Cette constatation suggère que ces allèles sont déterminants dans le risque de DT1, comme cela a été suggéré par le *T1D Genetics Consortium Families* (89) qui ont montré que le risque du DT1 est conféré par des allèles DRB1. Apparemment, allèles sensibles sont plus fréquentes que les allèles de protection et des mécanismes épigénétiques sont impliqués (182).

Entre les déterminants environnementaux indépendants de DT1 présentés dans le **chapitre 3**, quatre des cinq indicateurs sélectionnés sont connus comme étant des facteurs de risque de DT1: les rayons UV (214, 295, 304), les dépenses de santé par habitant (214), le pourcentage de couverture de la vaccination contre l'hépatite B (138) et la moyenne IMC (91). Le dernier indicateur est la proportion d'abonnements à un téléphonie mobile, en corrélation positive avec l'incidence DT1. C'est probablement un marqueur de style de vie qui n'a pas été capturé par l'une des 77 variables utilisées dans les analyses multiples effectuées.

Cette thèse a été initialement motivée par l'augmentation de l'incidence du DT1, et nous avons pu quantifier cette augmentation et montrer qu'elle était encore plus grande que ce qui avait été prédit dans une étude antérieure (231).

Après avoir utilisé un modèle APC, comme présenté dans le **chapitre 6**, nous avons observé que l'incidence du DT1 montre des tendances dynamiques à travers le monde. Un fort effet de cohorte de naissance et un effet apparent de période ont été observés. La courbe représentant l'effet de cohorte de naissance montre une augmentation constante après 1975; dans les années 1980 le risque relatif (RR) était = 1 et dans les années 2000, RR = 2,5. Étonnamment, une diminution de la courbe représentant un effet de période apparaît après le pic en 1987, principalement influencé par les données de la Finlande, le pays ayant la plus forte incidence de DT1 dans le monde. En outre, nous avons constaté que l'incidence du DT1

augment avec l'âge; le taux le plus élevé est celui des personnes de 10 à 14 ans. Nos résultats sont en accord avec l'hypothèse que des facteurs externes, y compris les déterminants de risque environnementaux, et d'autres causes non génétiques pourraient être des promoteurs ou des facteurs modificateurs impliqués dans le changement de tendances de l'incidence du DT1 à travers le monde.

Cette thèse a également profité de la disponibilité croissante de données publiques sur la variation des facteurs environnementaux et génétiques de pays à pays. Pour le moment, beaucoup de données manquent, certaines d'entre elles étaient de faible qualité, en particulier dans les pays à faibles revenus, où l'information sur l'incidence du DT1 n'est pas encore disponible. Cependant, nous sommes convaincus que dans un avenir proche des informations de qualité sur l'incidence du DT1 seront disponibles, ainsi que les informations sur les facteurs génétiques et environnementaux, permettant l'approfondissement de l'approche utilisée ici, et pouvant révéler de nouveaux indices sur les causes génétiques et environnementales du DT1.

Scientific production during the thesis

I. Production related with the Thesis

Accepted publications

Diaz-Valencia PA, Bougnères P, Valleron AJ (2015). "Global epidemiology of Type 1 diabetes in young adults and adults. A Systematic Review", *BMC Public Health*. 15(255). doi:10.1186/s12889-015-1591-y

Diaz-Valencia PA, Bougnères P, Valleron AJ (2015). "Covariation of the Incidence of Type 1 Diabetes with Country Characteristics Available in Public Databases", *PLoS ONE,* 10(2): e0118298. doi:10.1371/journal.pone.0118298.

Diaz-Valencia PA, Bougnères P, Valleron AJ (2014). "Incidence mondiale de diabète de Type 1: revue systématique et corrélation avec des bases de données publiques", *Revue d'Épidémiologie et de Santé Publique*. Volume 62, Supplement 5, September 2014; S225-226. http://dx.doi.org/10.1016/j.respe.2014.06.175

Publications in preparation

Diaz-Valencia PA, Boëlle PY, Bougnères P, Valleron AJ (2015). "Age-Period-Cohort analysis of the Global Incidence trends of Type 1 diabetes".

Diaz-Valencia PA, Le Fur S, Bougnères P, Valleron AJ (2015). "Geographical covariation of Type 1 Diabetes Incidence and genetic markers".

Oral presentation

Anticipation in the Age at Onset of Type 1 Diabetes increased incidence trends worldwide: a literature review (1975-2011). Diaz-Valencia PA. Director: Alain-Jacques Valleron, Co-director: Pierre Bougnères. "*5ª Jurnée des Doctorants et Posdoctorants de Saint-Antoine*". Grand Amphi Sorel, Hospital Trousseau. May, 10. 2012. Paris, France

Poster presentations

Incidence mondiale de diabète de Type 1: revue systématique et corrélation avec des bases de données publiques. Diaz-Valencia PA. Director: Alain-Jacques Valleron, Co-director: Pierre Bougnères. "*Seminaire Annuel: École Doctorale Pierre Louis de Santé Publique à Paris, Epidemiologie et Sciences de l'Information Biomédicale, Saint Malo 2014*"; Oct 20-22, 2014. Saint Malo, France.

Incidence mondiale de diabète de Type 1: revue systématique et corrélation avec des bases de données publiques. Diaz-Valencia PA. Director: Alain-Jacques Valleron, Co-director: Pierre Bougnères. "*VIe Congrès International d'Épidémiologie, organisé conjointement par l'Association des Épidémiologistes de langue française (Adelf) et par l'Association pour le développement de l'EPIdémiologie de TERrain (EPITER)",* Sept. 10-12, 2014. Nice, France.

New onset Type 1 diabetes in adults: an underestimated disease Diaz-Valencia PA. Director: Alain-Jacques Valleron, Codirector: Pierre Bougnères. "*Young Researchers in Life Sciences*". Institut Pasteur ; May 26-28, 2014. Paris, France.

Updating worldwide incidence in type 1 diabetes: a systematic literature review (1975-2012). Diaz-Valencia PA. Director: Alain-Jacques Valleron, Co-director: Pierre Bougnères. "*Seminaire Annuel: École Doctorale Pierre Louis de Santé Publique a Paris, Epidemiologie et Sciences de l'Information Biomédicale, Saint Malo 2012*". Oct. 9-11, 2012. Saint Malo, Bretagne, France.

Anticipation in the Age at Onset of Type 1 Diabetes increased incidence trends worldwide: a literature review (1975-2011). Diaz-Valencia PA. Director: Alain-Jacques Valleron, Co-director: Pierre Bougnères. "*Young Researchers in Life Sciences*". Universite Paris Diderot. Amphi Buffon – Bâtiment Buffon – Campus Paris Diderot. May 14-16, 2012. Paris, France.

Trends of type 1 diabetes incidence and age at onset: a literature review (1990-2011). Diaz-Valencia PA. Director: Alain-Jacques Valleron, Codirector: Pierre Bougnères. "*Seminaire Annuel: École Doctorale Pierre Louis de Santé Publique à Paris, Epidémiologie*

et Sciences de l'Information Biomédicale, Saint Malo 2014". Oct. 19-21, 2011. Saint Malo, France.

II. Production without relation to the thesis

Diaz-Valencia PA, Martinez E. Tabaquismo, contaminación ambiental y función pulmonar. Evaluación de los efectos del tabaquismo y la contaminación ambiental en la función pulmonar de personas adultas. *Editorial Académica Española*. 2014. ISBN: 978-3-659-08625-0. Book

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Martinez E, Diaz-Valencia PA. Capitulo 6. Enfermedades cardiovasculares, Tomo III: Morbilidad y mortalidad de la población colombiana. In: *Ministerio de la Protección Social y Universidad de Antioquia Facultad Nacional de Salud Pública*, editor. Análisis de la Situación de la Salud en Colombia, 2002-2007. Bogota-Colombia: 2011. ISBN: 978-958-8717-07-4. Book chapter

Martinez E, Diaz-Valencia PA, Juan Fernando Saldarriaga. Capitulo 7. Diabetes, Tomo III: Morbilidad y mortalidad de la población colombiana. In: *Ministerio de la Protección Social y Universidad de Antioquia Facultad Nacional de Salud Pública*, editor. Análisis de la Situación de la Salud en Colombia, 2002-2007. Bogota-Colombia: 2011. ISBN: 978-958-8717-07-4. Book chapter

Martinez E, Diaz-Valencia PA, Juan Fernando Saldarriaga. Capitulo 8. Sobrepeso y Obesidad, Tomo III: Morbilidad y mortalidad de la población colombiana. In: *Ministerio de la Protección Social y Universidad de Antioquia Facultad Nacional de Salud Pública*, editor. Análisis de la Situación de la Salud en Colombia, 2002-2007. Bogota-Colombia: 2011. ISBN: 978-958-8717-07-4. Book chapter

Diaz-Valencia PA, Peñaranda F, Cristanho S, Caicedo N, Garcés M, Alzate T, et al. Education for health: perspectives and experiences from higher education in the health

sciences, Medellin Colombia (Educación para la salud: perspectivas y experiencias de educación superior en ciencias de la salud). Medellín, Colombia. *Rev. Fac. Nac. Salud Pública* 2010; 28(3): 221-230. Research article

Contents

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Introduction

This thesis concerns the study of Type 1 Diabetes (T1D) and is based on the original articles presented in **Chapters 3, 4, 5 and 6**. Each chapter reproduces the articles with the kind permission of their authors, and in addition supplementary information is also presented at the end of each chapter.

The information has been arranged in six chapters following the chronological order of the study. Global incidence of T1D presented and analyzed in different ways throughout this thesis was retrieved using a systematic literature review presented in **chapter 1**.

Chapter 2 includes a general review of diabetes classification and the '*state of the art'* in the epidemiology of T1D, including reports of the literature before and after 1950. It also, briefly describes the pathogenesis and etiology of T1D seen from an epidemiological point of view.

The first part of **chapter 3** contains the analyses of global T1D incidence among children aged 0-14 years. The incidence of T1D was correlated with 77 independent variables covering four domains: *Climate and environment*, *Demography*, *Economy*, *Health conditions*. Stepwise Multiple Linear Regression (MLR) models were carried out. The supplementary materials of this chapter also include the Principal Component Analyses (PCA) of the variables included in the final model, as well as preliminary analyses discriminating countries for which information on the incidence of the T1D was - or was not - retrieved. The second part of this chapter includes the analyses of trends, the cumulative incidence from birth cohorts between 1924 and 2004, and the analyses of age at onset calculated in the entire database. A description of epidemiological reports describing changes in incidence trends affecting predominantly the youngest age group is presented at the end of this chapter.

We noticed that in addition to information on T1D incidence in children aged 0-14 years, some of the retrieved studies also reported the incidence of T1D in older age groups. During exploration of the cumulative incidence of T1D based on the first analyses of this thesis, trends in adults seemed to parallel those in children. Following this observation, we

undertook to explore in depth the epidemiology of T1D in adults, as presented here in **chapter 4**. The main methodological problem related to the study of the epidemiology of T1D in adults is to distinguish this disease from others, such as Type 2 diabetes or Latent Immune Diabetes in Adults (LADA). For that reason, this chapter includes a detailed description of the criteria used to diagnose T1D in adults, which is focused on autoantibody detection. Comparisons between the incidences retrieved in adults and those retrieved in children are also presented.

Chapter 5 describes the incidence trends of T1D and presents an APC analysis of global trends in incidence of T1D, from data collected between 1975 and 2014. By including a discriminating analysis by country, it was possible to model the effects of the age, the year and the birth cohort at diagnosis of T1D for children aged 0-14 among 89 countries worldwide.

The epidemiology of T1D would not be complete without mentioning the role of genetic causes, mainly the participation of the Human Leukocyte Antigen (HLA) as determinant factor in the development of T1D and in the heterogeneity of levels of incidence retrieved around the globe. **Chapter 6** presents the analyses of the genetic components of T1D, considering the latest *Type 1 Diabetes Genetics Consortium Families* (89); correlations and Stepwise MLR models were carried out as performed for the environmental component.

Final considerations and perspectives are presented in the **Conclusions** section.

Tables and figures are presented in order of appearance and are designated *SI Table/Figure* for those related with Supporting Information of the main publication of each chapter and for those presented in Additional Analyses, that include analyses or results unsuitable for publication but with additional information pertinent to this thesis, and *AP Table/Figure* for those published in the Appendix Section.

The databases mentioned here will be placed for public examination and access, in the author's Github website at: https://github.com/PaulaDiaz, once the press embargo of the manuscripts expires; **Appendix A.**

Interactive visualization of the data is available at http://www.isis-diab.org and https://public.tableau.com/profile/paula.diaz - !/.

Chapitre 1

Systematic Literature Reviews of Type 1 Diabetes

Contents

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1 Systematic literature reviews used in this thesis

Systematic literature reviews have become important in research and are often the starting point of any study. Here we used two systematic literature reviews to obtain data on the incidence of T1D around the world: the first concerns epidemiology of T1D in children, analyzed in **chapters 1, 3, 5** and **6**, and the second in adults, analyzed in **chapter 4**.

Heterogeneity of the information in any data collection is a main issue, and is the reason why we followed the PRISMA statement (Preferred reporting for systematic reviews and meta-analyses) (213) recommendations as a method to collect data in a standardized way and to assess the quality of information of the retrieved studies. Each retrieved study was identified and all the information was extracted in a comprehensive format developed in our team. Additional updates of the revisions and the final decision about inclusion or not, and some references were discussed periodically during meetings and group discussions.

Once we had the entire data collection, we selected the information to be included in the analyses that will be presented in the following chapters. **Chapter 1** presents the objectives of the systematic reviews and the methodology used to obtain information. In the final section, this chapter presents a comparison of the current review with others reviews on the epidemiology of T1D, and the summary of the information retrieved on global epidemiology of T1D using data collected from 1975 to 2014.

The selected information provided by the current review is presented in **chapter 3**, that describes the incidence of T1D among children, in **chapter 4**, the epidemiology among adults, in **chapter 5**, and the APC approach of the incidence trends of T1D, and in **chapter 6** the analyses of incidence of T1D and genetic determinants. For each particular study, we developed large databases that are presented in the respective chapters, and are publicly available as guarantees of the transparency of this research.

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1.1 Objectives of the systematic reviews

To study the global published information on the incidence of T1D since 1950s.

1.1.1 Specific objectives

- Describe the global incidence of T1D at the country level.
- Describe the epidemiology of T1D among children and adults worldwide.
- Study the co-variation, at the country level, of the incidence of T1D with environment and genetic determinants available in public databases.
- Analyze if the current global trend in incidence of T1D is compatible with a period or birth cohort effect.

1.2 Methodology of the systematic literature review

A systematic literature review following the PRISMA recommendations (213) was conducted to retrieve published articles on the incidence and the age at onset of T1D worldwide. Literature search was conducted in the databases: MedLine accessed through PubMed and Science Citation Index Expanded databases accessed via the Web of Science (Thomson Reuters). In addition, general searches and examination of cited references in Google scholar were carried out. Finally, citing references identified through the lecture of the papers were included periodically. The registration number in PROSPERO is: CRD42012002369 (available on http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369).

1.2.1 Validation of the query equation of the bibliographic search

An exploratory bibliographic search allows the selection of the first 92 articles reporting incidence of T1D published between 1 January 1990 and November 2011 (here called '*query # 0*'); **Appendix B**. On February 3rd 2012, during a group meeting[3] the query was assessed. After recommendations such as to include new MeSH (Medical Subject Headings) terms and to modify exclusion criteria, we developed a method based on 7 steps, to obtain a query equation in which all mentioned 92 articles previously retrieved were found

[3] Meeting assistants: Pr. Alain-Jacques Valleron, Pr. Pierre-Ives Boëlle, Sophie Valtat, Sofia Meurisse, Nga Mai, Pascal Championnat, Flavian Quintus, Thomas Obadia, Sthephany Gomme, Segolene Charaudeau. Place: Hopital Saint-Antoine.

but adding new references. The entire processes aimed at obtaining the most sensitive and specific bibliographic search equation to retrieved original publications reporting incidence of T1D worldwide; here identified as '*query # 9*'. Search equations were updated periodically, the last update dating to November 2014. Details of the seven proposed steps are presented in **Appendix C**.

Summary of the seven steps used to obtain the final query search:

- ***Step 1.*** To perform an analysis of the MeSH terms presented in the 92 selected articles included in the database.
- ***Step 2.*** To carry out new queries in the MeSH Advanced Search Builder of PubMed taking into account the main MeSH terms found in step 1.
- ***Step 3.*** To check the MeSH terms for irrelevant references, so as to recognize the most common irrelevant MeSH terms.
- ***Step 4.*** To introduce at the equation query of step 1 the most common MeSH terms found in irrelevant papers using the builder NOT to exclude irrelevant articles.
- ***Step 5.*** To compare references linked in the different alternative queries. For example if we have two queries, query A and query B, using a strategy such as Venn diagrams (A∪B, A∩B), the references linked in the queries will be explored: query A, NOT query B, and query B, NOT query A. The first 60 references in each query will be examined: query A, query B, query A NOT B, and query B NOT A so as to analyze if they are relevant papers, and which one is the most accurate, then to repeat steps 3 to 5 in the selected query until at least 50% (25/60) of the articles examined are pertinent. In this strategy we will identify the queries to which a specific number can be assigned according to the formulation of the queries.
- ***Step 6.*** To examine the results of the selected query to verify that all 92 database references are included.
- ***Step 7.*** Repeat steps 2 to 7 until a majority of 92 articles are included.

1.2.2 Article selection for the query # 0: the 1st 92 included papers

The inclusion criteria for preselected references were articles with reports of incidence of T1D from population data registers by year and age at diagnosis, in any country, city or region worldwide. There was no publication language restriction. A minimum degree of case-ascertainment was not required.

The literature search was finalized removing all articles with at least one of the following **exclusion criteria**: 1) if the main objective was not the study of incidence of T1D (e.g., genetic factors, complications, treatments); 2) if the length of the report (following registers) of the incidence was ≤5 years; 3) if the study was not population-based, instead it was performed in selected groups, for example, studies based on volunteer subjects or on persons that belong a specific health assurance organization; 4) if the study did not report using the World Health Organization (WHO) (1985 or 1999) or American Diabetes Association (ADA) (1997 or 2011) as criteria of diagnosis; 5) if the study describes the incidence of T1D as a general topic, with no description by year and age at diagnosis, 6) if we could not translate the article; and 7) if the full text of the article remained unavailable.

1.2.3 Bibliographic search used to retrieve incidence of T1D in adults

A modification of the final search query equation (*query # 9*) presented in **Appendix C** was introduced to retrieve specific information on adults, the last update dating to January 2015. The search included the following terms: "diabetes mellitus, type 1/epidemiology" AND "incidence" AND "adult", and it was conduced in English, French and Spanish. The entire query used to retrieve information is presented in **chapter 4** (**session 4.1.1.1**) of this thesis.

1.2.4 Data extraction

Raw data were extracted from articles and introduced manually into a standard data collection grid (**Appendix A: Database I**) using the Microsoft Excel software. Incidence data were taken from the individual studies as they were reported in the publications in text, tables or graphs; a computer program was used to retrieve the original (x, y) data from the images (1). The names of countries corresponding to world regions in the database were both those from the WHO and from the UN. If the information was not available it was identified in the grid as 'No available data' (NA). **Table 2** reports the main categories of data extraction included in the main database.

Table 2: Extracted information from the papers and included in the database

Information about the study	Information about incidence
Number of identification of the reference	Mean incidence by country-area
Name of first author	Age at onset and period during which onset occurred
Publication date (received / accepted / published)	Sexes: male, female and both sexes male and female
World region / country / area of study	Annual increase in incidence
Period of study start/end date	Number of incident cases
Duration of the study	Population at risk during the period
Range of age covered by the study	Criteria diagnosis of T1D
Data source of population information	**Additional information**
Study design, historical, prospective or both	Indicator about management of diabetes in 2010 (WHO)
Statistical analyses used in the study	Signal about the standardization of the information
Percentage of ascertainment	Source of extracted information (table, text or figure)

To further evaluate the quality of the information retrieved, we searched for the reported percentage of completeness (*ascertainment*)*:* the average percentage of concordance at least between two different independent sources of information containing incident cases of T1D in a specific region and period of time (179). Examples of *primary* sources of registers include data from hospitals, pediatricians, diabetologists, and others, and *secondary* sources, drug prescriptions, information from diabetes associations, summer camps, or general practitioners.

1.3 Reviews of the literature on global incidence of T1D

Among all retrieved information, seven studies classified as reviews and describing the epidemiology of T1D were published before 2014. A summary is provided in **Table 3**.

Table 3: Reviews reporting global incidence of T1D

Author, year of Publication	Ref	Period of analysis	Age of patients (range)	Details
Karvonen M., 1997	(160)	1965-1992	0-14	This reference shows the total incidence and incidence of T1D for males and females separately of 76 populations from 53 countries using data from the Diamond study. A female predominance of 59% was found in those aged 0-14 years.
Onkamo P., 1999	(231)	1960-1996	0-19	This study used a systematic search to retrieve information and analyzed 37 studies from 27 countries. A worldwide increase on average of 3.0% (95% CI 2.6,3.3) per year was observed.
Ascher P., 2002	(21)	1990-1994	0-14	The reference describes the incidence trends of TID in Latin America
Gale EA., 2002	(105)	1920-2000	0-29	The reference presents a historic review that describes the incidence of T1D before and after 1950.
Borchers A.T., 2010	(40)	1995-2009	0-14	The article shows selected data from the Diamond Project Group for 1990–1999 with recent update references.
Maahs DM., 2010	(201)	Unspecified	0-29	The article gives a description of data published in the Diamond, the Eurodiab, and the Search studies. It includes general comments of risk factors.
Vehik P., 2011	(343)	1965-2004	Unspecified	The article gives a description of data published in 10 countries and describes possible reasons for the increase of T1D incidence. It includes general comments of risk factors

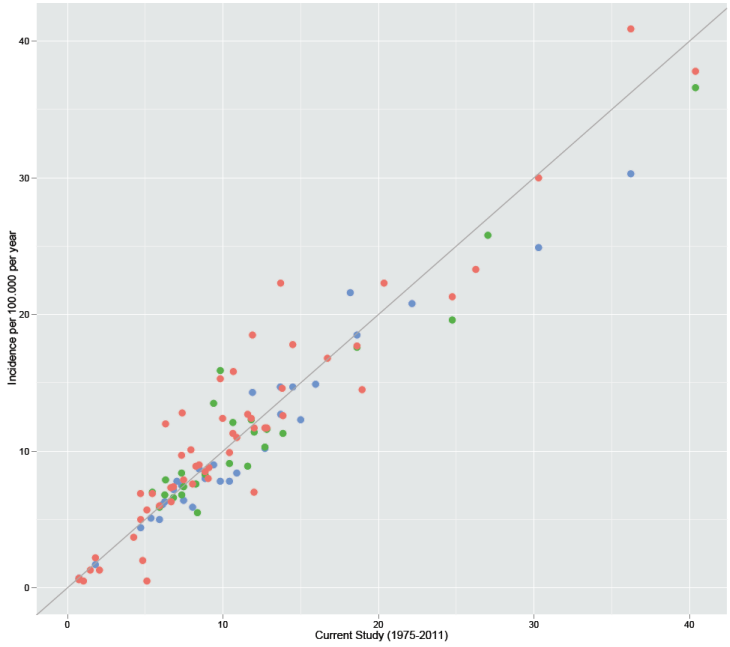
1.4 Comparison of incidence of T1D retrieved in the current review with other collaborative studies or reviews

By 2012, this thesis included the information available worldwide on the incidence of T1D from 226 populations, from 68 countries, published in 161 articles between 1975 and 2011; a comparison of the retrieved incidence of T1D with the Onkamo et al. (231) review, and with the studies Eurodiab (90) and Diamond (318) was then performed. Correlations between the current review and the studies were >0.95 in all cases; they are shown in **Table 4** and **Figure 3**.

Table 4: Comparison of age-standardized incidence of T1D in children 0-14 years of age reported in four studies

Study	Ref.	Study period	*n* ref. *	Correlation
Current Review (A)		1975-2011	161	
Diamond study (B)	(318)	1990-1999	112	0.95
Eurodiab (C)	(90)	1989-1994	45	0.96
Onkamo (D)	(231)	1960-1996	36	0.97

Ref. Reference (*) Number of references by country and area reported in each study.



Previous reports vertical (*y*) axis: in red dots Diamond (318) (1990-1999); in green, Eurodiab (90) (1989-1994); in blue, Onkamo et at. (231) review (1989-1994). In the horizontal axis *(x)* the current study.

Figure 3: Correlation of reported incidence of T1D among individuals 0-14 years reported in the thesis *vs* three previous studies.

1.5 Predicted and observed incidence of T1D by 2010

Incidence of T1D has been increasing during the last decades. Predictions performed by Onkamo et al. in 1999 (231) for 37 populations, announced that by 2010 the incidence of T1D would be 40% higher compared with 1998. Using data from the current review, it was possible to compare the predicted and observed incidence of T1D; the observed incidence is higher than the predicted incidence in 7 of 10 studies that reported information of T1D in the group 0-14 years after 2005; **Table 5**.

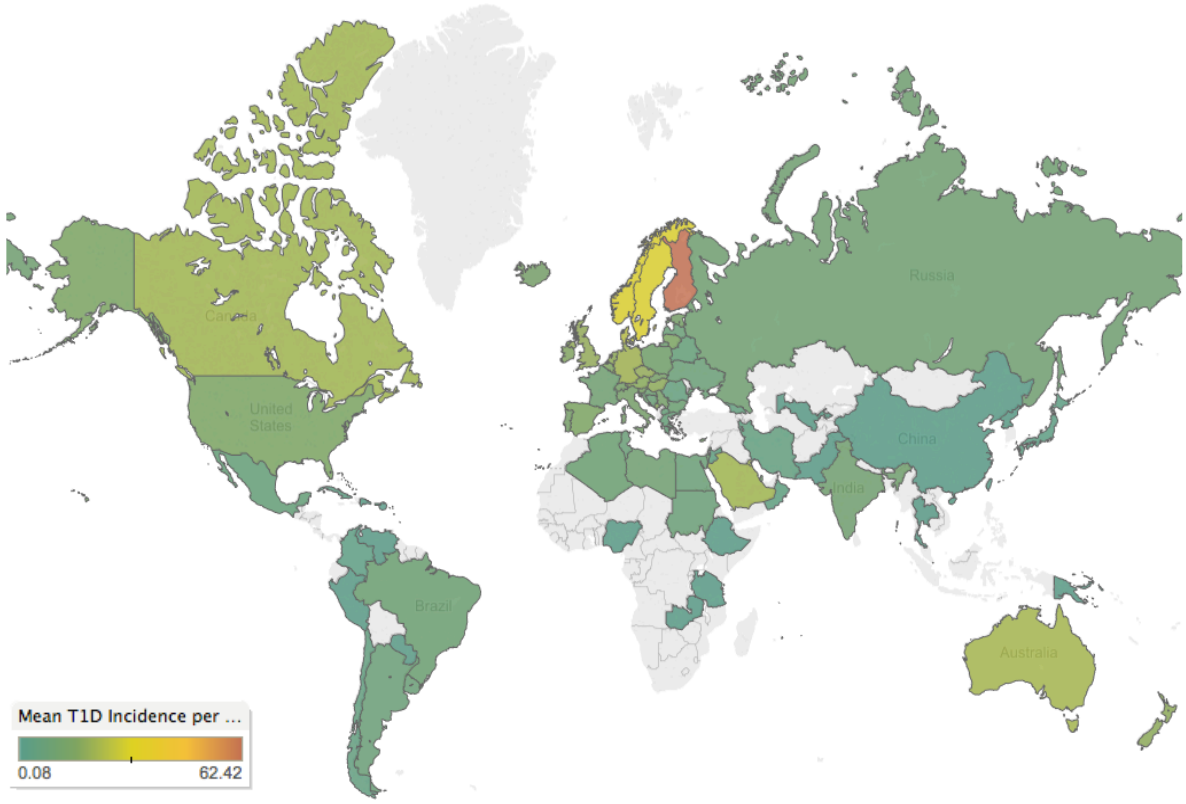
Table 5: Predicted and observed incidence of T1D in 10 studies

Country, area	Predicted incidence of T1D by 2010 (Onkamo et al., (231))		Observed incidence of T1D in 10 studies				Observed – Predicted incidence of T1D (b)
	Mean T1D Inc.*	Based on incidences from the study period	Mean T1D Inc. (a)	Based on incidences from the study period	Author, Publication year	Ref.	
Austria	**12.8**	1979-1993	**17.5**	2004-2008	Patterson C, 2012	(243)	**4.7**
Finland	**50.2**	1965-1996	**62.42**	2006-2011	Harjutsalo V, 2013	(128)	**12.22**
Hungary	**20.1**	1978-1987	**18.3**	2004-2008	Patterson C, 2012	(243)	**-1.8**
Israel, Yemenite Jews	**10.1**	1965-1993	**11.1**	1997-2010	Blumenfeld O., 2014	(39)	**1**
Lithuania	**7.5**	1983-1992	**14.2**	2004-2008	Patterson C, 2012	(243)	**6.7**
Malta	**16.8**	1980-1996	**23.87**	2006-2010	Formosa N, 2012	(100)	**7.07**
Norway	**41.8**	1973-1982	**32.8**	2004-2008	Patterson C, 2012	(243)	**-9**
Sweden	**32.2**	1978-1992	**32.3**	1983-2007	Dahlquist G. G., 2011	(74)	**0.1**
UK, Oxford	**33**	1985-1995	**25.10**	2004-2008	Eurodiab, 2012	(243)	**-7.9**
UK, Yorkshire	**21**	1978-1992	**25.50**	2004-2008	Eurodiab, 2012	(243)	**4.5**

(a) Mean incidence of T1D per 100.000 per year (b) Difference between predicted and observed incidence of T1D. Ref.: Reference.

1.6 Information retrieved in the current review

At the end of this thesis in 2015, among children aged 0-14 years, this systematic review retrieved 237 primary research papers from PubMed and GoogleScholar, covering 86 countries and four "territories", also referred as "90 countries" in this thesis. 28 additional papers, abstracts and updated information were from the International Diabetes Federation (IDF) Atlas (300). From these 265 references, we extracted 527 datasets. Among these 527 datasets, 298 were from individual studies, and 201 were from international collaborative studies (114 from the Diamond study in 2006 (318), 44 from the Eurodiab study in 2000 (90), 21 from the Eurodiab study in 2009 (242), 22 from the Eurodiab study in 2012 (243)), and 28 from the IDF Atlas (300). **Figure 4** and **Figure 5**; the detailed list and breakdown by place and time is in **Appendix A: Database II**. Information retrieved for those aged over 14 years corresponds to 70 articles from 35 countries, and is detailed on **chapter 4**.



Mean T1D incidence per 100.000 individuals aged 0-14 years per year is in color gradient. An interactive data visualization of this map is available at: https://public.tableau.com/profile/paula.diaz#!/vizhome/Globalincidenceoftype1diabetesinchildren/Dashboard1

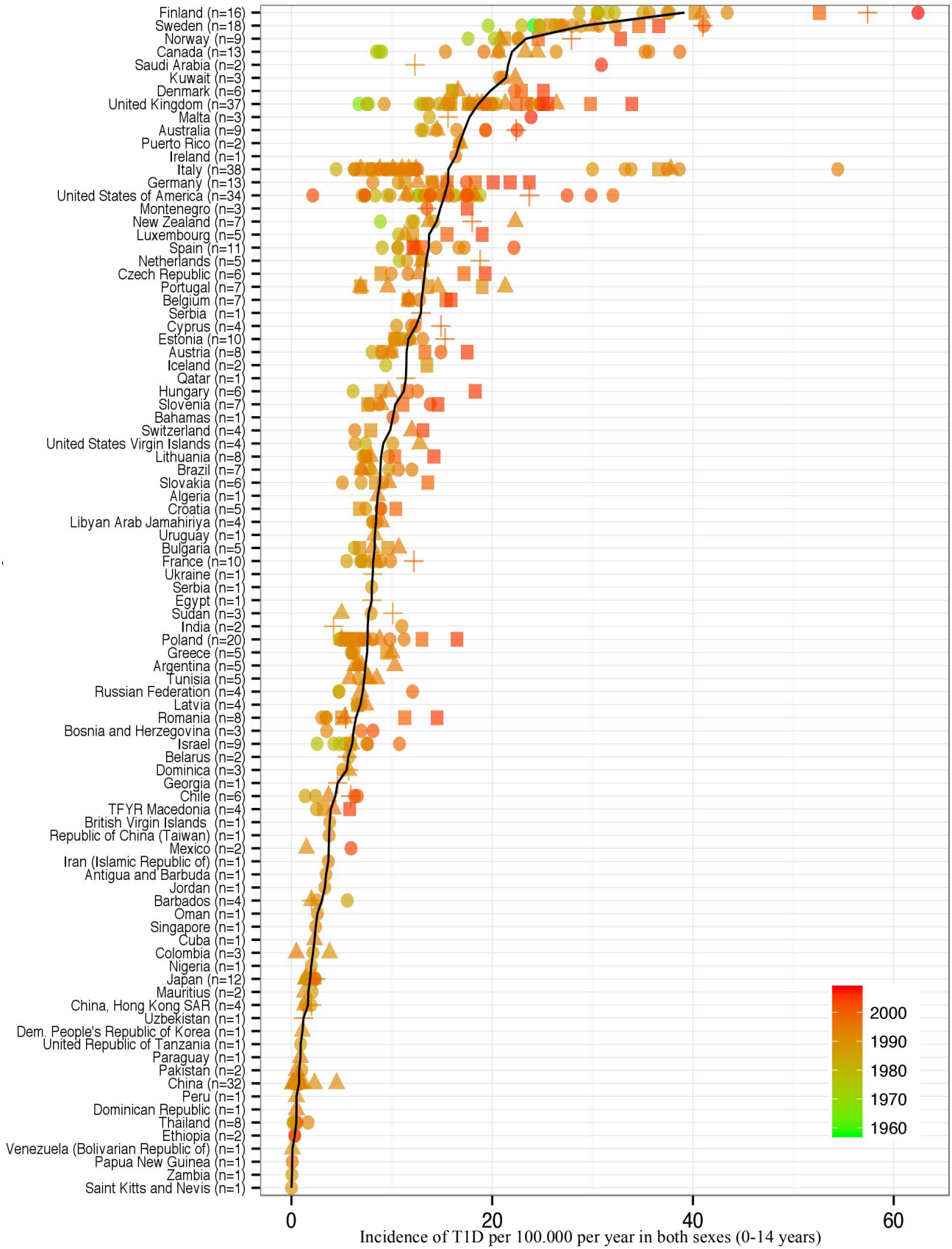
Figure 4: Geographical distribution of countries where T1D incidence has been reported in the literature 1975-2014

Information on the incidence of T1D for the 0-14 year-olds was found for 90 countries, covering 69% of the world population; **Figure 4** and **Figure 5**. This coverage varied widely depending on the WHO region (**Table 6):** the population coverage was 37% in the African region, where one country out of the 45 of the region reported a nation-wide study. It was 100% in the HIGH of the European WHO region. The epidemiological report of incidence of T1D shows no further references published after 2010 in Africa and Oceania. See details in **Figure 6.** Most of the retrieved publications were published between 1990-1999 (n= 102 publications) and between 2000-2010 (n = 119 publications). Distribution of retrieved articles by year of publication is presented in **Figure 7**.

Table 6: Distribution of the information available on the incidence of T1D worldwide

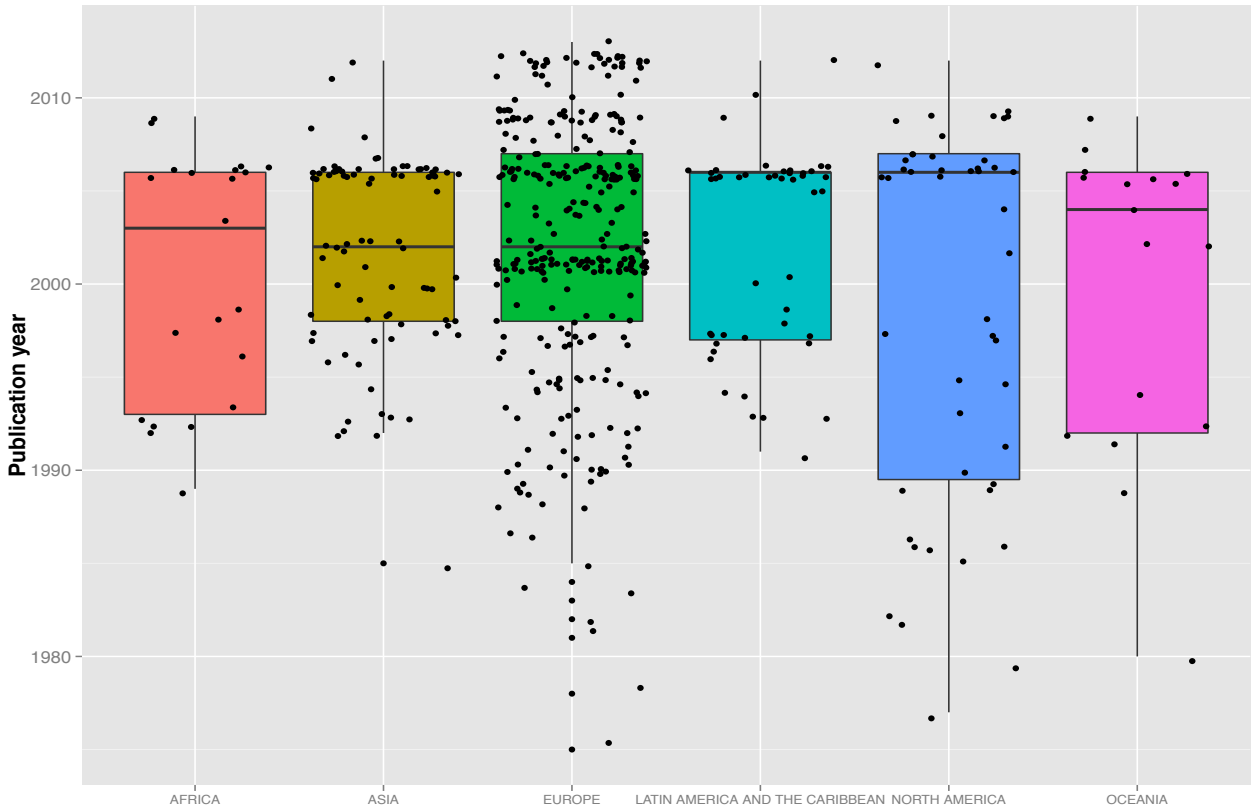
WHO region	AFRO	AMRO		EMRO		EURO		SEARO	WPRO		Non-WHO Countries	TOTAL
WHO categories of income	LMIC	HIGH	LMIC	HIGH	LMIC	HIGH	LMIC	LMIC	HIGH	LMIC		
Number of countries in the region	45	3	29	5	16	22	28	11	6	16	0	194
Countries and territories with incidence report	6	3	15	3	8	22	19	3	4	2	5	90
Countries with Nation-wide studies	1	1	8	2	2	18	12	1	4	1	3	53
0-14 years old population (thousands)	350,355	67,978	163,233	10,830	189,816	67,243	88,940	534,895	30,933	335,038	7,413	1,846,674
0-14 year old population with published information on T1D incidence (%)	37%	100%	83%	86%	68%	100%	63%	74%	77%	79%	11%	69%

The WHO sub-regions are: AFRO (Africa), AMRO (Americas), EMRO (Eastern Mediterranean), EURO (Europe), SEARO (South-East Asia) and WPRO (Western Pacific). WHO Member States are divided into high-income (HIGH) or low- and middle-income (LMIC) countries creating 10 groups (359). Non-WHO countries: country not in WHO classification.



In parenthesis: *n* = number of retrieved datasets by country. One dataset corresponds to the unique data retrieved from the literature. Geometric symbols: triangles indicate datasets from the Diamond study (*n*=114) (318), squares indicates databases from Eurodiab (*n*=87) (90, 242, 243), plus signs indicate data from the International Diabetes Federation (*n*=28) Atlas (241, 300) and circles are from the other publications that we retrieved (*n*=298); they were colored to visualize the trend in incidence (green: 1958 to red: 2009). The black line represents the mean country T1D incidence. For the detailed list of the studies / datasets see **Appendix A: Database II.**

Figure 5: Variation of T1D incidence found in 90 countries



Individual studies are represented by dots.

Figure 6: Publication year by World Region

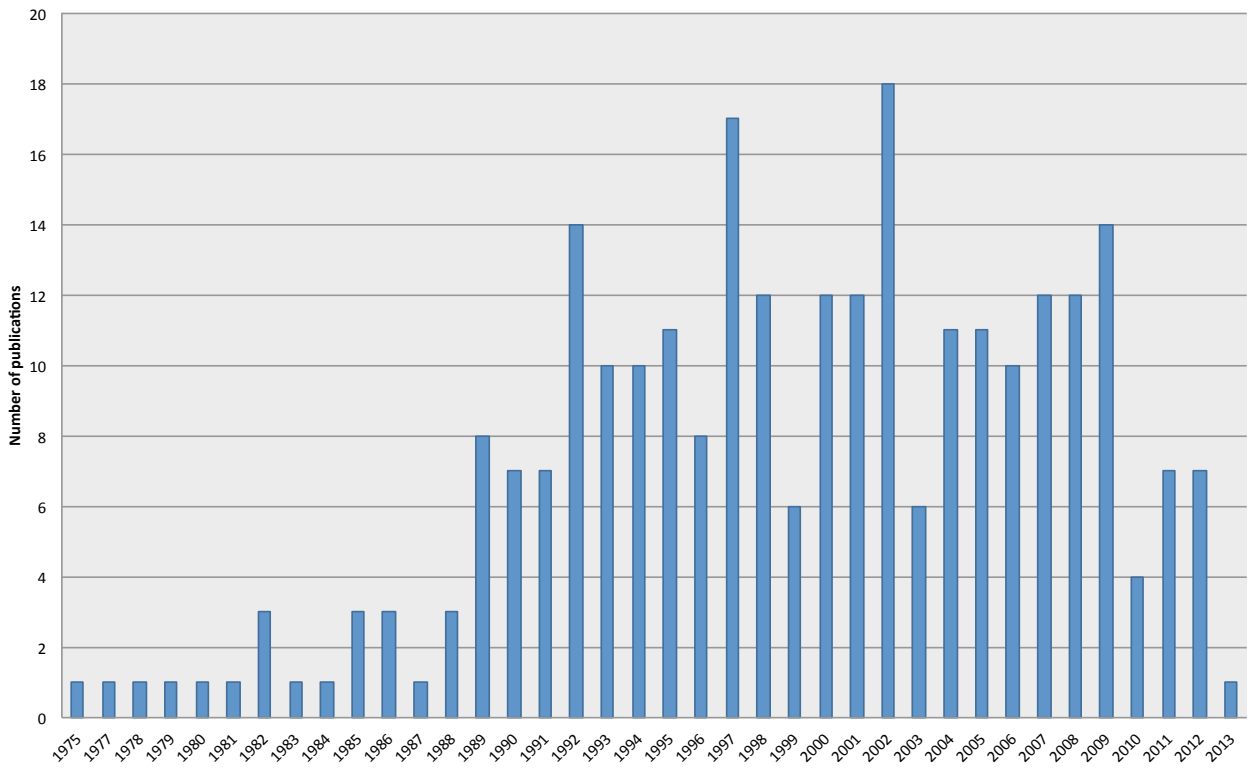


Figure 7: Year of publications among retrieved studies for 0-14 years of age

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Chapter 2

State of the art in Type 1 Diabetes

Contents

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2 General review of T1D

Chapter 2 briefly describes the *state of the art* in the epidemiology of T1D. This chapter has three main parts: in the first, a definition of diabetes is given, in the second, we present a review of the epidemiology of T1D before and after 1950, and in the third part, different hypotheses about the etiology of T1D are described.

Since there are no specific and standardized criteria to define T1D, the general classification based on blood glucose levels used in diabetes is applied to T1D. After detecting a blood glucose level compatible with diabetes, aspects of the clinical presentation make it possible to define the etiological classification of diabetes presented in this chapter in **section 2.1.1**; it is the most recent and extensively used classification used in the retrieved studies analyzed in this thesis. Nevertheless, diagnosis of diabetes has changed over time and epidemiology of T1D, based on the incidence value that could have been affected by the different classifications adopted at different periods; in **section 2.1.2** of this chapter we present a summary of the evolution of the diagnosis criteria used to define diabetes. Because of these changes in the diagnosis criteria of T1D over time, and to decide if a given study should be included or not in the systematic reviews presented in **chapter 1**, we pay particular attention to establish if it was truly about T1D, based on etiological classification and/or diagnosis criteria, especially when they were published before 1985.

Our current knowledge of the epidemiology of T1D is due in large part to intercontinental collaborative projects, such as Diamond, Eurodiab, Diabalt, multicenter studies at the country level such as the SEARCH study, and organizations such as the International Diabetes Federation (IDF), described briefly below in **chapter 2**.

The last part of this chapter shortly describes several etio-phathological hypotheses mentioned in the literature as causes of T1D, some related with genetic, environmental or gene-environmental factors. A personal summary of the related categories found in the literature is also presented. These categories, are also mentioned in the following chapters: **chapter 3** about epidemiology in children, **chapter 4** epidemiology in adults, **chapter 5** on global incidence trends of T1D using an APC model and **chapter 6** about genetic determinants of T1D.

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2.1 Diabetes

Diabetes is characterized by chronic disturbances of carbohydrate, fat and protein metabolism leading to long-term damage, dysfunction and failure of internal organs. The most important complications of diabetes include retinopathy, nephropathy, neuropathy and cardiovascular diseases (144). Global estimates of the prevalence suggest that in 2010 more than 285 million adults lived with some form of diabetes in the world (290), and the number of individuals with diabetes worldwide is expected to rise to 472 millions by 2030 (84).

2.1.1 Etiological classification

In 2011, the American Diabetes Association (ADA) (16) adopted the etiological classification of diabetes that includes four types:

- ***Type 1 diabetes*** (results from beta-cell destruction, usually leading to total insulin deficiency)
- ***Type 2 diabetes*** (results from a progressive insulin secretory defect on a background of insulin resistance)
- ***Gestational diabetes mellitus (GDM)*** (diabetes diagnosed during pregnancy that is not clearly overt diabetes)
- ***Other specific types of diabetes due to other causes***, e.g., genetic defects in B-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemically-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation)

In addition, sub-categories of T1D were introduced, Type 1A for diabetes cell-mediated autoimmune attack, and Type 1B for non-immune diabetes generally after ketosis (22). This latter classification is complex, depends on a sophisticated laboratory test, and is not included in the ADA classification proposed in 2011.

2.1.2 Diagnostic criteria of diabetes

Until the late 1970s, large variations in the level of glucose as diagnosis criterion of diabetes were reported (337). The first intent to standardize the diagnosis and classification system for diabetes worldwide was presented in 1978 by the WHO and the National Diabetes Data Group and modified in 1985 and 1999. Also, in 1995, ADA promoted the formation of an international expert group to review the diagnosis criteria and classification of diabetes, and after two years of discussions, the review and the new criteria were published. At the same time, the WHO convened a new consultation, and published the WHO results in 1999. The current ADA (2011) criteria for the diagnosis of all kinds of diabetes are the following: 1) symptoms of hyperglycemia including polyuria, polydipsia, weight loss plus random plasma glucose concentration >200 mg/dl (11 mM); 2), fasting (> 8 h fasting), plasma glucose > 126 mg/dl (7 mM); 3) 2 h postprandial glucose >200 mg/dl during an oral glucose tolerance test (OGTT) (22, 76). In addition the glycated hemoglobin (AIC) test recommended since 2009 by an International Expert Committee was adopted in 2010 (11, 16, 22) (**Table 7**).

Classification of T1D and Type 2 diabetes (T2D) by glucose levels is not always easy. Clinical manifestations and disease progression could share similarities in both types of diabetes. Some patients with T2D may present ketoacidosis, whereas patients with T1D may have a late onset and very slow progression of the disease and even so they have features of an autoimmune disease. Moreover, T1D can appear at any age and incidence of the disease may be as prevalent in adults as in young people (23). Thus to avoid misclassifications of T1D, the data analyzed here and considered as diagnosis of T1D requires both the necessity of insulin administration and the associated ADA or WHO criteria. All the studies included in this thesis report the incidence of T1D or Insulin-Dependent Diabetes Mellitus (IDDM), for papers published before 1985. Information of other kind of diabetes, such as T2D or secondary diabetes, was excluded.

Table 7: Comparison of diagnosis criteria of diabetes according to the WHO and the ADA

ADA 2011	ADA 1997	WHO 1999	WHO 1985
A1C ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*	…	…	…
FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*	FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*	FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*	FPG ≥ 140 mg/dl (7.8 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*	2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.**	2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.	2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.***
In a patient with classical symptoms of hyperglycemia or during a hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).	In a patient with classical symptoms of hyperglycemia or during a hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).	In a patient with classical symptoms of hyperglycemia or during a hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).	In a patient with classical symptoms of hyperglycemia or during a hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, the result should be confirmed by repeat testing. ** Not for routine test. *** Only recommended when the patient's glucose level is not determined. Note. One criterion is enough to made the diagnosis. ADA: American Diabetes Association, WHO: World Health Organization, A1C: Glycated hemoglobin, NGSP: National Glycohemoglobin Standardization Program, DCCT: Diabetes Control and Complications Trial Reference Method, FPG: fasting plasma glucose, OGTT: oral glucose tolerance test.

2.2 Type 1 diabetes

T1D represents 5–10% of all the cases of diabetes (22) and is the most prevalent metabolic disease in childhood (298). T1D is defined as a chronic, multi-causal and immune-mediated disease characterized by selective loss of insulin-producing beta-cells in the pancreatic islets with as final result, an absolute deficiency of insulin (23, 24). T1D has also been known as Juvenile Diabetes or Childhood Diabetes, because during the first studies, the peak expression was seen between 0 and 14 years. It was also called IDDM (insulin dependent diabetes mellitus) in the 80's.

In general, T1D develops slowly. It has a subclinical period that can take a few months to 10 years (219), before the appearance of clinical manifestations, complications or in some cases death, as the first manifestation (23). Nowadays, sophisticated diagnostic methods, such as detection of anti-beta cells autoantibodies, are available. Nevertheless the detection of hyperglycemia based on plasma - either the fasting plasma glucose or the OGTT (2-h value in the 75-g oral glucose tolerance test) - is the main diagnostic criterion.

2.3 Epidemiology of T1D

Epidemiology is the study of the distribution and magnitude of diseases in view of understanding their risk factors, causes or providing alternatives to prevent or to manage them. At the very basic, yet no less important level, is the measure of incidence; it quantifies the number of new events or cases of the disease that develops in a population of persons at risk during a specific time interval (118, 132). Studying incidence through registration of new cases of T1D has been seen as an opportunity to help people with diabetes.

Only after 1921, when insulin was discovered, could people have access to medical care and better diagnostic processes, and it was then that reports of incidence started; previously only clinical series and mortality statistics had been used to evaluate the incidence of T1D (105).

The first compilation of epidemiology knowledge of diabetes appeared in 1978 in Kelly West's book, 'Epidemiology of Diabetes and its Vascular Complications' (355). In this book, the standardization of methodologies as well as diagnostic criteria (377) to define diabetes were proposed. Before that time very few references were available, most of them lacked standardization, different case definitions and age-groups were included, and without any method of *ascertainment* for data collection (190).

2.3.1 Epidemiology of T1D before 1950

According to Gale (105) knowledge on the epidemiology of T1D before insulin discovery is based on three studies on death rates in children younger than 15 years. The first, in the United States, reported an increase in death rate due to T1D from 1.3 per 100.000 individuals per year in 1890, to 3.1 per 100.000 individuals per year in 1920; the second, from Denmark, reported a change in the death rate for T1D from 2 per 100.000 individuals per year in the period 1905-1909 to 3.1 per 100.000 individuals per year, in 1915-1919; and in the third, from Norway, an increase in the incidence of T1D from 2 to 7 per 100.000 individuals per year between 1900 and 1920 was described (105).

Later, between 1920 and 1950, the introduction of insulin prolonged the survival of patients and the incidence was reported in several countries. The landmark sources of incidence and prevalence for this period were two retrospective surveys in Oslo and Bergen

in Norway. The Oslo survey identified 4251 individuals aged less than 30 years with T1D, and the incidence remained relatively constant over the period 1925-1954; the average incidence was 4.1 per 100.000 individuals per year in children aged less than 15 years. In the Bergen survey, during the period 1925-1939 the incidence was 7.9 per 100.000 individuals per year in individuals under 20 years; at that time, the rise in incidence was attributed to the increasing age of the population (105).

During wartime, in Vasterbötten in Northern Sweden, the highest available rate of T1D incidence was observed: it was 10.2 per 100.000 individuals per year, rising to 37.9 per 100.000 individuals per year during the period 1973-1977. In Finland, the country of the world with the highest incidence of T1D, the annual incidence in 1953 was estimated as 12.5 per 100.000 individuals per year (105).

2.3.2 Epidemiology of T1D after 1950

The evaluation of incidence trends has been more rigorous after the 60s when epidemiological methods were developed and better registration statistics were available. Onkamo et al. reviewed the incidence of childhood diabetes from studies published from 1960 to 1996. Thirty-seven studies from 27 countries were analyzed, and an increase in incidence of 3.0% per year (CI 95% 2.6-3.3) was reported (231).

In the last 30 years, knowledge of the incidence of T1D has improved substantially thanks to collaborative projects in which information from population-based registers, standardized definitions of T1D, and methods for data collection and validation (298) are used. The *Diabetes Epidemiology Research International Group* (DERI) was the first group to analyze the data collected on the incidence of T1D between the end of the 1970s and the beginning of the 1980s (79, 122), work pursued by studies such as the Diabetes Mondiale study (DIAMOND) (318) and the Europe Diabetes study (EURODIAB) (90). Examples of national projects are the *Registry for Type 1 Diabetes Mellitus in Italy* (RIDI) study (53, 60) in Italy and the *SEARCH for Diabetes in Youth* (SEARCH) study (282) in the United States. In addition the *Diabetes Atlas* of the IDF, an international "umbrella organization" of over 230 national diabetes associations in 170 countries and territories, is committed with the advocacy of global political priority for diabetes and accredited by the WHO and the UN (241, 300).

2.3.3 Global collaborative projects on the incidence of T1D

2.3.3.1 Diamond Study

The Diamond project Group started the study of the incidence and trends of childhood T1D worldwide in 1990 as an initiative of the WHO (360). The study aimed to determine the incidence of T1D in the period 1990-1999. It was carried out in 57 countries. In the period 1990-94 the increase in the incidence was 2.8 % (IC 95% 1.3-3.4%) and between 1995-99 it was 3.4% (IC 95% 2.7-4.3%) (318).

2.3.3.2 Eurodiab Study

The Eurodiab study was established in 1988 and involved 24 centers (120) in 1992; in 2000 forty-four centers represented most European countries and Israel: the average annual increase in the incidence of T1D between 1889 and 1994 in Europe was 3.4% per year (95% IC 2.5-4.4%) (90). The comparison of the information retrieved from 20 centers for the period 1989-2003 was 3.9% (242) and from 23 centers for the periods 1989-1998 and 1999-2008 was: 3.4% per year and 3.3% per year (243).

2.3.3.3 Diabalt Study

The Diabalt study is a collaborative project focused on the T1D incidence in countries around the Baltic Sea: Finland, Estonia, Latvia and Lithuania, and started in 1989. Data collected between 1983 and 1992, demonstrated a wide variation in the incidence of the disease, Finland had an average age-standardized incidence of 35 per 100.000 individuals per year, Estonia 10.2 per 100.000 individuals per year, Lithuania 7.1 per 100.000 per year and Latvia 6.5 per 100.000 individuals per year. During the period of the study, the incidence only increased in Finland and Lithuania, 1% and 1.4% on average per year, respectively (236).

2.4 Pathogenesis and etiology of T1D

Multiple factors in a complex interaction promote the pathogenesis of T1D. Pathological studies from necropsies of patients with T1D show the presence of insulitis, characterized by mononuclear cell infiltration (predominantly T cells, macrophages and B-lymphocytes) within the pancreas islets with a severe selective loss of beta cells. These studies showed that at the same time there are islets where the beta cells have been destroyed, others that are being destroyed, and some that have not been destroyed (24). Other studies form biopsies of patients with recent onset of T1D suggest an interaction between the proteins of the cell surface that belongs to the tumor necrosis factor and play important role in immune regulation, Fas on beta cells and Fas ligand on infiltrating cells. This interaction could be the trigger of apoptosis of beta cells in the pancreas, as a mechanism of beta-cell destruction (23, 24). According to the natural evolution of the autoimmune disease, when the beta-cell mass is considerably lowered, the development of diabetes is irreversible (92); at the end, insulin secretion is reduced to such an extent that it is no longer sufficient to maintain a normal level of blood glucose, and clinical diabetes supervenes.

The mechanisms of beta-cell destruction remain unknown; in humans these mechanisms are related with genetic and non-genetic factors. The genetic factors are of major importance (167). Also, exogenous factors play a major role in the development of T1D for many reasons, such as the following: a) less that 10% of individuals with HLA-conferred diabetes susceptibility progress to clinical disease, b) a pair-wise concordance of T1D of <40% among monozygotic twins, c) a more than 10-fold difference in disease incidence among Caucasians living in Europe, d) considerable increase in incidence over the past 50 years, and e) migration studies indicating that the disease incidence has increased in population groups that moved from a low-incidence to a high-incidence region (167).

2.4.1 Genetic factors associated with T1D

The genetic influence on T1D has been studied and the researches show that some genes provide protection against T1D and others provide susceptibility. Nevertheless, twin- and family-based studies have shown that genetic factors play an important role in modifying disease risk in T1D (186); the rapid increase in incidence of T1D is not explained by Mendelian inheritance (202) and is insufficient to explain 35–75% of the cases (202). About

85% of patients with recent diagnosis have no family history of diabetes (23) and T1D only appears in approximately 6% of siblings of patients with the disease (358).

Only 2 chromosomal regions has been associated with T1D: the major histocompatibility complex (MHC) human leukocyte antigen (HLA) class II region on chromosome 6p21 [insulin-dependent diabetes mellitus 1 (IDDM1)] and the insulin gene region on chromosome 11p15 [insulin-dependent diabetes mellitus 2 (IDDM2)] (219). Genes located within the HLA-II account for approximately 50% of genetic risk of T1D. The HLA alleles associated with T1D susceptibility include HLA DR3, DR4, DQ2 (DQB1*0201–DQA1*0501–DRB1*03), and DQ8 (DQB1*0302-DQA1*0301–DRB1*04). These alleles are present in 90% of the children with T1D (111), whereas, other HLA alleles are associated with disease protection, such as DR2, DQA1*0102, DQB1*0602, and children with these diabetes-protective HLA are unlikely to develop T1D (111, 158, 185, 219, 358). More details are presented in **chapter 5**: « Genetic Determinants of T1D ».

2.4.2 Environmental factors associated with T1D

The none-genetic risk factors include the environmental risk determinants and others none-genetic disease-modifying factors. These factors could be promoters of the activation of autoimmunity; this process appears after an apparent imbalance in the immune system of the patient in order to attack foreign pathogens (219) and culminates in the destruction of pancreatic beta cells (76). Despite intensive searches for environmental triggers, the number of candidates being assessed in clinical trials remains small (for example: viruses (40, 144, 301), proteins from cow milk (66, 200, 276, 315), timing of vaccination (78) and relative lack of vitamin D). However, the exact etiology and pathogenesis of T1D is still unknown (6). Numerous factors such as epigenetic, microbiome, microbiology, metabolism, nutrient intake, and climatic, and environmental exposures have also been proposed as triggers of T1D (41, 69, 173). Other environmental determinants are presented here in **chapter 2:** «Incidence of T1D Incidence and Determinants Among Children».

2.4.3 Interaction between genetic and environmental factors

Our current knowledge on T1D supports the possibility hat the change in incidence trends of T1D around the world could be due to the interaction of genetic and non-genetic risk factors. In this case, non-genetic factors could be a) *promoters* of the activation of

autoimmunity, this process appears after an apparent imbalance in the immune system of the host in order to attack foreign pathogens (219) and culminates in the destruction of pancreatic beta cells (76), b) *modifiers* of disease pathogenesis rather than as triggers, or c) *protectors* attenuating the disease during different stages of the development, and depending on the quantity and the time of exposure (23). **Table 8** lists some examples of non-genetic risk and of protecting factors in childhood at onset of T1D reported in the literature.

Table 8: Risk and protectors related to T1D

Factors associated with increased risk of T1D
Age at day-care entry (proxy of maternity leave and viral load)
Caesarian section delivery
Climatic influences
Early infant diet
Fall in birth-weight
Food processing consumption
High maternal age
Improvement of socio-economic conditions
Increased body mass
Lifestyle habits
Linear growth during early childhood
Overweight and obesity
Psychological stress
Relative lack of Vitamin D, E and Omega-3 fatty acids
Reduced frequency of early infections
Stressful life events
Toxins
Vaccine administration (probably coincidental)
Viral infection during pregnancy
Viral infections during childhood
Factors associated with reduced risk of T1D
Atopic diseases
Breastfeeding/ duration of breastfeeding
Early age at preschool day-care entry
Early introduction of Vitamin D supplementation
Healthy gut micro and macro biota
Low birth weight
Short birth length

For more details see the following paragraphs in this **chapter 2**.

2.4.3.1 Seasonality and T1D

There are differences in the variation of T1D diagnosis depending on the season, a peak in both sexes and in all age groups usually occurring in the winter; it is more pronounced in countries with marked differences between summer and winter temperatures. Knip et al. (167) found that diagnosis of T1D has a seasonal pattern, being more common during the cold season (171, 293), with variations from year to year. In addition, T1D does not necessarily induce beta-cell autoimmunity at the same time in all genetically susceptible siblings in the same family (167). As hypothesis, incidence of T1D could be related with changes in the epidemiology of enterovirus infections, been higher during cold weather (301), and for this reason, the diagnosis of T1D onset could be related to seasons (144, 200). Other possible explanations are that seasonal variation of onset could be stimulating factors of the disease processes, or related with nutritional factors that can be different depending on the seasons. The possibility exists that certain foods harbouring unknown infectious or potentially toxic agents (26) are also implicated.

In this thesis, using information collected up to November 2011, an exploratory analysis of the seasonal and diagnosis of T1D was carried out based on references containing the word "season" in the title or abstract. The season in which T1D was diagnosed was reported in 87% (60 of 69) of the studies; the incidence peak was in winter, followed by autumn, spring and summer; **Figure 8.**

The season of birth of the patients with T1D diagnosis was reported in 10% (7 of 69) of the studies, spring being the season with most births, followed by summer, autumn and winter; **Figure 9**.

The month of birth of the patients with T1D was indicated in 7.2% (5 of 69) of the studies, birth in December and January being the months leading to the subsequent highest incidence of T1D diagnosis. **Figure 10.**

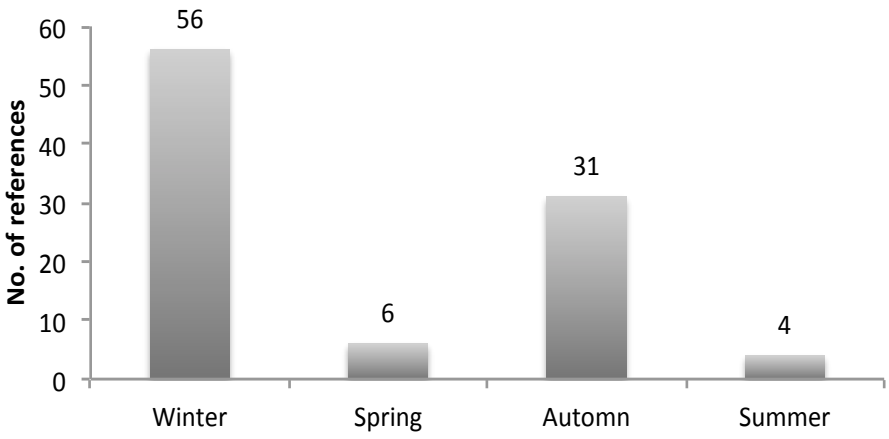


Figure 8: Peak of incidence of T1D by season of onset in the literature

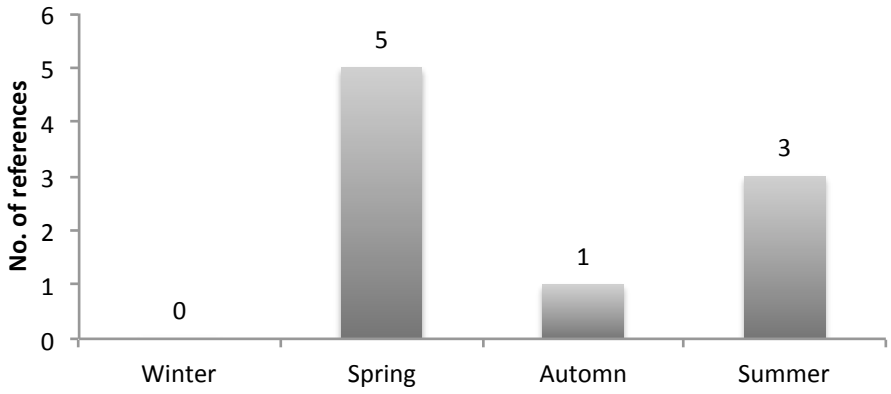


Figure 9: Season of birth in patients with T1D in the literature

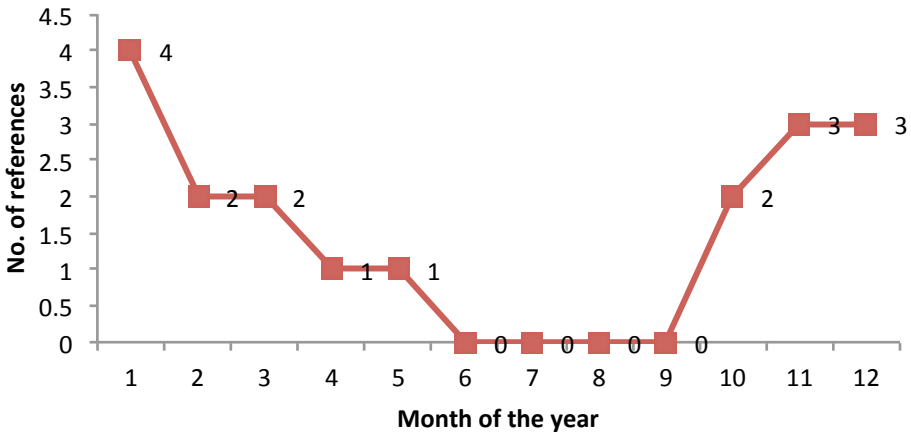


Figure 10: Month of birth of patients with T1D in the literature

2.4.3.2 Frequency of recruited patients of the Isis-Diab cohort by month of diagnosis and month of birth

Figures 11 and **12** show the distribution of recruited patients aged 0-16 years of the *Isis-Diab cohort*, an ongoing prospective cohort of French patients with T1D since 2007. More information about the *Isis-Diab cohort* on: http://www.isis-diab.org.

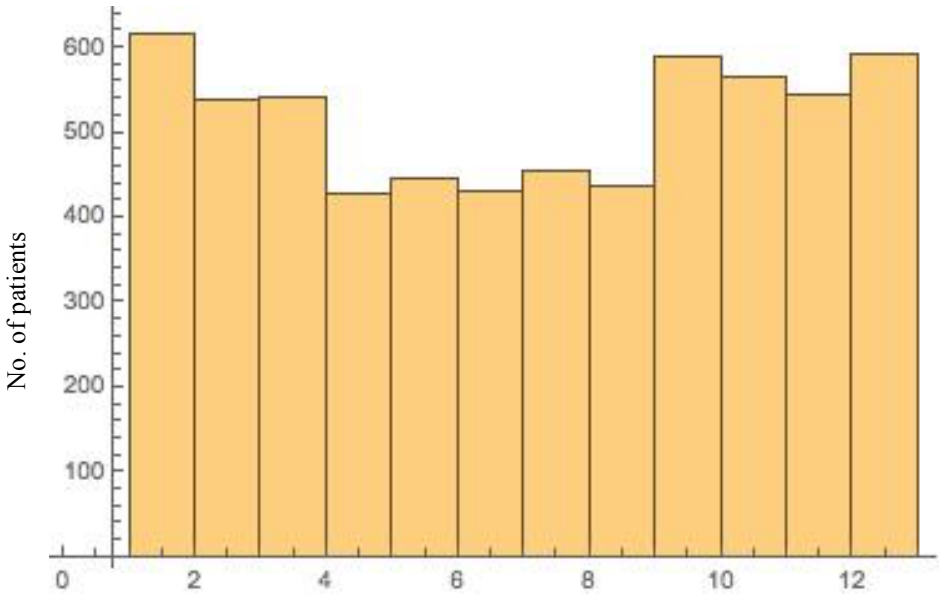


Figure 11: Month of diagnosis of patients with T1D in the Isis-Diab cohort

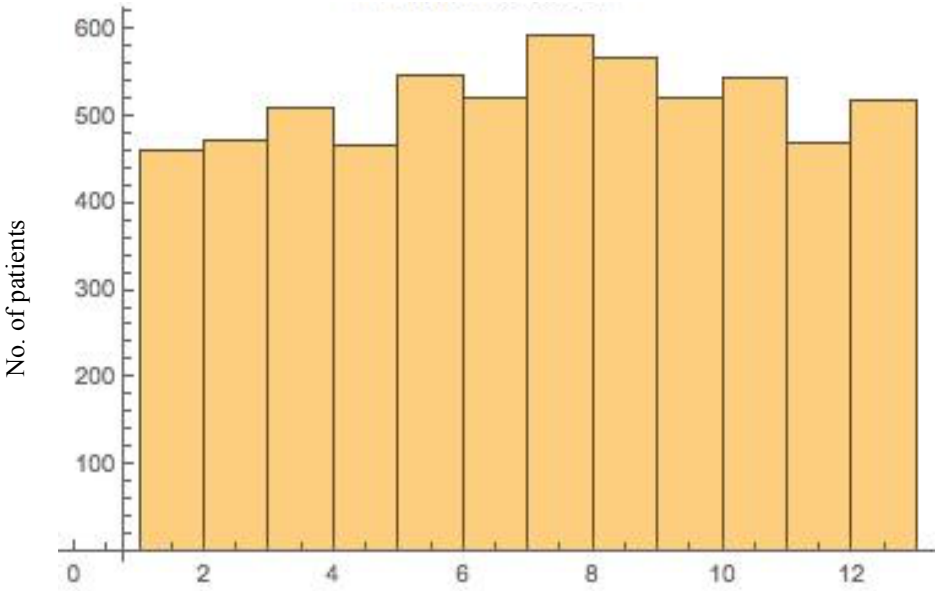


Figure 12: Month of birth of patients with T1D in the Isis-Diab cohort

2.4.4 Hypotheses related with etiology of T1D

With time, several hypotheses has been proposed to explain possible etiological factors of T1D, the most favored being the following:

2.4.4.1 Hygiene Hypothesis

The hygiene hypothesis proposed by Strachan (1989) (306) suggests that exposure to pathogens early in life, such as by contact with older siblings, or acquired prenatally from an infected mother by contact with her older children, prevents autoimmune diseases; however, in modern society individuals lack exposure to such factors, they could be genetically predisposed to diseases of the immune system but cannot protect themselves from autoimmune phenomena (301). Bach (2002) described potential mechanisms affecting the immune system (25). Kolb and Elliot proposed that an improved hygienic environment could be responsible of the increase in incidence trends of T1D (169). Later, Gale concluded that early exposure to micro-organisms, such as parasites and indigenous biota of the gut, could have a protective effect against T1D mediated by regulatory T lymphocytes (104). Experiments in animal models have shown that infection might inhibit the development of diabetes (66, 200). On the other hand, some viral infections appear as triggers of T1D.

2.4.4.1.1 Polio Hypothesis

This is an extension of the hygiene hypothesis. It suggests that certain viruses, such as poliovirus, will become less frequent by efficient mass vaccination programs, and by increasing the standards of hygiene. Paradoxically, the incidence of paralytic polio, a complication of acute polio infection, began to increase when the frequency of acute poliovirus infections started to decrease at the beginning of the last century, possibly due to decreased levels of protective maternal poliovirus antibodies transferred transplacentally and through breast milk to the infant. Similarly, diabetes is increasing rapidly in countries such as Finland and Sweden where thanks to vaccination programs the frequency of enterovirus infections has tended to decrease over the last decades (167, 346). This situation could however increase the susceptibility of young children to the diabetogenic effect of different enteroviruses (167, 200, 301).

2.4.4.1.2 Virus Hypothesis

Population-based studies have suggested that viruses probably play an important role in initiating autoimmunity toward beta cells and therefore in initiating or accelerating T1D pathogenesis (144, 301). In two prospective series of young children an increased genetic susceptibility to T1D after infection by viruses was reported (167). Data from retrospective and prospective epidemiological studies suggest that the principal viruses associated with the development of T1D are viruses of the *Enterovirus* genus, mainly Coxsackievirus B4 (CoxB4 or CV-B4). These viruses are ubiquitous and are largely transmitted by the fecal–oral route via the ingestion of water or food containing contaminated faeces. Enteroviruses belong to the *Picornaviridae* family, that includes the *Rhinovirus, Hepatovirus, Parechovirus, Cardiovirus, Kobuvirus, Aphthovirus, Erbovirus* and *Teschovirus* genera. CoxB4 has a natural tropism for beta cells and a molecular mimicry which favors the destruction of beta-cell islets (315). Other viruses associated with T1D although less intensively are Rubella virus, Mumps virus, Cytomegalovirus, retroviruses, and rotaviruses (144, 167). In addition, several studies suggest that possibly many common viral RNA infections may induce islet autoimmunity in genetically susceptible individuals (6). Such infections would begin a vicious circle affecting gut microbiota (the principal intestinal mucosa barrier) and altering intestinal immune responsiveness. This in turn would encourage changes of the composition of the microbiota and disturb the role of gut as modulator of beta-cell autoimmunity and/or as the place to initiate beta-cell autoimmunity. It is conceivable that if a decreased microbial load occurs at an early age, this may have an important impact on the programming of the immune system by altering gut-associated lymphoid tissue (167); finally together with viral infections, these modifications would trigger T1D (336, 354).

2.4.4.2 Cow's Milk Hypothesis

Antibodies to proteins of cow's milk have been detected in the serum of in children with T1D as of 1988. For Savilahti et al. (276), the introduction of antigenic bovine insulin via cow's milk in food increases the immune reaction leading to the hypothesis that early introduction of cow's milk proteins in the infant's diet may play a role in the development of autoimmunity to T1D (66, 200, 315). In a study made in Chile the level of anti-BSA-IgG was measured (BSA: bovine serum albumin), as well as of other antibodies. The anti-BSA-IgG was positive (using a cut-off point of 25.6 ng/ml) in 98% of diabetic children and absent from

the control population (15). On the other hand, some studies support the hypothesis that breastfeeding may play a protective role against the development of T1D (6, 200, 315).

In babies, beta lactoglobulin, which is present in cow's milk but not in human milk, may initiate an immune response that is cross-reactive with glycodelin (a glycoprotein that belongs to the lipocalin superfamily), and this response could interfere with the ability of glycodelin, to modulate immune responses (66, 113). This situation is similar to the one that occurred with the celiac disease and gluten, the wheat-deficient diet in World War II in the Netherlands: its postwar improvement identified the culprit, and autoimmune disease-causing agent (307). It has been proposed that association of HLA in celiac disease, in which HLA DR3-DQ2 is the dominant susceptibility haplotype, can be explained by the superior ability of the DQ2 molecule to bind proline-rich gluten peptides that have survived gastrointestinal digestion and have been deamidated by tissue transglutaminase (166). In agreement with this model, insulin is a crucial autoantigen in T1D because it is the only autoantigen specific of beta cells in postnatal life and because bovine insulin present in cow's milk differs from human insulin by three amino acids: two in the A chain and one in the B chain (167). These formulas generally are the first dietary source of foreign complex proteins to which an infant is exposed in developed countries.

In a multiple logistic regression analysis, Knip et al. (167) observed that IgA antibodies against B-lactoglobulin were strongly associated with an increased risk of diabetes during childhood, independent of the islet cell antibody status and of early weaning to a cow's milk–based formula. There apparently exists an immune response, initially induced by bovine insulin that cross-reacts and may target human insulin in beta cells. These observations could be interpreted as supporting the idea that enhanced consumption of cow's milk before the presentation of clinical T1D is a risk factor (167).

2.4.4.3 Accelerator Hypothesis

This theory by Wilkin (2001) (362) focus on obesity and insulin resistance as major accelerator of diabetes; it suggests that increasing body mass plays a key role in the development of both T1D and T2D. The combination of beta-cell up-regulation (insulin resistance, determined by weight gain) and autoimmunity (genetically regulated by the HLA genotype) determines the rate of beta-cell apoptosis (361, 363). According this hypothesis,

the increasing worldwide obesity stresses susceptible beta cells, and as consequence its early demise (358).

2.4.4.4 Spring harvest Hypothesis

This theory is based on the finding that the overall rise in T1D incidence was observed in very young children; according to this hypothesis, environmental factors determine and modulate the progression of diminishing beta-cell mass in susceptible individuals. In this theory Gale (2005) (106) emphasizes T1D progression rather than disease initiation, in which protection against environmental events in early life should be the focus.

2.4.4.5 Unifying Hypothesis

Ludvigsson (2006) (200) proposed that a patient may have peculiarities or both T1D and T2D, because certain mechanisms lead to islet inflammation and others to insulin demand that at the end cause insulin deficiency – mediated by autoimmune reaction in genetically predisposed individuals - and clinical manifestations of diabetes. According to the author, related with deficiency of immune system are increased hygiene and vitamin D deficiencies, while related with the autoimmune reaction, certain viruses, dietary bovine insulin, or toxic agents could be implicated.

2.4.4.6 Overload Hypothesis

Dahlquist (2006) has suggested that environmental determinants, via different mechanisms, “overload beta-cells”. Insulin resistance or increased insulin requirement could cause beta-cell overload. If so, the focus should be placed on “accelerating factors rather than potential triggers of autoimmunity” that operate after the initiation of autoimmunity. Accelerating factors have been proposed as implicated in this process: high growth rate, infections, psychological stress and cold climate (72).

2.4.4.7 Diet Hypothesis

This theory proposes that dietary factors play a role in the development of T1D. Intake of agents such as nitrite / nitrate (239, 339) or early introduction of solid foods (cereals) (226, 227) are implicated. In contrast, the duration of breastfeeding (66, 200, 276, 315) is a factor associated with reduced risk of T1D.

2.4.4.8 Human contamination by environmental chemicals

Based on epidemiological evidence, Howard (2012) (137) argues that several environment chemicals, such as N-nitroso compounds, air pollutants and persistent organic pollutants can act as "endocrine disruptors" affecting the development and function of the immune system, and as a consequence contribute to the development of T1D. According to this theory the principles of dose-effect and timing of exposure are determinant in their biological effects.

2.4.4.9 Multidisciplinary approach

Vehik et al. (2013) (342) discuss how advances in epidemiology, genetics, microbiology and immunology have provided new frontiers to understand the etiology of T1D. The relationship between early life environment – in utero and early postnatal period -, the development of gut immunity (microbiome) and epigenetic factors affect the risk of T1D (mediated by the innate or adaptive immune system). Environmental factors involved are for example a diet early in life, vitamin D levels, mode of delivery and enteroviral infections.

2.4.5 Personal summary of factors related with etiology and incidence of T1D

Throughout this study, several factors related with the etiology of T1D, and mentioned above in various hypotheses, were explored. In view of summarizing the knowledge reviewed during this thesis, three main related categories of determinants were identified: i) *autoimmunity*, and ii) *life style* and iii) *social determinants* of health.

In the *autoimmune* category, emerging elements are: a) the gut immune mechanisms (affected by diet and composition of the micro / macrobiota flora), b) the lymphocyte T helper (Th1/Th2) response to infections (depending on the kind and timing in which the infection was produced), c) the vitamin D deficiency related with exposure to UV radiation (this could be determined by the effect of seasons, geographic location, outdoor activities, etc.), and d) the accelerated weight gain (producing insulin resistance and an overload of beta cells); **Figure 13**.

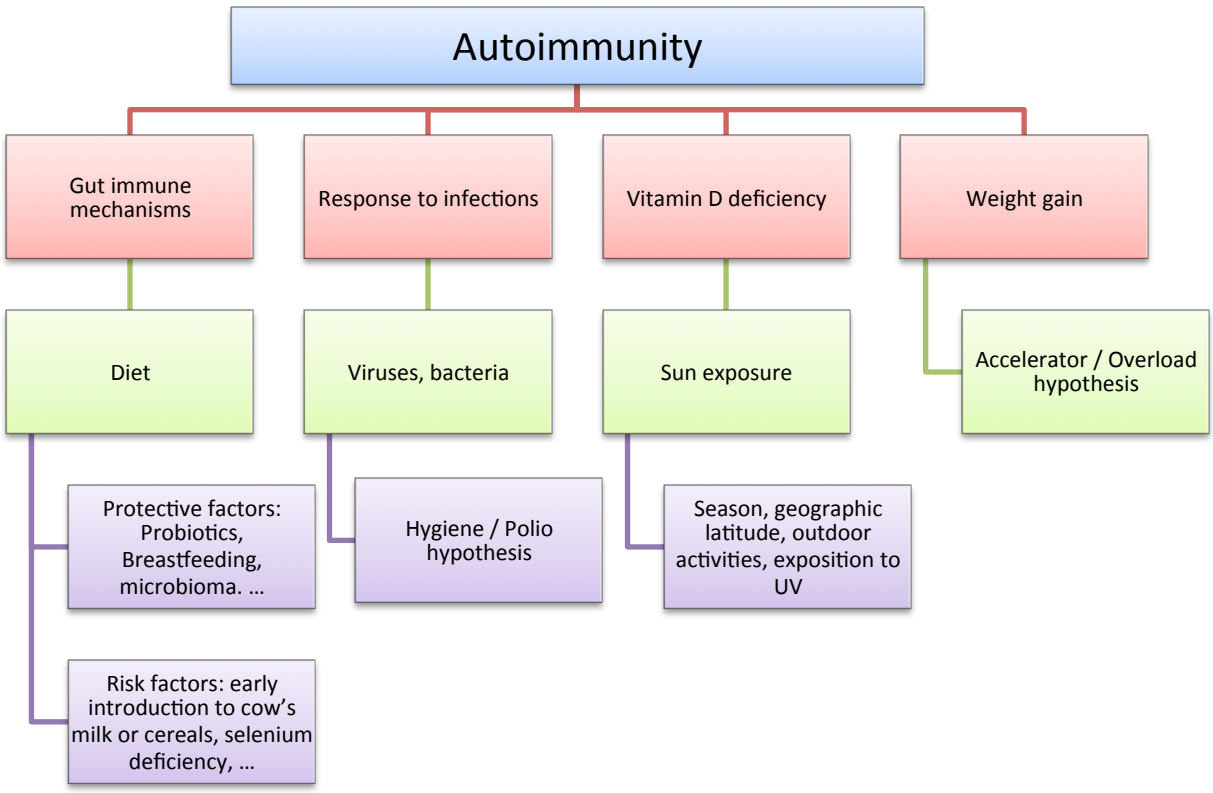


Figure 13: Tentative clarification of the autoimmunity related factors with T1D

In the category related with *life style,* emerging factors are: a) the current obesity trends and accelerated weight gain childhood and adolescence observed mainly in Western countries (in line with the Accelerator and the Overload Hypothesis), b) the sedentary life style that could be associated with less outdoor activities, less exposition to UV radiation, increased technology dependence, and also with higher obesity rates, and c) the wealth of the countries associated with access to modern facilities, processed food, environment pollution, etc., factors that could be new or unknown triggers or accelerators of autoimmunity processes; also related with more developed countries are higher percentage of urban population and changes in patterns of childhood diseases (related with the Hygiene and Polio Hypothesis); **Figure 14**.

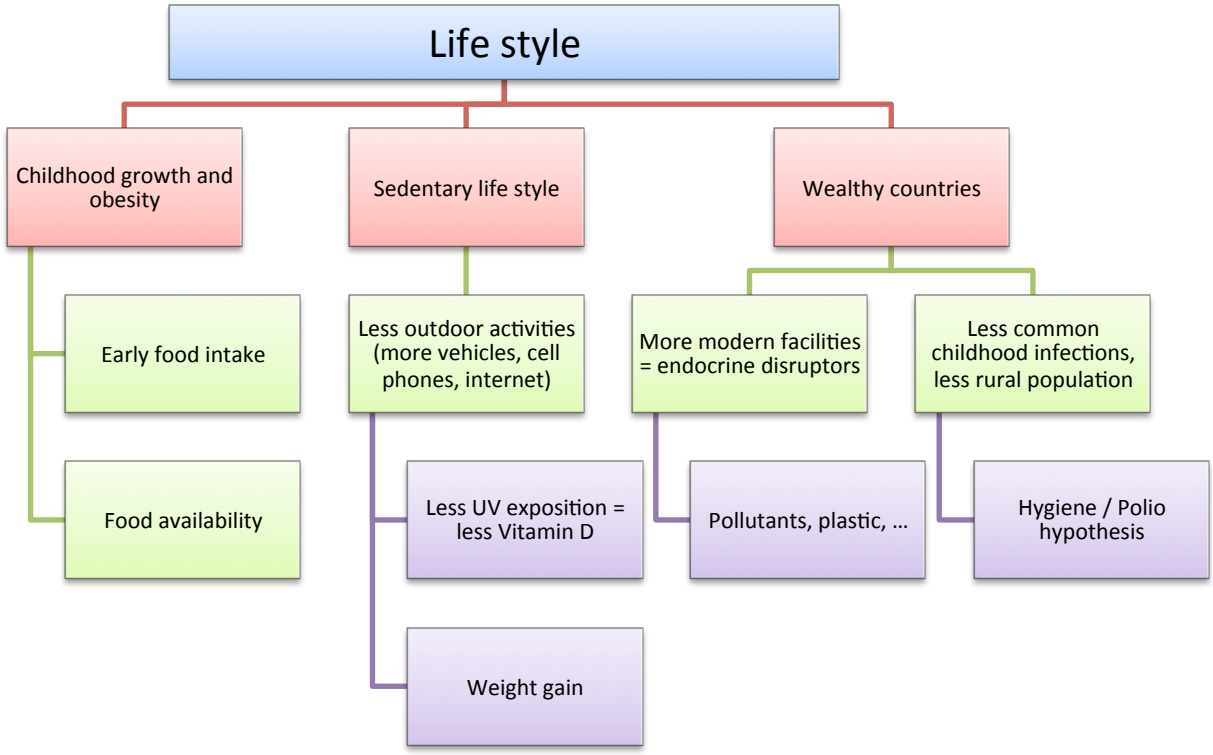
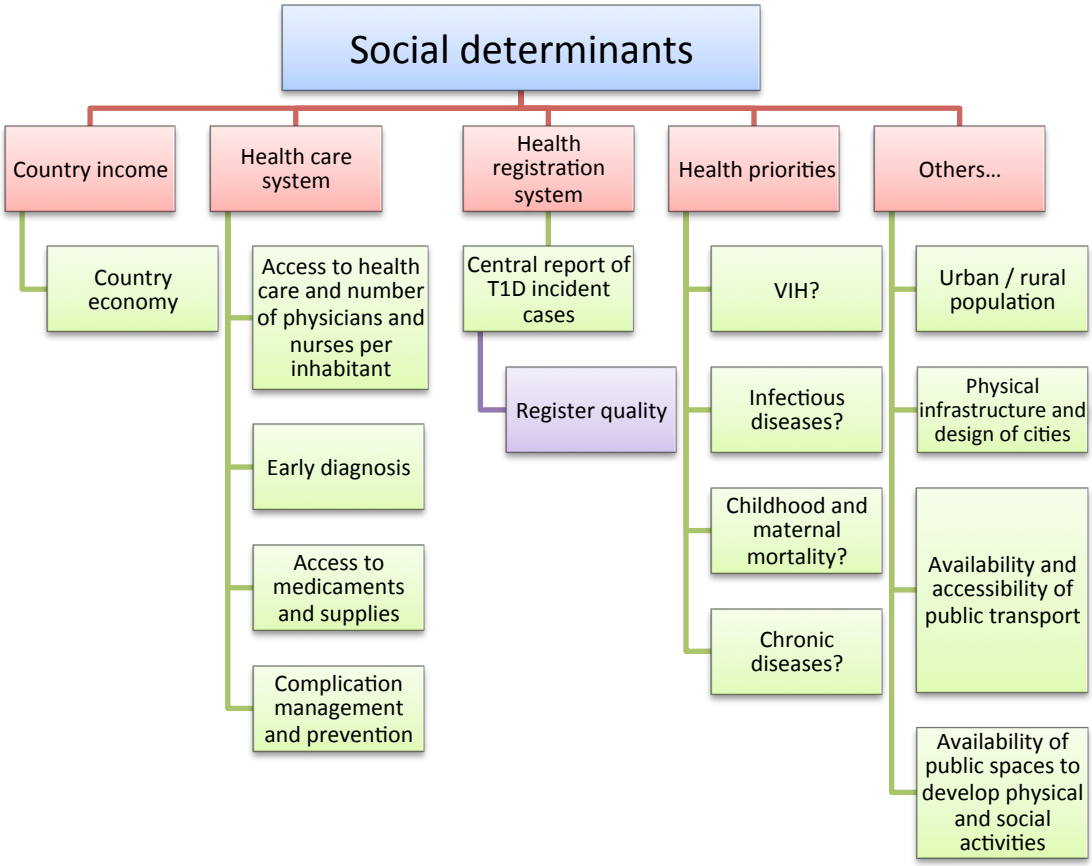


Figure 14: Tentative clarification of the life style related factors with T1D

Finally, epidemiology of T1D is influenced by *social determinants,* resulting from differences in economy and health care systems of the countries. Emerging factors of this category are: a) country income (determined by indicators such as Gross Domestic Product

(GDP) or Gross National Income (GNI)), b) health care system (that determines the access to health care and the number of physicians and nurses specialized in diabetes care per inhabitant, and as consequence better and early diagnosis, access to medicaments and supplies such as syringes and reimbursements, and complications management and prevention), c) health registration system (including central registers of incidence cases), d) health priorities of the country (Is T1D considered an health priority in the country, as compared with other diseases?), and e) other social factors, such as relation urban/rural population, physical structure of the city, availability and accessibility of public transport and public space could affect the epidemiology of T1D; **Figure 15**.



GDP: Gross Domestic Product, GNI: Gross National Income.

Figure 15: Tentative clarification of the social determinants and T1D

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Chapter 3

Incidence of Type 1 Diabetes and Determinants Among Children

Contents

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3 Epidemiology of T1D among children

T1D is one of the most common chronic diseases in children: each year 79.000 children develop the disease worldwide (241). The disease has been increasing by 3% per year (318) and despite geographical variations, a global epidemic is now recognized (99). To explain this increase in the incidence and the geographical differences, diverse factors have been implicated; nevertheless the role of these factors remains unclear.

The fist part of **chapter 3** is focused on the global conditions as key triggers. The results addressed here were published as an abstract in 2014 in the *Revue d'Épidémiologie et de Santé Publique* and in 2015, as a full research article in *PLoS ONE*. In this chapter we propose the analysis of predictors of T1D incidence using information of independent variables retrieved in public databases (the World Health Organization (WHO), the United Nations (UN) and the World Bank (WB)). In these databases we searched for indicators, with as few missing values as possible until a maximum of 5% was reached, that could be correlated with the incidence of T1D in 80 countries. Using regression models and stepwise backward selections, we present significant predictors of T1D among 77 independent variables in four domains: *Climate and Environment*, *Demography*, *Economy*, and *Health Conditions.* In addition, a comparison between such indicators for countries with and without available information is presented in the Supplemental Materials of this chapter. The significant predictors of T1D described in this chapter are also used to understand the gene-environment relation shown in unpublished analyses of **chapter 5** about APC analyses and in **chapter 6** about genetic determinants of T1D.

The second part of **chapter 3** is focused on the cumulative incidence of T1D. To study the descriptive epidemiology of T1D, one of basic instruments – but no less important – is the incidence. The measure of incidence quantifies the number of new events or cases of the disease that occur in a population of individuals at risk during a specific time interval. It may be expressed in absolute numbers (cumulative incidence) or in rates (incidence rate or density). Cumulative incidence is the proportion of individuals who become diseased during a specific period of time, and it provides an estimate of the probability, or risk, that an individual will develop a disease during a specified period of time (118, 132).

The first step in studying the incidence is typically the evaluation of geographic and temporal variations in the disease; this was presented in **chapter 1,** and **chapter 3** will explore such variability in depth.

In addition, **chapter 3** presents preliminary analyses on epidemiological changes of T1D by continents and countries, the time course of the cumulative incidence of T1D in successive cohorts of children born since 1924, and a review of studies reporting the early age at onset of T1D observed in some countries (242). Elements that have motivated the development of the APC analyses are presented in **chapter 5**.

In summary, **chapter 3** presents new results through the systematic examination of the correlation of the incidence of T1D in children with various environmental variables and a variety of additional information on the descriptive epidemiology of T1D. The results presented here could be considered as an attempt to show the power of data published in public databases in answering fundamental questions in public health.

3.1 Covariation of the Incidence of T1D with Country Characteristics Available in Public Databases

PLOS | ONE

RESEARCH ARTICLE

Covariation of the Incidence of Type 1 Diabetes with Country Characteristics Available in Public Databases

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background

The incidence of Type 1 Diabetes (T1D) in children varies dramatically between countries. Part of the explanation must be sought in environmental factors. Increasingly, public databases provide information on country-to-country environmental differences.

Methods

Information on the incidence of T1D and country characteristics were searched for in the 194 World Health Organization (WHO) member countries. T1D incidence was extracted from a systematic literature review of all papers published between 1975 and 2014, including the 2013 update from the International Diabetes Federation. The information on country characteristics was searched in public databases. We considered all indicators with a plausible relation with T1D and those previously reported as correlated with T1D, and for which there was less than 5% missing values. This yielded 77 indicators. Four domains were explored: *Climate and environment, Demography, Economy*, and *Health Conditions*. Bonferroni correction to correct false discovery rate (FDR) was used in bivariate analyses. Stepwise multiple regressions, served to identify independent predictors of the geographical variation of T1D.

Findings

T1D incidence was estimated for 80 WHO countries. Forty-one significant correlations between T1D and the selected indicators were found. Stepwise Multiple Linear Regressions performed in the four explored domains indicated that the percentages of variance explained by the indicators were respectively 35% for *Climate and environment*, 33% for *Demography*, 45% for *Economy*, and 46% for *Health conditions*, and 51% in the *Final model*, where all variables selected by domain were considered. Significant environmental predictors of the country-to-country variation of T1D incidence included UV radiation, number of

mobile cellular subscriptions in the country, health expenditure per capita, hepatitis B immunization and mean body mass index (BMI).

Conclusions

The increasing availability of public databases providing information in all global environmental domains should allow new analyses to identify further geographical, behavioral, social and economic factors, or indicators that point to latent causal factors of T1D.

Introduction

It has long been noticed that the incidence of Type 1 Diabetes (T1D) is highly variable from one country to another. For example, the 62.42/100.000 persons/year incidence found in Finland [1] was 780-fold larger than the 0.08/100.000 persons/year incidence in Papua New Guinea [2]; differences in T1D incidence are also observed between countries where the health care systems are comparable. The variability of T1D incidence is even visible within countries; for example, in Italy, T1D incidence varied between 54.4/100.000 persons/year in Sardinia [3] and 4.4/100.000 persons/year in Lombardia [4]. The reason for these differences is not precisely known, but is most unlikely due to classification bias, as the disease cannot go untreated, and the diagnosis is relative easy to perform in children [5]. The country-to-country T1D variability is known to be partly explained by genetic variations. Indeed, HLA (human leukocyte antigen) and 33 other genes are associated with elevated risk of T1D (*T1Dbase* Version 4.18 updated on 30/9/2014 available at http://www.t1dbase.org) [5–11]. The genetic characteristics of several populations have been found to—at least partially—explain the level of their T1D incidence [12]. For example, the low incidence in Japan, and more generally in southeast Asia, was strongly associated with the absence of highly susceptible haplotypes, such as DRB1∗03-DQB1∗0201 and DRB1∗04-DQB1∗0302 found in Caucasian populations [13] or DRB1∗030101-DQB1∗0201 [14] found in Arab populations (Bahrainis, Lebanese, and Tunisians). Instead, the major susceptible HLA haplotypes in the Japanese and Korean populations were DRB1∗0405-DQB1∗0401 and DRB1∗0901-DQB1∗0303 [15].

Another peculiarity of T1D epidemiology is that a dramatic increase of the incidence (on average 3% per year [16]) was observed over the last decades in many countries, in particular European countries with previously low incidences. This increase cannot be explained by genetic factors, since the genetic structure of these countries cannot have varied greatly over such a short period of time. The reasons are more likely to be found in environmental factors (taking here environment broadly, as encompassing physical, chemical, social and life-style factors). However, no single environmental factor, or configuration of factors, that could explain the patterns of differences has ever been identified. More likely, there are complex networks of environmental causes, and of gene-environmental causes that remain to be discovered.

The search of genetic factors of T1D was facilitated during the last 10 years by the GWAS (genome-wide association studies) technology that replaced the gene candidate approaches and instead scanned the entire genome to find SNPs (Single-Nucleotide Polymorphisms) that were significantly associated with T1D [17]. The discovery of an SNP was not the discovery of a "gene", but was a marker leading to the possible discovery of a gene. Here, we translate this data-driven approach to search for environmental markers related to variations of T1D incidence that might eventually lead to environmental causes, possibly in interaction with genetic factors. One could indeed expect that, in this age of information, plenty of environmental

characteristics could be readily available, insofar as local and global organizations collect such data, and provide them free to researchers, with easy interface on the Internet. A limitation commonly advocated is that country statistics are in many cases of too low quality. However, for two related reasons, this argument does not hold, or will not hold for long: a) why collect, maintain and publish such statistics if they cannot be used by researchers? and b) how can one encourage a better quality for these statistics—meaning more resources devoted to them—if they are never used?

Here, we present the attempt we made to use open public data to identify climate and environmental, demographic, economic, and health characteristics correlated with variations in T1D incidence between countries.

Material and Methods

Incidence of T1D data by country

The country T1D incidence was obtained thanks to a systematic review following the PRISMA recommendations [18] (**S1 Checklist**). All relevant original papers published in English between 1975 and 2014 including reviews (Diamond [16] and Eurodiab studies [19–21], the International Diabetes Federation (IDF) atlas [22, 23]) were analyzed (see Flow diagram of the literature search in **S1 Fig.**, the full search strategy on **S1 Table**, and the list of selected publications in **S2 Table**), registration number in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42012002369 (**S1 Protocol**).

The T1D incidence value per 100.000 persons/year for individuals in the age group 0–14 years for both sexes used here for each country was obtained as follows. 1) When only one dataset was available for a given country, the figure obtained from this study was used, even if the study was not nationwide. 2) If more than one dataset was available including nationwide and local studies, the most recent published nationwide study in the country was used. 3) If only local studies in a single area within the country were available, the most recent dataset was selected. 4) If local studies reporting incidences were available for different areas in the country, the mean incidence after grouping the most recent published studies for each area was used.

Country indicators

Three open public databases from the World Health Organization (WHO) [24], the United Nations (UN) [25] and the World bank (WB) [26] were used to search indicators in four domains: *Climate and environment* (land use and physical environment), *Demography, Economy* (including health resources and expenses), and *Health*. We only kept indicators with less than 5% missing values in the 80 countries for which we could estimate T1D incidence (see Results, below).

In total we used 77 indicators: two (latitude and longitude) were obtained thanks to Google Maps [27], 29 were retrieved from the WHO [24], three from the UN [25] and 43 from the WB [26]. When several values were available for one indicator, the value obtained in 2012, or on the date closest to 2012 was chosen (see Fig. 1 for a list of the 77 indicators, and **S1 Database** for the entire database used in the calculation of the correlations).

Statistics

The R software (version 3.0.1) served for statistical and graphic analyses [28]. Spearman correlation was used to compute the correlation between the 77 selected country indicators and the T1D incidence. To account for multiple testing leading to a false discovery rate (FDR), the

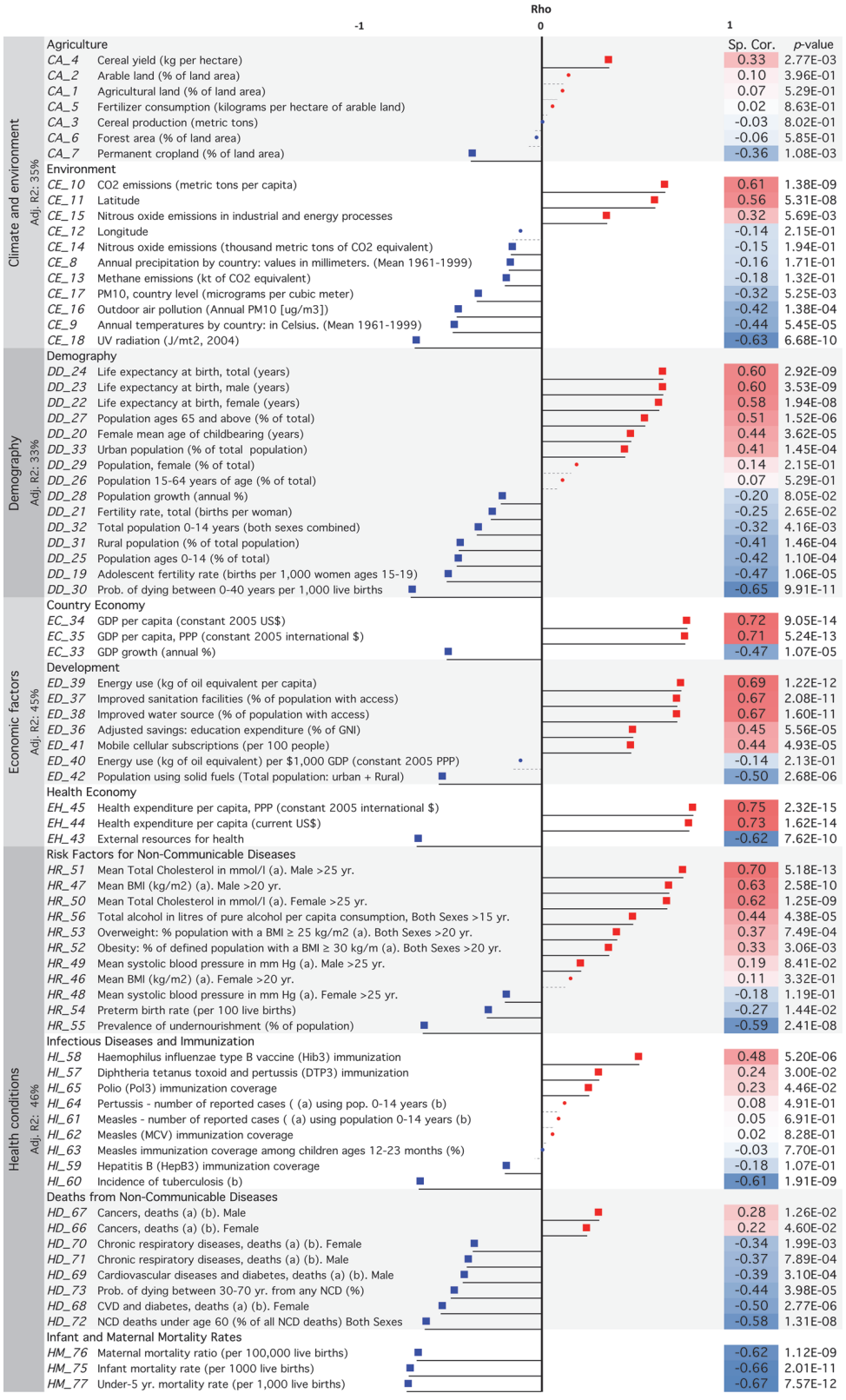

Fig 1. Correlations between T1D incidence and 77 country indicators. The correlations were computed in the 80 WHO countries where T1D incidence could be estimated. Dots: no significant correlations. Squares: significant correlations with $p \leq 0.2$. Significant correlations after Bonferroni correction (p-value ≤ 0.000649) are highlighted. Abbreviations: PM: particular matter, UV: ultraviolet, GDP: Gross Domestic Product, GNI:

Gross National Income, BMI: Body Mass Index, CVD: Cardiovascular Diseases, CA: Cancer, DM: Diabetes Mellitus, CHRD: Chronic Respiratory Diseases, Adj. R2: Adjusted-R^2. Red: positive correlations, blue: negative correlations. (a) Age-standardized estimate; (b) Per 100,000 individuals; (c) Coverage among 1-year-olds (%). See **S1 Database** for the entire database.

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Bonferroni correction was used [29]: a p-value ≤ 0.000649 (= 0.05/77 variables) was considered as indicating significance at the 5% level.

We employed Stepwise Multiple Linear Regression (SMLR) methods to obtain the best predictors of T1D incidence within the original list of 77 variables. This process was carried out in two times: first, SMLR served to select independent predictors of T1D within each of the 4 environmental domains considered; second, the final subset of independent variables using the four sets of predictors obtained in the first step was selected.

In the by-domain analysis, all variables were entered for which the p value testing the correlation with incidence was smaller than 0.20. When a couple of variables was correlated with $r>0.80$, only one of the variables was used in the regression analysis to avoid computational issues associated with colinearity.

Then, starting with the full model, we made a manual backward selection of the variables, selecting at each step one variable. This variable was the one that, after being dropped, maximized the adjusted R^2. The process was stopped at the step where the adjusted R^2 decreased [30]. Then, taking the list of variables obtained, a new SMLR was performed that identified the smallest subset, based on the Akaike information criterion (AIC) [31]. Model assumptions for linear models were checked by visual inspection of the residuals.

The same process was used in the final analysis, starting with all significant predictors found in the analyses by domain. 10-Fold Cross-validation after bootstrapping [32] served to evaluate the predictive value of the final model. Graphic representation used the DAAG package [33].

Results

Incidences were retrieved for 80 countries; they varied widely between continents, countries and regions (see **S2 Table** and **S1 Database** for the incidences). Among children aged 0–14 years the lowest nationwide incidences ($\leq$ 1 per 100.000/year) were in Eastern Asia (China), South-East Asia (Thailand), Melanesia Oceania (Papua New Guinea), and South America and the Caribbean (Dominican Republic, and Paraguay). The highest nationwide incidences ($\geq$ 30 per 100.000/year) were in Northern Europe (Finland, Sweden, Norway).

The correlations between the incidence and the 77 selected independent variables grouped into four domains are shown in Fig. 1 (for details and sources of information see **S1 Database**). Forty-one of 77 variables survived the Bonferroni correction and were significantly correlated with incidence at a significant p-value ≤ 0.000649 (= 0.05/77). Thirty-five variables, for which the correlation between any two of them was less than 0.8, and had a correlation coefficient with T1D incidence with $p<0.20$ were entered in the stepwise regression models.

The detail of the 35 (of 77) variables that were entered in stepwise multiple regressions is shown in **Fig. 2 (panel A)** and the results of multivariate models by domains in **S3 Table**. In the *Climate and Environment* domain, seven of the 18 original variables qualified to be entered in the model; after the SLRM selection, the three selected variables were: UV radiation, CO_2 emissions and outdoor air pollution (particular matter: PM10 $\mu g/m^3$). The adjusted % of variance explained (R^2) in the model was 35.2%. The four excluded variables were: % of agricultural land, latitude, nitrous oxide emissions and annual precipitations.

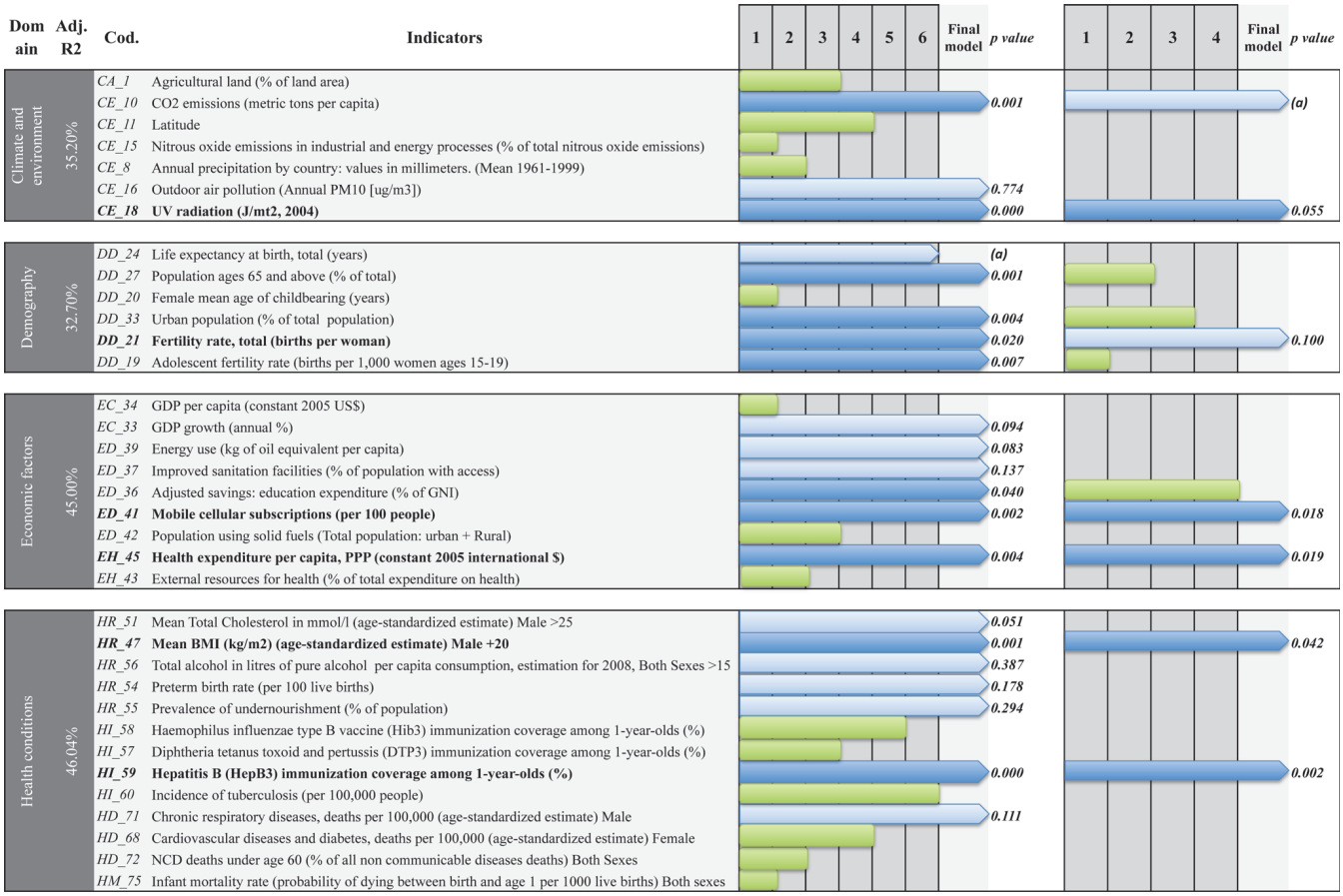

Fig 2. Stepwise identification of predictors of T1D Incidence (a) by domain and (b) final. The lines are the 35/77 variables with $p<0.2$. Green bars indicate variables that were excluded during the stepwise multiple regression (the length of the bar indicates the number of steps at which it was excluded). Blue bars indicate that variables were selected after SMLR was applied. The dark blue bars indicate that the independent predictors of T1D were highly significant; panel (A): in the by-domain analysis; panel (B): in the final model. The final analysis was performed on the variables selected in the by-domain analysis (shown in dark blue in panel (A). Abbreviations: Dom: Domain, PM: particular matter, UV: ultraviolet, GDP: Gross Domestic Product, BMI: Body Mass Index, CVD: Cardiovascular Diseases, CA: Cancer, DM: Diabetes Mellitus, CHRD: Chronic Respiratory Diseases, Adj.R2: Adjusted-R2. (a) Variable dropped after applied Akaike information criterion (AIC).

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In the *Demography* domain, six of the 15 original variables qualified to be entered in the model; after the SLRM selection the four selected variables were: adolescent fertility rate, total fertility rate, proportion of the population aged over 65 years, and proportion of urban population; (adjusted R^2 32.7%). The two excluded variables were: life expectancy at birth, and female mean age of childbearing.

In the *Economy* domain, nine of the 13 original variables qualified to be entered in the model; after the SLRM selection the six selected variables were: energy use, proportion of mobile cellular subscriptions, education expenditure, % of improved sanitation facilities, health expenditure per capita, and % of annual Gross domestic product (GDP) growth; (adjusted R^2 45.0%). The three excluded variables were: GDP per capita, population using solid fuels and external resources for health.

In the *Health domain*, 13 of the 31 original variables qualified to be entered in the model; after the SLRM selection the seven selected variables were: deaths from chronic respiratory diseases, hepatitis B immunization coverage in <1 year of age, alcohol consumption, mean body mass index (BMI) in male >20, mean total cholesterol in male >25, preterm birth rate, and

Table 1. Final Stepwise MLR model.

Code	Coefficients	Estimate	Std. Error	*p* Value
	(Intercept)	-25.240	15.390	0.106
CE_18	UV radiation (J/mt2, 2004)	-0.002	0.001	0.055
DD_21	Fertility rate, total (births per woman)	2.181	1.309	0.100
ED_41	Mobile cellular subscriptions (per 100 people)	0.066	0.027	0.018
EH_45	Health expenditure per capita (constant 2005 intern. $)	0.001	0.001	0.019
HI_59	Hepatitis B (HepB3) immunization coverage [(a)]	-0.085	0.027	0.002
HR_47	Mean BMI (kg/m2) Male >20 years of age [(b)]	1.263	0.611	0.042

The model included all significant predictors found in the analyses by domain.

(a) Among 1-year-olds (%)

(b) age-standardized estimate.

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prevalence of undernourishment in the population (adjusted R^2 46%). The six excluded variables were: infant mortality rate, cardiovascular diseases and diabetes, deaths for non-communicable diseases $\leq$ 60, incidence of tuberculosis, haemophilus influenza type B (Hib3) vaccine immunization, and diphtheria tetanus toxoid and pertussis (DTP3) immunization.

In the final model, the five independent predictors were: UV radiation, number of mobile cellular subscriptions, health expenditure per capita, hepatitis B immunization and mean BMI (Table 1, details in **S3 Table**). The predicted incidence variation associated with the variation of each predictor can be computed from the values shown in Table 1: for example, for one unit increase in UV radiation in J/mt^2, a mean 0.2% decrease in the incidence of T1D is expected. For an increase of 1% in the percentage of hepatitis B vaccination among 1 year-olds, an 8.5% decrease in the incidence of T1D is expected; for one unit increase in the percentage of BMI in males, a 1.3% increase in the incidence of T1D can be expected. The predictive value of the regression equation was visualized by comparing the predicted incidences with the observed incidences. Finland is noticeably an outlier in this empirical covariation predicted by the model (**Fig. 3**). 10-fold cross-validation indicated that the fraction of the variability of the global incidence of T1D was estimated to be 41% (**S2 Fig.**).

Discussion

Our work explored whether the information available in public databases could help to study the environmental part of the country-to-country variations of T1D incidence. We found 77 variables with less than 5% missing values in the 80 countries for which the systematic review we carried out provided an estimate of the 0–14 T1D incidence.

These 77 variables explored four domains (*Climate and environment, Demography, Economy, Health*). In each of these domains, a stepwise multiple regression analyses identified the subset of variables of the domain which were independent predictors of the variation in the geographical T1D incidence. Then, analyzing these 4 subsets of domain variables, we identified five final independent environmental indicators: four of the five were known as risk factors of T1D: UV radiation [34–36], health expenditure per capita [34], coverage of hepatitis B vaccination [37] and mean BMI [38]. The last indicator was the proportion of mobile subscriptions, positively correlated with T1D incidence. It is probably a marker of a life-style that was not captured by any of the 77 variables used in the multiple analyses.

Coming to the domain-by-domain analysis **Fig. 2** **(Panel B)**, in the *Climate and Environment* domain, the first indicator that emerged was UV radiation. This may be related to

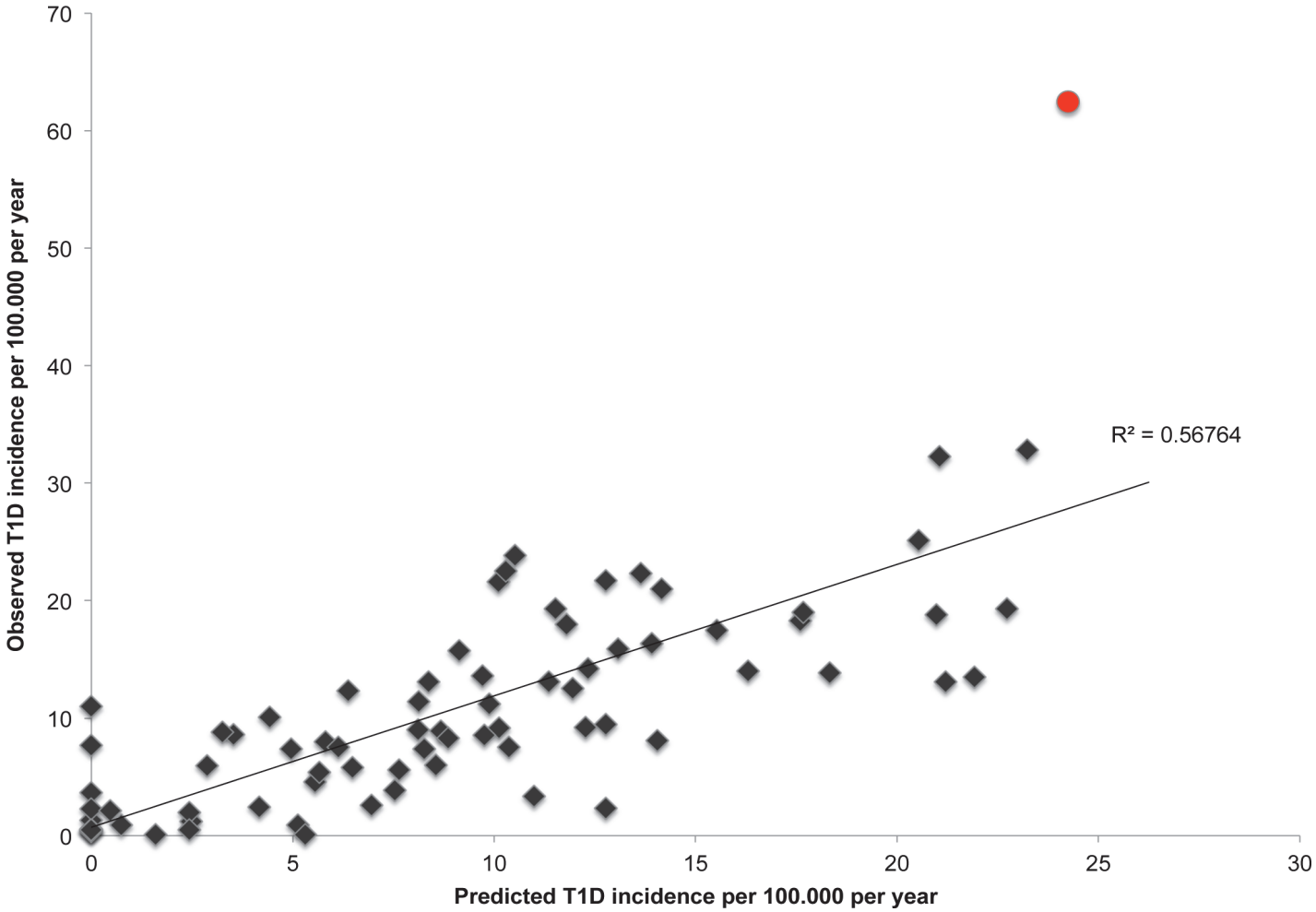

Fig 3. The predicted incidence of T1D among 80 countries vs. the observed incidence. Red dot: Finland. See S2 Fig. for predicted indices obtained after 10-fold Cross-validation.

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vitamin D deficiency [39] as reported in previous studies [34]. The second indicator of this domain was CO_2 emissions. An association between air pollution and T1D incidence has been recently described [40].

In the *Demography* domain, the only indicator that emerged in the final model was total fertility rate. The predictors dropped were: the adolescent fertility rate, the proportion of the population aged over 65 years, and the proportion of urban population. Concerning the proportion of urban population that was positively correlated with T1D incidence in this study as found in Lithuania [41], there are conflicting results in the literature: higher incidences was found in rural areas of the United Kingdom [42], and in semirural areas of Sweden [43], while no urban-rural difference in the incidence of T1D was found in Estonia [44].

In the *Economy* domain, three variables emerged, among which two were in the final list of independent predictors: proportion of mobile cellular subscriptions and health expenditure per capita. The third one was education expenditure. Higher incidences in wealthy countries, as measured by the GDP [45] and health expenditure per capita [34], have been described previously. In addition, other studies from Sweden [43, 46, 47], the United Kingdom [42, 48], and Canada [49] described similar associations between T1D and socioeconomic variables.

Within the *Health* domain, seven independent predictors were identified, among which two were in the final list: mean BMI in male >20, that had already been identified as risk factor [38], and hepatitis B immunization coverage in children <1 year of age, also recently proposed as a potential protector factor [37].

A first limitation of this study is that we could only rely on a relatively short set of variables retrieved in the public databases that met the condition of an acceptable fraction of missing data that we set arbitrarily at 5%. A second limitation was the differences in the temporality of the T1D data collected and the predictors. The mean year of the studies we used to estimate T1D incidence was 1997, while the mean year of the data for the 77 selected predictors was 2009. An important drawback, shared by all ecological studies, is that the correlations cannot be directly interpreted in terms of causality of the disease. However, they can be considered as providing signals that may help to unravel latent, yet unknown causes.

Furthermore, an important part of the variation in T1D incidence cannot be captured by an approach that only focuses on environmental factors. It is well known to be in a large part explained by genetic characteristics of the populations that were not analyzed here. Indeed, ethnic differences in T1D incidence between countries, and even within countries, have long been reported [13, 15, 50] and the most susceptible and protective haplotype determinants of T1D were identified [50]. However one difficulty is that this genetic information is lacking in many countries of the world, which limits the possibility of extending to genetics the kind of global analysis we presented here. For example, we explored the Allele Frequency Net at http://www.allelefrequencies.net/ [51], a public electronic repository for allele frequency of populations; we found that information on the haplotype DRB1∗0405—DQA1∗0301—DQB1∗0302 for which the T1D Odd Ratio was extremely high (11.37 reported by the Type 1 Diabetes Genetics Consortium Families [50]) was available in only 6 countries. Moreover, the genetic characteristics of a country are much less homogeneous than the environmental characteristics, because of the presence of various ethnic groups within the same country, while many of the environmental variables that we studied can be considered as identical (latitude, geographical characteristics) in the subgroups of a country.

In the future, it can be expected that analyses similar to this one, taking advantage of the increased availability and quality of public databases characterizing the human populations would be a path to help identify some of the still unknown causes, and networks of causes, of TID.

Supporting Information

S1 PRISMA Checklist. CONSORT PRISMA checklist.
(DOC)

S1 Fig. Flow diagram literature search for T1D incidences.
(TIFF)

S2 Fig. 10-Fold Cross-Validation.
(TIFF)

S1 Table. Search strategy.
(DOCX)

S2 Table. Publications list of the incidence of T1D by country and area. Table showing the list of publications reporting T1D incidence used in the analyses (∗). Information source: (PBDR) population based data register, (MBR) medical-based record, (OPD) other population denominators, (NS) non-specified. % Ascertainment: percentage of completeness between

primary and secondary sources of registers. Data collection process reported in the article: (P) prospective—incident cases collected prospectively-, (H) historical-incident cases collected retrospectively-. First author and year of publication. Number of reference. NW: Nationwide study. Note: the age range for the reported incidence was 0–14 years, except in the following cases: (a) 0–12, (b) 0–13, (c) 0–18, (d) 0–19, (e) updated International Diabetes Federation (IDF) 2013.
(DOCX)

S3 Table. Models by domains and final summary model. CI, Confidence Intervals. (a) Age-standardized estimate; (b) per 100,000 individuals; (c) Coverage among 1-year-olds (%).
(DOCX)

S1 Protocol. PROSPERO protocol. International Prospective Register of Systematic Reviews.
(PDF)

S1 Database. Database global incidence of T1D and independent variables. Excel table containing the database used in the correlations of 77 independent variables and the incidence of T1D among 80 countries.
(XLSX)

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Author Contributions

Conceived and designed the experiments: PDV PB AJV. Analyzed the data: PDV PB AJV. Wrote the paper: PDV PB AJV. Data acquisition: PDV.

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3.1.1 Supporting Information

3.1.1.1 CONSORT PRISMA checklist

SI Table 9: CONSORT PRISMA checklist

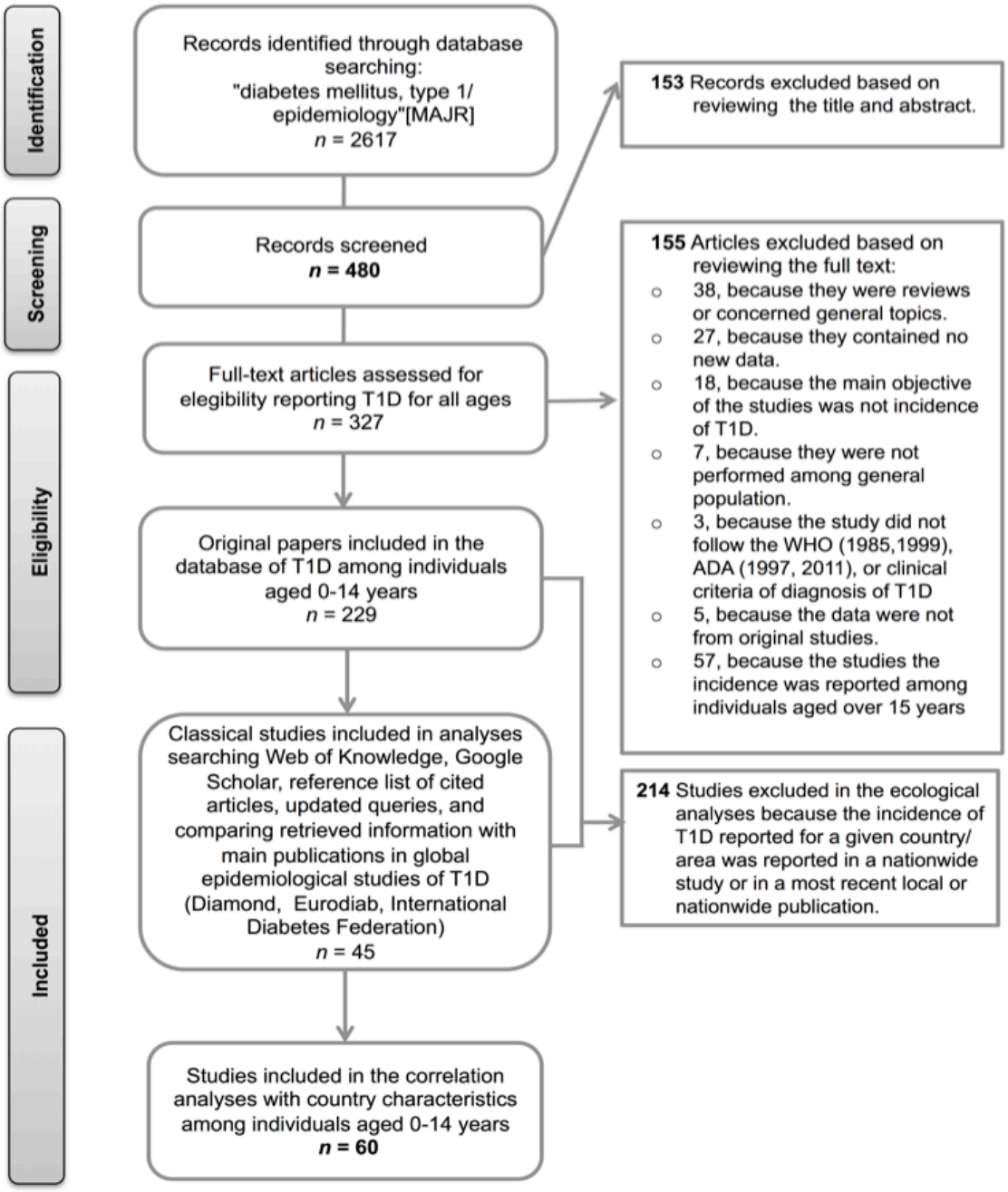
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	72
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	72
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	73
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	74 Protocol S1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	74, Figure S1, Table S1,
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	74, Figure S1, Table S1.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1, Figure S1,
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	74 - Protocol S1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	74 - Protocol S1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	74 - Protocol S1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the	Protocol S1

Section/topic	#	Checklist item	Reported on page #
		study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	74 - Protocol S1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	74 - Protocol S1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	73 - Protocol S1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	76, Figure S1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table S2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table S2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table S2, Database S1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	78
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	78
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	78
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	72

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

3.1.1.2 Flow diagram literature search for T1D incidences



SI Figure 16: Flow diagram literature search for T1D incidences

3.1.1.3 Publication list of the incidence of T1D by country and area

SI Table 10: Publication list of the incidence of T1D by country and area

Country, Area	Study period	Mean T1D Inc*	Inc. by area	Ascertainment %	Info. Source	Data collection	Author, Pub yr.	Ref.
Algeria								
Oran	1990_1999	**8.60**	**8.60**	NA	PBDR	P or H	Diamond, 2006	(318)
Argentina								
Cordoba	1991_1992	**7.55**	**7.00**	90.0	PBDR	P or H	Diamond, 2006	(318)
Avellaneda	1990_1996	**7.55**	**6.30**	94.0	PBDR	P or H	Diamond, 2006	(318)
Tierra del Fuego	1993_1996	**7.55**	**10.30**	100.0	PBDR	P or H	Diamond, 2006	(318)
Corrientes	1992_1999	**7.55**	**6.60**	95.0	PBDR	P or H	Diamond, 2006	(318)
Australia								
NW	2000_2006	**22.50**	**22.50**	97.1	PBDR	P	Catanzariti L, 2009	(58)
Austria								
NW	2004_2008	**17.50**	**17.50**	97.2	PBDR	P	Patterson C, 2012	(243)
Bahamas								
NW	2001_2002	**10.10**	**10.10**	NA	MBR	P	Peter S A, 2005	(246)
Barbados								
NW	1990_1993	**2.00**	**2.00**	NA	PBDR	P or H	Diamond, 2006	(318)
Belarus								
Gomel, Minsk	1997_2002	**5.60**	**5.60**	100.0	PBDR	NA	Zalutskaya A, 2004	(374)
Belgium								
Antwerp	2004_2008	**15.90**	**15.90**	94.9	PBDR	P	Patterson C, 2012	(243)
Bosnia and Herzegovina								
Tuzla Canton	1995_2004	**7.53**	**6.93**	100.0	PBDR	P	Tahirovic H, 2007	(312)
Republic of Srpska	1998_2010	**7.53**	**8.13**	100.0	PBDR	P	Radosevic B, 2013	(256)
Brazil								
Sao Paulo (Bauru)	1986_2006	**8.83**	**10.66**	94.7	PBDR	P	Negrato C, 2010	(221)
Rio Grande do Sul (Passo Fundo)	1996_1999	**8.83**	**7.00**	82.5	PBDR	P or H	Diamond, 2006	(318)
Bulgaria								
Eastern	1989_1994	**8.53**	**6.80**	99.9	PBDR	P	Eurodiab, 2000	(90)
Varna	1990_1999	**8.53**	**8.10**	100.0	PBDR	P or H	Diamond, 2006	(318)
Western	1990_1999	**8.53**	**10.70**	99.5	PBDR	P or H	Diamond, 2006	(318)
Canada								
Toronto [(c)]	1976_1978	**21.73**	**9.00**	97.2	PBDR	P, H	Ehrlich R M, 1982	(86)
Manitoba	1985_1993	**21.73**	**20.65**	95.0	PBDR	P	Blanchard J F, 1997	(36)
Prince Edward Island	1990_1993	**21.73**	**24.50**	100.0	PBDR	P or H	Diamond, 2006	(318)
Alberta (Edmonton)	1990_1996	**21.73**	**23.30**	85.5	PBDR	P or H	Diamond, 2006	(318)
Calgary	1990_1999	**21.73**	**20.60**	100.0	PBDR	P or H	Diamond, 2006	(318)
Québec	1989_2000	**21.73**	**15.34**	NA	PBDR	P	Legault L, 2006	(184)
Newfoundland and Labrador	1987_2010	**21.73**	**38.68**	NA	PBDR	P, H	Newhook L A, 2012	(225)
Chile								
IX Region	1980_1993	**3.84**	**1.37**	97.0	PBDR	P	Larenas G, 1996	(180)
Santiago of Chile (Communes of Metropolitan region)	2000_2005	**3.84**	**6.30**	100.0	PBDR	P	Torres-Avilés F, 2010	(323)
NW	1988_1994	**0.47**	**0.47**	93.0	PBDR	P, H	Yang Z, 2005	(371)
Colombia								
Bogota	1990_1990	**2.15**	**3.80**	97.0	PBDR	P or H	Diamond, 2006	(318)
Cali	1995_1999	**2.15**	**0.50**	NA	PBDR	P or H	Diamond, 2006	(318)
Croatia								
NW	1995_2003	**8.90**	**8.90**	98.5	PBDR	P	Stipanic G, 2012	(305)
Cuba								
NW	1990_1999	**2.30**	**2.30**	62.5	PBDR	P or H	Diamond, 2006	(318)
Cyprus								
NW	1990_2009	**12.34**	**12.34**	50.0	PBDR	NA	Skordis N, 2012	(294)
Czech Republic								
NW	2004_2008	**19.30**	**19.30**	97.4	PBDR	P	Patterson C, 2012	(243)
Dem. People's Republic of Korea								
Seoul	1990_1991	**1.10**	**1.10**	NA	PBDR	P or H	Diamond, 2006	(318)
Denmark								

Country, Area	Study period	Mean T1D Inc*	Inc. by area	Ascertainment %	Info. Source	Data collection	Author, Pub yr.	Ref.
NW	2004_2008	**25.10**	**25.10**	99.2	PBDR	P	Patterson C, 2012	(243)
Dominican Republic								
NW	1995_1999	**0.50**	**0.50**	53.0	PBDR	P or H	Diamond, 2006	(318)
Egypt								
Alexandria, Damanhour	1992_1992	**8.00**	**8.00**	NA	OPD	NA	Arab M, 1992	(18)
Estonia								
NW	1983_2006	**13.09**	**13.09**	98.0	PBDR	P, H	Teeaar T, 2010	(316)
Ethiopia								
Gondar	1995_2008	**0.33**	**0.33**	NA	MBR	P	Alemu S, 2009	(12)
Jimma	2002_2008	**0.33**	**0.33**	NA	MBR	P	Alemu S, 2009	(12)
Finland								
NW	2006_2011	**62.42**	**62.42**	NS	OPD	NA	Harjutsalo V, 2013	(128)
France								
Franche-Comté	1980_1998	**9.24**	**7.01**	80.6	PBDR	H	Mauny F, 2005	(208)
Aquitanie, Lorraine, Normandia Basse, Normandia Haut	1990_1994	**9.24**	**8.50**	97.0	PBDR	P or H	Diamond, 2006	(318)
Aquitaine	1998_2004	**9.24**	**12.20**	NA	OPD	NA	Barat P, 2008	(28)
Georgia								
NW	1998_1999	**4.60**	**4.60**	NA	OPD	NA	Amirkhanashvili, 2000	(17)
Germany								
Düsselforf	1999_2003	**20.98**	**18.30**	95.4	PBDR	P	Patterson C, 2009	(242)
Baden-Württemberg	2004_2007	**20.98**	**21.80**	100.0	PBDR	P	Patterson C, 2012	(243)
North Rhine-Westphalia	2004_2008	**20.98**	**23.70**	98.6	PBDR	P	Patterson C, 2012	(243)
Saxony	2004_2008	**20.98**	**20.10**	93.6	PBDR	P	Patterson C, 2012	(243)
Greece								
NW	1992_1992	**6.03**	**6.03**	NA	PBDR	P	Dacou-Voutetakis C, 1995	(70)
Hungary								
18 of 19 countries (All, less Budapest)	2004_2008	**18.30**	**18.30**	98.7	PBDR	P	Patterson C, 2012	(243)
Iceland								
NW	1989_1994	**13.50**	**13.50**	100.0	PBDR	P	Eurodiab, 2000	(90)
India								
Madras	1991_1994	**11.00**	**11.00**	90.0	PBDR	H	Ramachandran A, 1996	(258)
Iran (Islamic Republic of)								
Fars	1991_1996	**3.68**	**3.68**	100.0	PBDR	P	Pishdad G R, 2005	(248)
Ireland								
NW	1997_1997	**16.37**	**16.37**	90.6	PBDR	P	Roche E F, 2002	(267)
Israel								
NW: Population: Arabs	1997_2003	**9.17**	**7.59**	NA	PBDR	P	Koton S, 2007	(171)
NW: Population: Jews and others	1997_2003	**9.17**	**10.76**	NA	PBDR	P	Koton S, 2007	(171)
Italy								
NW_39.7% population	1990_2003	**12.55**	**12.55**	NA	PBDR	P	Bruno G, 2010	(43)
Japan								
NW	1998_2001	**2.35**	**2.35**	NA	PBDR	P	Kawasaki E, 2006	(163)
Jordan								
NW	1992_1996	**3.33**	**3.33**	95.0	NS	P, H	Ajlouni K, 1999	(9)
Kuwait								
NW	1992_1999	**22.30**	**22.30**	87.5	PBDR	P or H	Diamond, 2006	(318)
Latvia								
NW	1990_1999	**7.40**	**7.40**	NA	PBDR	P or H	Diamond, 2006	(318)
Libyan Arab Jamahiriya								
Benghazi	1991_1999	**9.00**	**9.00**	NA	PBDR	P or H	Diamond, 2006	(318)
Lithuania								
NW	2004_2008	**14.20**	**14.20**	NA	PBDR	P	Patterson C, 2012	(243)
Luxembourg								
NW	2004_2008	**19.00**	**19.00**	100.0	PBDR	P	Patterson C, 2012	(243)
Malta								
NW	2006_2010	**23.87**	**23.87**	100.0	PBDR	P	Formosa N, 2012	(100)
Mauritius								

Country, Area	Study period	Mean T1D Inc*	Inc. by area	Ascertainment %	Info. Source	Data collection	Author, Pub yr.	Ref.
NW	1990_1994	**1.30**	**1.30**	67.5	PBDR	P or H	Diamond, 2006	(318)
Mexico								
NW [d]	2000_2010	**5.93**	**5.93**	NA	PBDR	H	Gomez-Diaz RA, 2012	(114)
Montenegro								
NW	2004_2008	**17.50**	**17.50**	100.0	PBDR	P	Patterson C, 2012	(243)
Netherlands								
NW	1996_1999	**18.80**	**18.80**	NA	OPD	NA	Van Wouwe J P, 2002	(340)
New Zealand								
NW	1999_2000	**18.00**	**18.00**	95.0	PBDR	NA	Campbell-Stokes PL, 2005	(51)
Norway								
NW	2004_2008	**32.80**	**32.80**	92.0	PBDR	P	Patterson C, 2012	(243)
Oman								
NW	1993_1995	**2.59**	**2.59**	96.0	PBDR	P	Soliman A T, 1996	(297)
Pakistan								
Karachi	1990_1999	**0.50**	**0.50**	51.0	PBDR	P or H	Diamond, 2006	(318)
Papua New Guinea								
NW	1996_2000	**0.08**	**0.08**	NA	MBR	P	Ogle, 2001	(230)
Paraguay								
NW	1990_1999	**0.90**	**0.90**	NA	PBDR	P or H	Diamond, 2006	(318)
Peru								
Lima	1990_1994	**0.50**	**0.50**	67.5	PBDR	P or H	Diamond, 2006	(318)
Poland								
NW	1989_2004	**11.23**	**11.23**	NA	PBDR	P	Jarosz-Chobot P, 2011	(148)
Portugal								
Algarve	1990_1994	**13.10**	**14.60**	87.0	PBDR	P or H	Diamond, 2006	(318)
Portalegre	1990_1994	**13.10**	**21.30**	93.0	PBDR	P or H	Diamond, 2006	(318)
Coimbra	1990_1999	**13.10**	**9.60**	100.0	PBDR	P or H	Diamond, 2006	(318)
Madeira Island	1990_1999	**13.10**	**6.90**	100.0	PBDR	P or H	Diamond, 2006	(318)
Qatar								
NW	1992_1996	**11.40**	**11.40**	NA	OPD	NA	Al-Zyoud M, 1997	(10)
Romania								
NW	2000_2004	**5.40**	**5.40**	NA	OPD	NA	Serban V, 2005	(285)
Russian Federation								
Novosibirsk	1990_1999	**9.48**	**6.90**	93.5	PBDR	P or H	Diamond, 2006	(318)
Moscow	1996_2005	**9.48**	**12.07**	94.0	PBDR	P	Pronina E A, 2008	(251)
Saudi Arabia								
Eastern Province	1986_1997	**21.59**	**12.30**	100.0	PBDR	NA	Kulaylat N A, 2000	(174)
Al-Madinah (North West) [a]	2004_2009	**21.59**	**30.88**	NA	PBDR	P	Habeb A M, 2011	(125)
Serbia								
Belgrade [e]	2000_2004	**12.90**	**12.90**	NA	OPD	NA	Vlajinac H D, 1995	(347)
Singapore								
NW [a]	1992_1994	**2.42**	**2.42**	92.2	PBDR	P	Lee WW, 1998	(183)
Slovakia								
NW	1999_2003	**13.60**	**13.60**	100.0	PBDR	P	Patterson C, 2009	(242)
Slovenia								
NW	1998_2010	**13.83**	**13.83**	100.0	PBDR	P	Radosevic B, 2013	(256)
Spain								
Madrid	1985_1988	**15.75**	**10.60**	90.0	PBDR	H	Serrano Rios M, 1990	(287)
Caceres [b]	1988_1999	**15.75**	**16.67**	99.2	PBDR	H	Lora-Gomez R E, 2005	(198)
Badajoz	1992_1996	**15.75**	**17.23**	95.0	PBDR	P	Morales-Perez F M, 2000	(218)
Navarre	2003_2004	**15.75**	**22.17**	99.6	PBDR	P	Bahíllo M, 2007	
Catalonia	2004_2008	**15.75**	**12.10**	97.6	PBDR	P	Patterson C, 2012	(243)
Sudan								
Gezira	1990_1990	**7.68**	**5.00**	100.0	PBDR	P or H	Diamond, 2006	(318)
Khartoum	1991_1995	**7.68**	**10.10**	97.0	PBDR	NA	Elamin et al, 1997	(87)
Sweden								
NW	1983_2007	**32.28**	**32.28**	98.0	PBDR	P	Dahlquist G G, 2011	(74)
Switzerland								
NW	2004_2008	**13.10**	**13.10**	91.3	PBDR	P	Patterson C, 2012	(243)
TFYR Macedonia								

Country, Area	Study period	Mean T1D Inc*	Inc. by area	Ascertainment %	Info. Source	Data collection	Author, Pub yr.	Ref.
NW	2004_2008	**5.80**	**5.80**	100.0	PBDR	P	Patterson C, 2012	(243)
Thailand								
Northeastern	1996_2005	**0.58**	**0.58**	NA	MBR	H	Panamonta O, 2011	(238)
Tunisia								
Beja, Monastir, Gafsa	1990_1994	**7.40**	**6.69**	96.0	PBDR	P	Ben Khalifa F, 1997	(32)
Kairoan	1991_1993	**7.40**	**7.60**	NA	PBDR	P or H	Diamond, 2006	(318)
Beja	1990_1999	**7.40**	**7.70**	NA	PBDR	P or H	Diamond, 2006	(318)
Gafsa	1990_1999	**7.40**	**8.50**	NA	PBDR	P or H	Diamond, 2006	(318)
Monastir	1990_1999	**7.40**	**5.80**	NA	PBDR	P or H	Diamond, 2006	(318)
Ukraine								
NW	1985_1992	**8.10**	**8.10**	NA	OPD	NA	Timchenko O I, 1996	(321)
United Kingdom								
NW	1991_2008	**19.32**	**19.32**	NA	PBDR	P	Imkampe AK, 2011	(141)
United Republic of Tanzania								
Dar es Salaam	1982_1991	**0.92**	**0.92**	NA	MBR	P	Swai A B, 1993	(311)
United States of America								
Seven areas (Population: African American Young)	2002_2005	**14.01**	**17.53**	NA	PBDR	P	Bell R, 2009	(31)
Seven areas (Population: Asian-Pacific Islander Young)	2002_2005	**14.01**	**7.30**	NA	PBDR	P	Bell R, 2009	(31)
Seven areas (Population: Hispanic Young)	2002_2005	**14.01**	**15.60**	NA	PBDR	P	Bell R, 2009	(31)
Seven areas (Population: Navajo Young)	2002_2005	**14.01**	**2.13**	NA	PBDR	P	Bell R, 2009	(31)
Seven areas (Population: Non-Hispanic Withe Young)	2002_2005	**14.01**	**27.47**	NA	PBDR	P	Bell R, 2009	(31)
Uruguay								
Montevideo	1992_1992	**8.30**	**8.30**	97.0	PBDR	P or H	Diamond, 2006	(318)
Uzbekistan								
NW	2000_2000	**1.20**	**1.20**	NA	OPD	NA	Rakhimova G G N, 2002	(257)
Venezuela (Bolivarian Republic of)								
Caracas	1990_1994	**0.10**	**0.10**	NA	PBDR	P or H	Diamond, 2006	(318)

Table showing the list of publications reporting T1D incidence used in the analyses (*). Information source: (PBDR) population-based data register, (MBR) medical-based record, (OPD) other population denominators, (NS) non-specified. % Ascertainment: percentage of completeness between primary and secondary sources of registers. Data collection process reported in the article: (P) prospective - incident cases collected prospectively -, (H) historical -incident cases collected retrospectively -. First author and year of publication. Number of reference. NW: Nationwide study. Note: the age range for the reported incidence was 0-14 years, except in the following cases: (a) 0-12, (b) 0-13, (c) 0-18, (d) 0-19, (e) updated International Diabetes Federation (IDF) 2013.

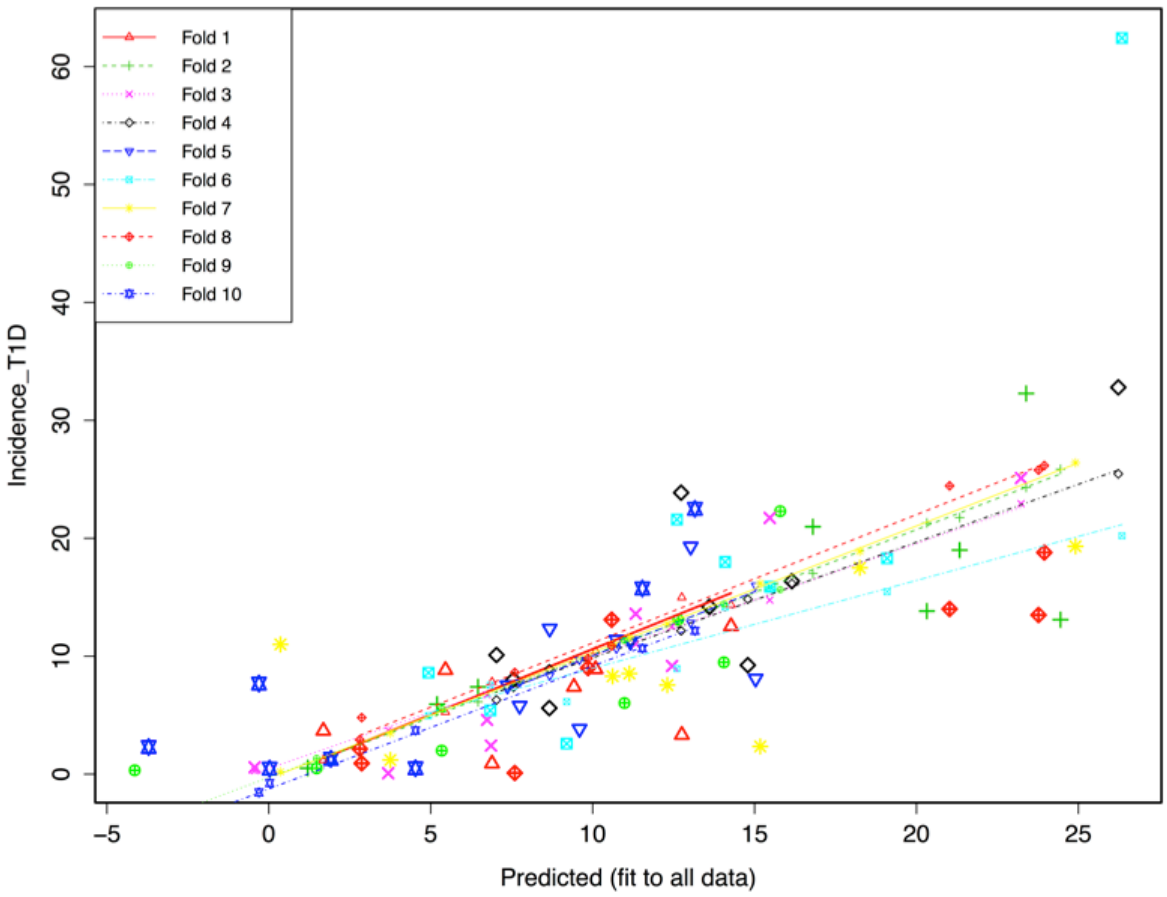
3.1.1.4 Details of the models by domains and final summary model

Code	Coefficients	Estimate	CI 2.5%	CI 97.5%	Std. Error	t-value	*p*-value
	(Intercept)	18.113	13.071	23.155	2.530	7.160	0.000
CE_10	CO2 emissions (metric tons per capita)	0.462	0.189	0.735	0.137	3.371	0.001
CE_16	Outdoor air pollution (Annual PM10 [μg/m3])	-0.008	-0.060	0.045	0.026	-0.288	0.774
CE_18	UV radiation (J/mt2, 2004)	-0.003	-0.005	-0.002	0.001	-4.427	0.000
	(Intercept)	-12.909	-79.608	11.928	6.690	-1.930	0.057
DD_19	Adolescent fertility rate (births per 1,000 women ages 15-19)	-0.121	-0.199	-0.019	0.043	-2.776	0.007
DD_21	Fertility rate, total (births per woman)	4.071	0.956	8.011	1.716	2.373	0.020
DD_27	Population ages 65 and above (% of total)	0.744	0.181	1.125	0.217	3.430	0.001
DD_33	Urban population (% of total population)	0.147	-0.032	0.237	0.049	2.986	0.004
	(Intercept)	-1.488	-11.044	8.068	4.786	-0.311	0.757
ED_39	Energy use (kg of oil equivalent per capita)	0.001	0.000	0.001	0.000	1.761	0.083
ED_41	Mobile cellular subscriptions (per 100 people)	0.105	0.039	0.172	0.033	3.151	0.002
ED_36	Adjusted savings: education expenditure (% of GNI)	1.131	0.052	2.209	0.540	2.092	0.040
ED_37	Improved sanitation facilities (% of population with access)	-0.097	-0.225	0.031	0.064	-1.506	0.137
EH_45	Health expenditure per capita, (constant 2005 international $)	0.002	0.001	0.003	0.001	2.999	0.004
EC_33	GDP growth (annual %)	-0.473	-1.028	0.083	0.278	-1.700	0.094
	(Intercept)	-105.151	-163.500	-46.802	29.216	-3.599	0.001
HD_71	Chronic respiratory diseases, deaths. (a)(b) Male	0.074	-0.018	0.166	0.046	1.615	0.111
HI_59	Hepatitis B (HepB3) immunization (c)	-0.118	-0.174	-0.062	0.028	-4.208	0.000
HR_56	Total alcohol in liters of pure alcohol >15yr.	-0.194	-0.640	0.251	0.223	-0.872	0.387
HR_47	Mean BMI (kg/m2) (a) Male >20 yr.	3.319	1.411	5.228	0.956	3.474	0.001
HR_51	Mean Total Cholesterol in mmol/l (a) Male >25yr.	8.205	-0.026	16.437	4.122	1.991	0.051
HR_54	Preterm birth rate (per 100 live births)	-0.604	-1.489	0.281	0.443	-1.363	0.178
HR_55	Prevalence of undernourishment (% of population)	0.189	-0.168	0.545	0.178	1.058	0.294
	(Intercept)	-25.240	-55.934	5.460	15.390	-1.640	0.106
CE_18	UV radiation (J/mt2, 2004)	-0.002	-0.003	0.000	0.001	-1.952	0.055
DD_21	Fertility rate, total (births per woman)	2.181	-0.430	4.793	1.309	1.666	0.100
ED_41	Mobile cellular subscriptions (per 100 people)	0.066	0.012	0.121	0.027	2.428	0.018
EH_45	Health expenditure per capita (constant 2005 international $)	0.001	0.000	0.003	0.001	2.401	0.019
HI_59	Hepatitis B (HepB3) immunization (c)	-0.085	-0.139	-0.032	0.027	-3.187	0.002
HR_47	Mean BMI (kg/m2) (a) Male >20 yr.	1.263	0.045	2.480	0.611	2.068	0.042

CI, Confidence Intervals. (a) Age-standardized estimate; (b) per 100,000 individuals; (c) Coverage among 1-year-olds (%).

SI Table 11: Models by domains and final summary model

3.1.1.5 Visualisation of 10-Fold Cross-Validation 10 fold-Cross validation of the final model



Small symbols show cross-validation predicted values of T1D incidence. Raw R^2 = 0.55, 10-Fold cross-validated R^2 =0.409

SI Figure 17: 10-Fold Cross-Validation

3.2 Additional analysis of the article: Covariation of the incidence of T1D with country characteristics available in public databases

3.2.1 Correlations between T1D reported in 80 countries vs. 77 global indicators

Table 12 includes all the information presented in **Figure 1** of the paper published in Plos One (81) shown in **chapter 3**. In addition the number of countries with available information, the summary measures for each variable, and the reference are presented. The tidy database is available on **Appendix A: Database III**. See **Appendix D** for the correlation matrix between incidence of T1D and independent variables by domains and **Appendix E** for the variable selection of the models.

Table 12: Spearman Correlation: Type 1 Incidence reported in 80 countries vs. 77 global variables

Category	Code	Variable	Countries with available inf. on T1D for each variable (n of 80)	Spearman Correlation: Estimate/ p-value		Mean	SD	Ref	
Climate and environment	**Agriculture**								
	CA_1	Agricultural land (% of land area)	80	0.07	5.29E-01	37.41	21.00	WB	
	CA_2	Arable land (% of land area)	80	0.10	3.96E-01	17.03	14.28	WB	
	CA_3	Cereal production (metric tons)	79	-0.03	8.02E-01	27600000	80200000	WB	
	CA_4	Cereal yield (kg per hectare)	78	0.33	2.77E-03	4419.00	2079.00	WB	*
	CA_5	Fertilizer consumption (kilograms per hectare of arable land)	76	0.02	8.63E-01	233.10	487.80	WB	
	CA_6	Forest area (% of land area)	80	-0.06	5.85E-01	28.53	19.39	WB	
	CA_7	Permanent cropland (% of land area)	79	-0.36	1.08E-03	1.83	2.79	WB	*
	Environment								
	CE_8	Annual precipitation by country: values in millimeters. (Mean 1961-1999)	77	-0.16	1.71E-01	845.60	582.50	WB-C	*
	CE_9	Annual temperatures by country: values in degrees Celsius. (Mean 1961-1999)	77	-0.44	**5.45E-05**	13.76	8.48	WB-C	*
	CE_10	CO_2 emissions (metric tons per capita)	80	0.61	**1.38E-09**	7.16	6.57	WB	*
	CE_11	Latitude	80	0.56	**5.31E-08**	29.88	26.30	GM	*
	CE_12	Longitude	80	-0.14	2.15E-01	15.08	59.45	GM	
	CE_13	Methane emissions (kt of CO_2 equivalent)	75	-0.18	1.32E-01	81100.00	219000.00	WB	*
	CE_14	Nitrous oxide emissions (thousand metric tons of CO2 equivalent)	75	-0.15	1.94E-01	30500.00	79200.00	WB	*
	CE_15	Nitrous oxide emissions in industrial and energy processes (% of total nitrous oxide emissions)	75	0.32	5.69E-03	17.68	12.29	WB	*
	CE_16	Outdoor air pollution (Annual PM10 [ug/m^3])	77	-0.42	**1.38E-04**	52.07	39.62	WHO	*
	CE_17	PM10, country level (ug/m^3)	76	-0.32	5.25E-03	32.57	26.88	WB	*
	CE_18	UV radiation (J/mt2, 2004)	80	-0.63	**6.68E-10**	3153	1395	WHO	*
Demography	**Demography**								
	DD_19	Adolescent fertility rate (births per 1,000 women ages 15-19)	80	-0.47	**1.06E-05**	26.89	25.70	WB	*
	DD_20	Female mean age of childbearing (years)	80	0.44	**3.62E-05**	28.88	1.59	UN	*
	DD_21	Fertility rate, total (births per woman)	80	-0.25	2.65E-02	1.99	0.78	WB	*
	DD_22	Life expectancy at birth, female (years)	80	0.58	**1.94E-08**	78.60	5.62	WB	*

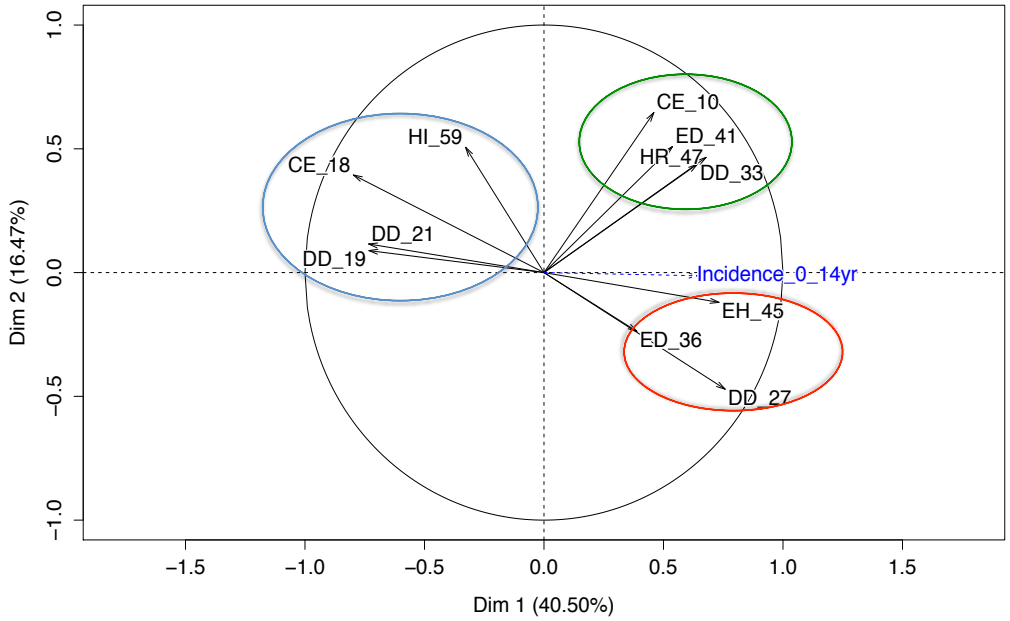
	DD_23	Life expectancy at birth, male (years)	80	0.60	**3.53E-09**	73.17	5.65	WB	*
	DD_24	Life expectancy at birth, total (years)	80	0.60	**2.92E-09**	75.82	5.52	WB	*
	DD_25	Population ages 0-14 (% of total)	80	-0.42	**1.10E-04**	21.17	7.58	WB	*
	DD_26	Population 15-64 years of age (% of total)	80	0.07	5.29E-01	67.12	4.60	WB	
	DD_27	Population ages 65 and above (% of total)	80	0.51	**1.52E-06**	11.72	5.74	WB	*
	DD_28	Population growth (annual %)	80	-0.20	8.05E-02	0.98	1.51	WB	*
	DD_29	Population, female (% of total)	80	0.14	2.15E-01	50.01	3.87	WB	
	DD_30	Probability of dying between birth and the age of 40 years (both sexes combined) (deaths under age 40 per 1,000 live births)	80	-0.65	**9.91E-11**	51.96	47.70	UN	*
	DD_31	Rural population (% of total population)	80	-0.41	**1.46E-04**	30.14	19.79	WB	*
	DD_32	Total population 0-14 years (both sexes combined)	80	-0.32	4.16E-03	15200.00	49900.00	UN	*
	DD_33	Urban population (% of total population)	80	0.41	**1.45E-04**	69.86	19.79	WB	*
Economic factors		**Country Economy**							
	EC_33	GDP growth (annual %)	79	-0.47	**1.07E-05**	3.42	3.87	WB	*
	EC_34	GDP per capita (constant 2005 US$)	79	0.72	**9.05E-14**	17800.00	17900.00	WB	*
	EC_35	GDP per capita, PPP (constant 2005 international $)	78	0.71	**5.24E-13**	20100.00	14500.00	WB	*
		Development							
	ED_36	Adjusted savings: education expenditure (% of GNI)	75	0.45	**5.56E-05**	4.75	1.91	WB	*
	ED_37	Improved sanitation facilities (% of population with access)	78	0.67	**2.08E-11**	88.06	21.23	WB	*
	ED_38	Improved water source (% of population with access)	79	0.67	**1.60E-11**	93.68	12.83	WB	*
	ED_39	Energy use (kg of oil equivalent per capita)	79	0.69	**1.22E-12**	3303.00	3045.00	WB	*
	ED_40	Energy use (kg of oil equivalent) per $1,000 GDP (constant 2005 PPP)	77	-0.14	2.13E-01	183.60	113.80	WB	
	ED_41	Mobile cellular subscriptions (per 100 persons)	80	0.44	**4.93E-05**	113.30	35.84	WB	*
	ED_42	Population using solid fuels (total population: urban + rural)	80	-0.50	**2.68E-06**	11.32	22.71	WHO	*
		Health Economy							
	EH_43	External resources for health (% of total expenditure on health)	79	-0.62	**7.62E-10**	2.06	7.28	WB	*
	EH_44	Health expenditure per capita (current US$)	79	0.73	**1.62E-14**	1942.00	2198.00	WB	*
	EH_45	Health expenditure per capita, PPP (constant 2005 international $)	79	0.75	**2.32E-15**	1924.00	1721.00	WB	*
Health conditions		**Risk Factors for Non-Communicable Diseases**							
	HR_46	Mean BMI (kg/m^2) (age-standardized estimate) Female +20	80	0.11	3.32E-01	26.19	2.003	WHO	
	HR_47	Mean BMI (kg/m^2) (age-standardized estimate) Male +20	80	0.63	**2.58E-10**	26.2	1.728	WHO	*
	HR_48	Mean systolic blood pressure in mm Hg (age-standardized estimate) Female +25	80	-0.18	1.19E-01	124.9	4.037	WHO	*
	HR_49	Mean systolic blood pressure in mm Hg (age-standardized estimate) Male +25	80	0.19	8.41E-02	131	3.671	WHO	*
	HR_50	Mean total Cholesterol in mmol/l (age-standardized estimate) Female+25	80	0.62	**1.25E-09**	5.018	0.2841	WHO	*
	HR_51	Mean total Cholesterol in mmol/l (age-standardized estimate) Male +25	80	0.70	**5.18E-13**	4.95	0.3504	WHO	*
	HR_52	Obesity: % of defined population with a BMI ≥ 30 kg/m^2 (age-standardized estimate) Both Sexes +20	80	0.33	3.06E-03	21.18	8.347	WHO	*
	HR_53	Overweight: % population with a BMI ≥ 25 kg/m2 (age-standardized estimate) Both Sexes +20	80	0.37	7.49E-04	52.52	14.03	WHO	*
	HR_54	Preterm birth rate (per 100 live births)	79	-0.27	1.44E-02	8.46	2.46	WHO	*
	HR_55	Prevalence of undernourishment (% of population)	75	-0.59	**2.41E-08**	8.25	8.31	WB	*
	HR_56	Total alcohol in liters of pure alcohol per capita consumption, estimation for 2008, both sexes +15	79	0.44	**4.38E-05**	8.55	5.09	WHO	*
		Infectious Diseases and Immunization							
	HI_57	Diphtheria tetanus toxoid and pertussis (DTP3) immunization coverage among 1-year-olds (%)	80	0.24	3.00E-02	93.51	7.43	WHO	*
	HI_58	Haemophilus influenzae type B vaccine (Hib3) immunization coverage among 1-year-olds (%)	80	0.48	**5.20E-06**	81.96	29.99	WHO	*
	HI_59	Hepatitis B (HepB3) immunization coverage among 1-year-olds (%)	80	-0.18	1.07E-01	77.83	33.97	WHO	*
	HI_60	Incidence of tuberculosis (per 100,000 persons)	80	-0.61	**1.91E-09**	49.38	72.24	WB	*

	HI_61	Measles - number of reported cases (standardized using population 0-14 years, per 100,000 persons)	80	0.05	6.91E-01	1753.85	12200.35	WHO	
	HI_62	Measles (MCV) immunization coverage among 1-year-olds (%)	80	0.02	8.28E-01	93.18	6.91	WHO	
	HI_63	Measles immunization coverage among children ages 12-23 months (%)	79	-0.03	7.70E-01	92.75	8.35	WB	
	HI_64	Pertussis - number of reported cases (standardized using population 0-14 years, per 100,000 persons)	76	0.08	4.91E-01	2112.76	16092.82	WHO	
	HI_65	Polio (Pol3) immunization coverage among 1-year-olds (%)	80	0.23	4.46E-02	93.58	7.37	WHO	*
	Deaths from Non-Communicable Diseases								
	HD_66	Cancers, deaths per 100,000 (age-standardized estimate) Female	80	0.22	4.60E-02	94.44	16.25	WHO	*
	HD_67	Cancers, deaths per 100,000 (age-standardized estimate) Male	80	0.28	1.26E-02	146.00	43.67	WHO	*
	HD_68	Cardiovascular diseases and diabetes, deaths per 100,000 (age-standardized estimate) Female	80	-0.50	**2.77E-06**	229.60	125.00	WHO	*
	HD_69	Cardiovascular diseases and diabetes, deaths per 100,000 (age-standardized estimate) Male	80	-0.39	**3.10E-04**	325.60	170.20	WHO	*
	HD_70	Chronic respiratory diseases, deaths per 100,000 (age-standardized estimate) Female	80	-0.34	1.99E-03	22.79	20.95	WHO	*
	HD_71	Chronic respiratory diseases, deaths per 100,000 (age-standardized estimate) Male	80	-0.37	7.89E-04	41.85	30.49	WHO	*
	HD_72	NCD deaths under age 60 (% of all non communicable diseases deaths) Both sexes	80	-0.58	**1.31E-08**	21.06	10.76	WHO	*
	HD_73	Probability of dying between exact ages 30 and 70 from any cardiovascular disease, cancer, diabetes, or chronic respiratory disease (%)	80	-0.44	**3.98E-05**	18.58	6.52	WHO	*
	Infant and Maternal Mortality Rates								
	HM_75	Infant mortality rate (probability of dying between birth and age 1 per 1000 live births) Both sexes	80	-0.66	**2.01E-11**	11.44	12.84	WHO	*
	HM_76	Maternal mortality ratio (modeled estimate, per 100,000 live births)	80	-0.62	**1.12E-09**	55.82	109.00	WB	*
	HM_77	Mortality rate, under-5 (probability of dying by age 5 per 1000 live births)	80	-0.67	**7.57E-12**	14.15	17.12	WB	*

Note: in gray correlations reporting a p-value ≤ 0.000649 (Using Bonferroni correction [0.05/n variables]), (*) p-value ≤0.2. References: (WB) World Bank (2012) Indicators. Available from http://data.worldbank.org/indicator, accessed 11-08 2012; (WB-C) World Bank (2012) Climate Change Knowledge Portal: Historical Data. Available from http://data.worldbank.org/developers/climate-data-api, accessed 11-08 2012; (WHO) WHO (2012) Global Health Observatory Data Repository. Available from http://apps.who.int/gho/data/?vid=2472, accessed 11-08 2012; (UN) United Nations, Department of Economic and Social Affairs (2011) World Population Prospects, the 2010 Revision. Available from http://esa.un.org/wpp/Excel-Data/population.htm, accessed May 31 2012; (GM) Google Maps API Geographical coordinates 2013. Available from **http://universimmedia.pagesperso-orange.fr/geo/loc.htm**. See also Figure 2 in the Plos One paper.

3.2.2 Principal component analyses of the variables included in the final model

Principal Component Analyses (PCA) were performed to evaluate the final full model of the article presented in **chapter 3** (81) before the backward selection presented in **AP Table 35.** The principal components using the set of all significant variables (at p-value ≤0.05) after applying MLM for each domain are presented in **SI Figure 18**. Related with the incidence of T1D three clusters were identified: associated with the geographic position (circle in blue), with urban conditions (circle in green), and with develop and wealthy (circle in red). The variable that best summarize negative correlations was UV radiation (CE_18) in the geographic cluster, related with *lack of sun exposition and vitamin D3 hypothesis* (338, 367); for positive correlations, the percentage of urban population (DD_33) and the BMI in males (HR_47), in the urban conditions cluster were noted, related with the "*accelerator hypothesis*" (361), the "*overload hypothesis"* (71), and the presence of *endocrine disruptors* (136, 137), and population aged over 65 years (DD_27) in the developing and wealthy cluster. See **Appendix D** for the correlation matrix between incidence of T1D and independent variables by domains, and **Appendix E** for the variable selection of the models.



CE_10: CO_2 emissions (metric tons per capita); **CE_18:** UV radiation (J/mt2, 2004); **DD_19:** Adolescent fertility rate (births per 1,000 women aged 15-19); **DD_21:** Fertility rate, total (births per woman); **DD_27:** Population aged 65 and above (% of total); **DD_33:** Urban population (% of total population); **ED_41:** Mobile cellular subscriptions (per 100 persons); **ED_36:** Adjusted savings: education expenditure (% of GNI); **EH_45:** Health expenditure per capita, PPP (constant 2005 international $); **HI_59:** Hepatitis B (HepB3) immunization coverage among 1-year-olds (%); **HR_47:** Mean BMI (kg/m2) (age-standardized estimate) Male >20 years of age.

SI Figure 18: Variables Factor Map (PCA): significant variables for all domains

3.2.3 Published Abstract: Incidence mondiale du diabète de type 1: revue systématique et corrélation avec des bases de données publiques

A preliminary version of the analyses presented in the paper: Covariation of the incidence of T1D with country characteristics available in public databases (81) was presented during the VI International Congress of Epidemiology, and published in French in the Revue d'Epidémiologie et de Santé Publique (80).

P5-4

Incidence mondiale de diabète de type 1 : revue systématique et corrélation avec des bases de données publiques

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Introduction L'incidence du diabète de type 1 (DT1) varie considérablement selon les pays au niveau mondial ; on observe une augmentation significative de cette incidence au cours des dernières décennies.

Méthodes Une revue systématique de la littérature a été effectuée. L'incidence du DT1 chez les enfants âgés de 0 à 14 ans a été corrélée avec les données publiques disponibles au niveau mondial dans les domaines de l'environnement, la démographie, l'économie et la santé. Les recommandations de PRISMA ont été respectées.

Résultats Au total, 527 ensembles de données concernant l'incidence du DT1 ont été obtenus à partir de 265 publications originales (1975–2013). Les articles contenaient des informations sur 90 territoires, 69 % de la population globale des enfants de 0–14 ans. L'incidence varie de 0,08/100 000 en Papouasie-Nouvelle-Guinée à 62,42/100 000 en Finlande. En effectuant une régression multiple, on met en évidence une corrélation positive entre l'incidence du DT1 et l'indice de masse corporelle ainsi que deux variables liées aux revenus du pays (la consommation d'énergie électrique et le nombre d'abonnés à la téléphonie mobile). Des corrélations négatives ont été trouvés avec : le rayonnement UV, les émissions de CO_2, la consommation d'alcool, et la vaccination contre l'hépatite B (toutes les valeurs de $p < 0{,}05$).

Discussion Les incidences de DT1 sont plus hautes dans les pays à revenu élevé. Les variations entre les pays sont encore inexpliquées. La disponibilité d'informations sur l'incidence et l'accès aux bases de données publiques, permettra de faire plus d'analyses systématiques d'association et ainsi d'identifier les facteurs associés à la maladie.

Mots clés Épidémiologie ; Incidence ; Revue systématique ; Diabète de type 1

Déclaration d'intérêts Les auteurs n'ont pas transmis de déclaration de conflits d'intérêts.

http://dx.doi.org/10.1016/j.respe.2014.06.175

3.3 Additional analyses of the epidemiology of T1D among children

3.3.1 Comparison of countries with and without information using 95 indicators

Eighty countries with information on incidence of T1D and 116 without information were compared. For these analyses, the criteria of variable selection did not consider the exclusion of variables when information was unavailable in "less than 5% of the countries". This yielded 95 independent variables in total, 18 more indicators than presented above, see **SI Table 13.**

When compared to the countries with T1D information, those for which such information was lacking had: a four-fold higher under-five mortality rate (p=3.40×10^{-18}), a two-fold higher premature mortality rate (p=6.28×10^{-19}), 1.5 more deaths labeled as "cardiovascular diseases and diabetes" (p=4.78×10^{-11}); their fraction of urban population was 50% lower (p=1.70×10^{-15}), and their health expenditures per capita (319) were 8.7 fold lower (p=3.25×10^{-15}).

SI Table 13: Comparison of 95 indicators in countries with and without information of T1D

Category	Variable	Total countries with inf.	Countries with available information on T1D			Countries without available information on T1D			Mann–Whitney U test	Ref
			Mean	SD	*n*	Mean	SD	*n*		
Climate and Environment	**Agriculture**									
	Agricultural Land area in Km^2. (Mean 2000-2008)	194	39	20	74	40	23	111	8.57E-01	UN
	Agricultural land: % of land area. (Mean 2000-2009)	185	438100	1012000	74	139300	268700	120	3.08E-02	WB
	Alternative and nuclear energy: % of total energy used. (Mean 2000-2010)	134	12	18	71	6	11	63	1.91E-02	WB
	Arable Land area in Km^2. (Mean 2000-2008)	194	138800	335400	74	29800	58200	120	4.61E-04	WB
	Fertilizer consumption: kilograms (Kg) per hectare of arable land. (Mean 2002-2009)	153	269	470	70	166	489	83	5.50E-07	UN
	Forest Area in Km^2. (Mean 2010)	192	406900	1226000	73	83380	190000	119	4.88E-02	WB
	Land under Permanent Crops in km^2. (Mean 2008)	188	10660	24230	73	5941	16760	115	3.38E-01	UN
	Use of Fertilizers per 1000 hectares of Agricultural Land Area: Nitrogen. (Mean 2002-2008)	143	193	1201	65	37	114	78	4.62E-07	WB
	Use of Fertilizers per 1000 hectares of Agricultural Land Area: Phosphate. (Mean 2002-2008)	142	19	25	64	6	11	78	2.80E-09	UN
	Use of Fertilizers per 1000 hectares of Agricultural Land Area: Potash. (Mean 2002-2008)	142	30	104	65	6	15	77	6.86E-08	UN
	Climate									
	Annual precipitation by country: values in millimeters (mm). (Mean 1961-1999)	169	882	553	71	1294	872	98	3.77E-03	WB-C
	Annual temperatures by country: values in degrees Celsius. (Mean 1961-1999)	169	13	8	71	22	6	98	2.03E-10	WB-C
	Latitude	196	30	26	75	11	19	121	6.04E-10	GM
	Longitude	196	13	59	75	20	71	121	2.55E-01	GM
	UV radiation. (Mean 2004)	176	3056	1369	70	4711	1093	106	9.77E-13	WHO

Category	Variable	Total countries with inf.	Countries with available information on T1D			Countries without available information on T1D			Mann–Whitney U test	Ref
			Mean	SD	*n*	Mean	SD	*n*		
	Environment									
	CO_2 emissions in metric tons per capita. (Mean 2000-2009)	182	7	5	73	3	7	109	5.42E-14	WB
	Combustible renewables and waste: % of total energy. (Mean 2000-2010)	134	10	16	71	33	32	63	3.45E-03	WB
	NOx emissions per capita in Kg. (Mean 2010)	140	46	189	60	61	407	80	7.93E-07	WB
	Percentage of renewable Electricity Production. (Mean 2007)	188	23	28	70	31	35	118	7.35E-01	WB
	PM10, country level in micrograms per cubic meter. (Mean 2000-2009)	171	41	36	70	54	30	101	7.54E-06	WB
Demography	**Demography**									
	Adolescent fertility rate (births per 1,000 women ages 15-19 (Mean 2000-2010)	187	29	27	75	73	48	112	7.14E-13	WB
	Births by five-year age group of mother, major area, region and country, 1980-2100 (thousands) age of mothers: 20-24 yr. (Mean 2005-2010)	196	585	2847	75	317	659	121	2.23E-01	UN
	Births by five-year age group of mother, major area, region and country, 1980-2100 (thousands) age of mothers: 25-29 yr. (Mean 2005-2010)	196	1840	7853	75	662	1218	121	7.82E-01	UN
	Births by five-year age group of mother, major area, region and country, 1980-2100 (thousands) age of mothers: 30-34 yr. (Mean 2005-2010)	196	1506	5151	75	602	1123	121	1.33E-01	UN
	Births by five-year age group of mother, major area, region and country, 1980-2100 (thousands) age of mothers: 35-39 yr. (Mean 2005-2010)	196	850	2142	75	397	770	121	1.84E-02	UN
	Births by five-year age group of mother, major area, region and country, 1980-2100 (thousands) age of mothers: 40-44 yr. (Mean 2005-2010)	196	363	772	75	205	402	121	4.81E-02	UN
	Births by five-year age group of mother, major area, region and country, 1980-2100 (thousands) age of mothers: 45-49 yr. (Mean 2005-2010)	196	94	210	75	72	151	121	5.11E-01	UN
	Births by five-year age group of mother, major area, region and country, only 2005-2010 (thousands) (15-19 yr). (Mean 2005-2010)	196	16	48	75	19	46	121	9.04E-02	UN
	Birth rate. (Mean 2010)	187	14	6	75	27	10	112	6.68E-17	WB
	Life expectancy at birth (both sexes combined) by major area, region and country. (Mean 2000-2005)	196	76	5	75	65	10	121	1.09E-14	UN
	Life expectancy at birth (both sexes combined) by major area, region and country. (Mean 2005-2010)	196	75	5	75	63	11	121	1.38E-15	UN
	Population 0-14 years of age (% of total population). (Mean 2010)	187	21	7	75	34	9	112	1.42E-16	WB
	Population density (people per km^2 of land area). (Mean 2010)	187	325	1133	75	320	1836	112	5.71E-01	WB
	Probabilistic projections of population aged 0-14 years old. (Mean 2010)	186	14720	53870	71	5979	11260	115	2.14E-01	UN
	Rural population (% of total population). (Mean 2000-2010)	187	29	18	75	56	21	112	2.04E-14	WB
	Rural population (% of total population). (Mean 2011)	187	28	18	75	54	21	112	5.31E-14	WB
	Sex ratio (male(s)/female) under 15 years. (Mean 2011)	166	1	0	66	1	0	100	6.02E-10	UN
	Total fertility rates (estimation: median). (Mean 2005-2010)	186	2	1	71	4	2	115	2.80E-16	WB
	Total fertility rates: births per woman. (Mean 2010)	187	2	1	75	3	1	112	3.04E-15	WB
	Urban population (% of total population. (Mean 2010)	186	73	16	73	45	21	113	1.70E-15	WB
Economic factors	**Economic factors**									
	Expenditure per student, primary (% of GDP per capita). (Mean 2000-2010)	141	18	8	60	13	6	81	8.18E-07	WB
	GDP, PPP (current international 100,000 U $) PPP GDP is gross domestic product converted to	187	9077000	227300 00	75	926500	2311000	112	1.09E-10	WB

Category	Variable	Total countries with inf.	Countries with available information on T1D			Countries without available information on T1D			Mann–Whitney U test	Ref
			Mean	SD	*n*	Mean	SD	*n*		
	international dollars. (Mean 2011)									
	GNI per capita, PPP (current international $). (Mean 2011)	187	20360	17020	75	5309	10160	112	9.41E-11	WB
	Gross capital formation (annual % growth). (Mean 2008)	187	4	11	75	5	11	112	5.00E-01	WB
	Health expenditure per capita (current US$). (Mean 2010)	187	1951	2235	75	225	333	112	3.25E-15	WB
	Improved sanitation facilities (% of population with access). (Mean 2000-2010)	174	89	19	69	56	30	105	7.88E-14	WB
	Improved sanitation facilities: urban (% of urban population with access). (Mean 2000-2010)	176	93	14	70	67	26	106	2.19E-13	WB
	Physicians (per 1,000 people). (Mean 2010)	187	2	2	75	1	1	112	2.63E-13	WB
	Poverty gap at $2 a day (PPP) (%). (Mean 2000-2010)	111	6	11	35	24	17	76	5.51E-10	WB
Health conditions	**Infancy and childhood**									
	Diarrhea treatment (% of children under 5 receiving oral rehydration and continued feeding). (Mean 2000-2010)	98	49	13	18	40	14	80	1.56E-02	WB
	Exclusive breastfeeding (% of children under 6 months). (Mean 2010)	187	2	11	75	7	18	112	1.22E-02	WB
	Immunization, DPT (% of children ages 12-23 months). (Mean 2000-2010)	178	93	7	72	80	17	106	1.75E-09	WB
	Immunization, measles (% of children ages 12-23 months). (Mean 2000-2010)	178	92	7	72	79	17	106	5.46E-08	WB
	Low-birth weight babies (% of births). (Mean 2000)	187	2	3	75	6	7	112	3.00E-05	WB
	Malnutrition prevalence, weight for age (% of children under 5). (Mean 2000-2010)	123	2	5	32	6	5	91	1.63E-08	WB
	Morbi-mortality									
	Cancer deaths 2008	179	246	57	72	207	52	107	1.65E-06	WHO
	Cardiovascular diseases and diabetes (deaths per 100,000 individuals) (Mean 2008)	179	526	263	72	818	234	107	4.78E-11	WHO
	Diabetes deaths (per 1000 persons) (Mean 2008)	196	90990	67420	75	97730	77690	121	7.49E-01	WHO
	Maternal mortality ratio (national estimate, per 100,000 live births). (Mean 2000-2010)	133	83	189	41	365	346	92	8.41E-10	WB
	Mortality rate, under-5 (per 1,000 live births). (Mean 1990-2011)	179	19	21	71	76	55	108	3.40E-18	WHO
	Mortality rate, under-5 (per 1,000 live births). (Mean 2000-2010)	178	16	20	72	73	54	106	1.72E-18	WB
	Non-communicable diseases (deaths under age 60). (Mean 2008)	179	19	9	72	37	10	107	6.28E-19	WHO
	Notified cases of malaria (per 100,000 persons)	102	140000	360100	20	140200	315000	82	8.04E-01	WB
	Tuberculosis incident cases (per 100,000 persons). (Mean 2011)	178	39	58	71	192	214	107	4.35E-14	WB
	Overweight and obesity									
	Mean body mass index (BMI) in kg/m^2 of defined population (age standardized estimate), Female. Age + 20 years of age. (Mean 2008)	178	26	2	72	25	3	106	4.22E-02	WHO
	Mean body mass index (BMI) in kg/m^2 of defined population (age standardized estimate), Male. Age + 20 years of age. (Mean 2008)	178	26	2	72	24	2	106	5.82E-11	WHO
	Prevalence of obesity, BMI ≥ 30 (age standardized estimate), Both sexes. Age + 20 years of age. (Mean 2008)	178	21	8	72	15	12	106	8.98E-05	WHO
	Prevalence of obesity, BMI ≥ 30 (age standardized estimate), Female. Age + 20 years of age. (Mean 2008)	178	23	10	72	20	15	106	5.59E-02	WHO
	Prevalence of obesity, BMI ≥ 30 (age standardized estimate), Male. Age + 20 years of age. (Mean 2008)	178	19	8	72	11	10	106	2.84E-10	WHO
	Prevalence of overweight, BMI ≥ 25 (age	178	50	14	72	44	21	106	7.51E-02	WHO

Category	Variable	Total countries with inf.	Countries with available information on T1D			Countries without available information on T1D			Mann–Whitney U test	Ref
			Mean	SD	*n*	Mean	SD	*n*		
	standardized estimate), Both sexes. Age + 20 years of age. (Mean 2008)									
	Prevalence of overweight, BMI ≥ 25 (age standardized estimate), Female. Age + 20 years of age. (Mean 2008)	178	53	13	72	40	20	106	1.81E-05	WHO
	Prevalence of overweight, BMI ≥ 25 (age standardized estimate), Male. Age + 20 years of age. (Mean 2008)	178	55	14	72	35	21	106	2.49E-10	WHO
	Smoking									
	Current cigarettes smokers (youth rate), Both sexes. (Mean 2010)	147	15	10	49	9	7	98	6.83E-04	WHO
	Current cigarettes smokers (youth rate), Female. (Mean 2010)	147	13	11	49	6	6	98	8.77E-05	WHO
	Current cigarettes smokers (youth rate). Male. (Mean 2010)	147	16	9	49	13	9	98	1.60E-02	WHO
	Current smokers of any tobacco product (age standardized estimate), Female. (Mean 2009)	138	18	11	61	7	7	77	2.89E-08	WHO
	Current smokers of any tobacco product (age standardized rate), Both sexes. (Mean 2009)	136	26	9	60	19	10	76	9.34E-06	WHO
	Current smokers of any tobacco product (age standardized rate), Male. (Mean 2009)	139	35	11	60	31	15	79	5.06E-02	WHO
	Current users of any tobacco product (youth rate), Both sexes. (Mean 2010)	147	19	9	49	18	10	98	2.84E-01	WHO
	Current users of any tobacco product (youth rate), Female. (Mean 2010)	147	17	10	49	14	10	98	1.48E-01	WHO
	Current users of any tobacco product (youth rate), Male. (Mean 2010)	147	22	9	49	22	11	98	6.77E-01	WHO
	Exposure to smoke at home, both sexes. (Mean 2010)	140	45	18	45	36	14	95	1.90E-03	WHO
	Exposure to smoke at home, female. (Mean 2010)	140	46	19	45	35	15	95	9.16E-04	WHO
	Exposure to smoke at home, male. (Mean 2010)	140	44	17	45	37	14	95	7.13E-03	WHO
	Exposure to smoke outside home, both sexes. (Mean 2010)	139	59	17	45	53	13	94	9.27E-03	WHO
	Exposure to smoke outside home, female. (Mean 2010)	139	59	18	45	51	14	94	2.32E-03	WHO
	Exposure to smoke outside home. (Mean 2010)	139	59	16	45	55	13	94	4.66E-02	WHO
	Smoking prevalence, females (% of adults). (Mean 2009)	187	14	12	75	5	6	112	5.17E-07	WB
	Smoking prevalence, males (% of adults). (Mean 2009)	187	28	17	75	22	19	112	1.83E-02	WB
Life conditions	**Life conditions**									
	Internet users (per 100 people). (Mean 2000-2010)	186	35	22	75	9	12	111	2.02E-17	WB
	Literacy rate, adult total (% of people ages 15 and above. (Mean 2000)	187	13	32	75	21	35	112	5.67E-02	WB
	Literacy rate, youth total (% of people ages 15-24). (Mean 2010)	187	44	49	75	54	44	112	9.23E-01	WB
	Mobile cellular subscriptions (per 100 people). (Mean 2000-2010)	186	72	30	75	33	25	111	3.76E-15	WB
	Motor vehicles (per 1,000 people). (Mean 2000-10)	164	351	221	73	83	107	91	4.13E-16	WB

Note: in red correlations reporting a p-value ≤ 0.05. References: (WB) World Bank (2012) Indicators. Available from http://data.worldbank.org/indicator, accessed 11-08 2012; (WB-C) World Bank (2012) Climate Change Knowledge Portal: Historical Data. Available from http://data.worldbank.org/developers/climate-data-api, accessed 11-08 2012; (WHO) WHO (2012) Global Health Observatory Data Repository. Available from http://apps.who.int/gho/data/?vid=2472, accessed 11-08 2012; (UN) United Nations, Department of Economic and Social Affairs (2011) World Population Prospects, the 2010 Revision. Available from http://esa.un.org/wpp/Excel-Data/population.htm, accessed May 31 2012; (GM) Google Maps API Geographical coordinates 2013. Available from **http://universimmedia.pagesperso-orange.fr/geo/loc.htm**.

3.3.2 Analyses of cumulative incidence of T1D

3.3.2.1 Steps performed to obtain cumulative incidence of T1D

To obtain the cumulative incidence of T1D by age at onset and birth cohort, a protocol consisting in 3 steps was proposed and is the following:

3.3.2.1.1 Step 1. Grouping data

First, stratification by incidence level proposed in the Diamond study (161, 231, 318), which is an arbitrary distribution of the cases in five groups: i) very low, <1 case per 100.000 individuals per year; ii) low, 1-4.99 per 100.000 per year; iii) intermediate, 5-9.99 per 100.000 per year; iv) high, 10-19.99 per 100.000 per year; and v) very high, ≥ 20 per 100.000 per year. The identification of the correct level of incidence for each reference was performed after averaging all the data reported in each reference and comparing the result with the respective categories to classify the reference from very low to very high incidence level. Due to enormous variability in the incidence of T1D, it was conceivable that one country might belong to more than one category of incidence level; for example, in this thesis, 26 references reported the incidence in Italy: Sardinia was classified as very high incidence, the entire nation as high, and the Rome and Lazio region belonged to the intermediate category.

Second, the average of a specific place to summarize the available information in a specific area in a country was generated. The process consisted in pooled studies that belonged to a similar geographic area, such as all nation-wide, regional, or local studies performed in a specific country. For example, also in Italy, the mean for all studies reporting the incidence in Sardinia, the mean of Lombardia, the mean of Turin, and the mean of the whole nation were carried out independently.

Third, using dynamic tables operated by the Microsoft Excel software, six summary tables were obtained, one for each level of incidence (from very low to very high). Each retrieved table then represents the diagonal (Lexis's diagram) of the mean incidence for each category of incidence level. To compare the final results, all final tables presented the same structure of data-frame; each one contains in the rows the age at onset of T1D (listed from 0

to 40 years of age) and in the columns the mean incidence by each birth cohort (1924 to 2008). To complete the data-frame non-available data were identified as “NA”.

3.3.2.1.2 Step 2. Generating cumulative incidence

To obtain cumulative incidence the final tables were independently exported to the R program (255). Using the function *cumsum,* the cumulative sum of incidences by birth cohort and age at onset for each category of analysis was generated. The average of the cumulative incidences each five-years of birth cohorts was obtained later. The result was exported as a list containing three columns each one respectively, with the age at onset from 0 to 40 years, 5-year-periods of birth cohort (starting in 1924 and extending to 2008), and the cumulated incidence. Any treatment was considered for non-available data.

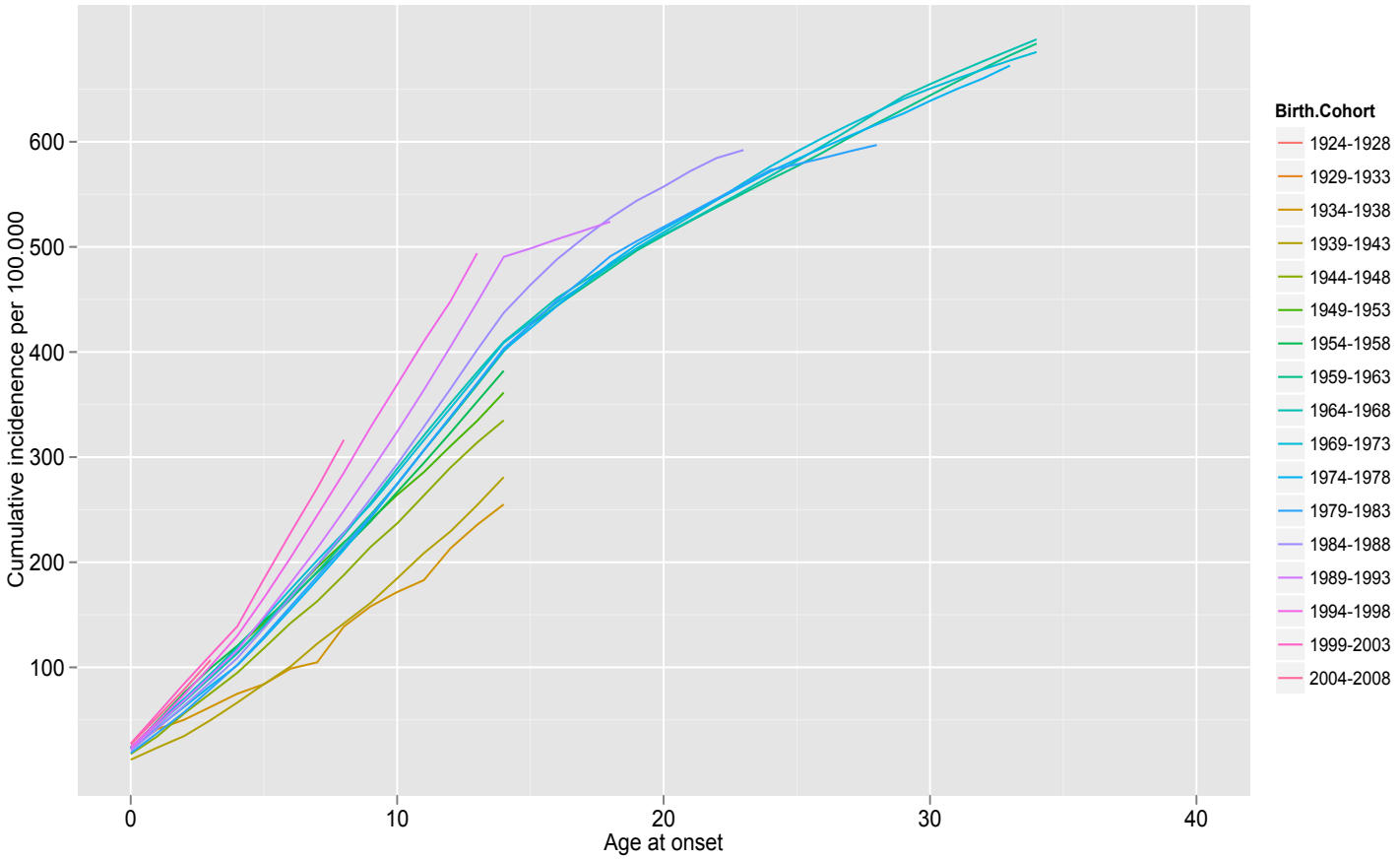
3.3.2.1.3 Step 3. Plotting data

Using the library *ggplot 2* in the R program (255) and the information exported into the lists described above, the curves representing the mean cumulative incidence country level by 5-year-periods of birth cohorts, and by age at onset were plotted; **SI Figures 19-23.**

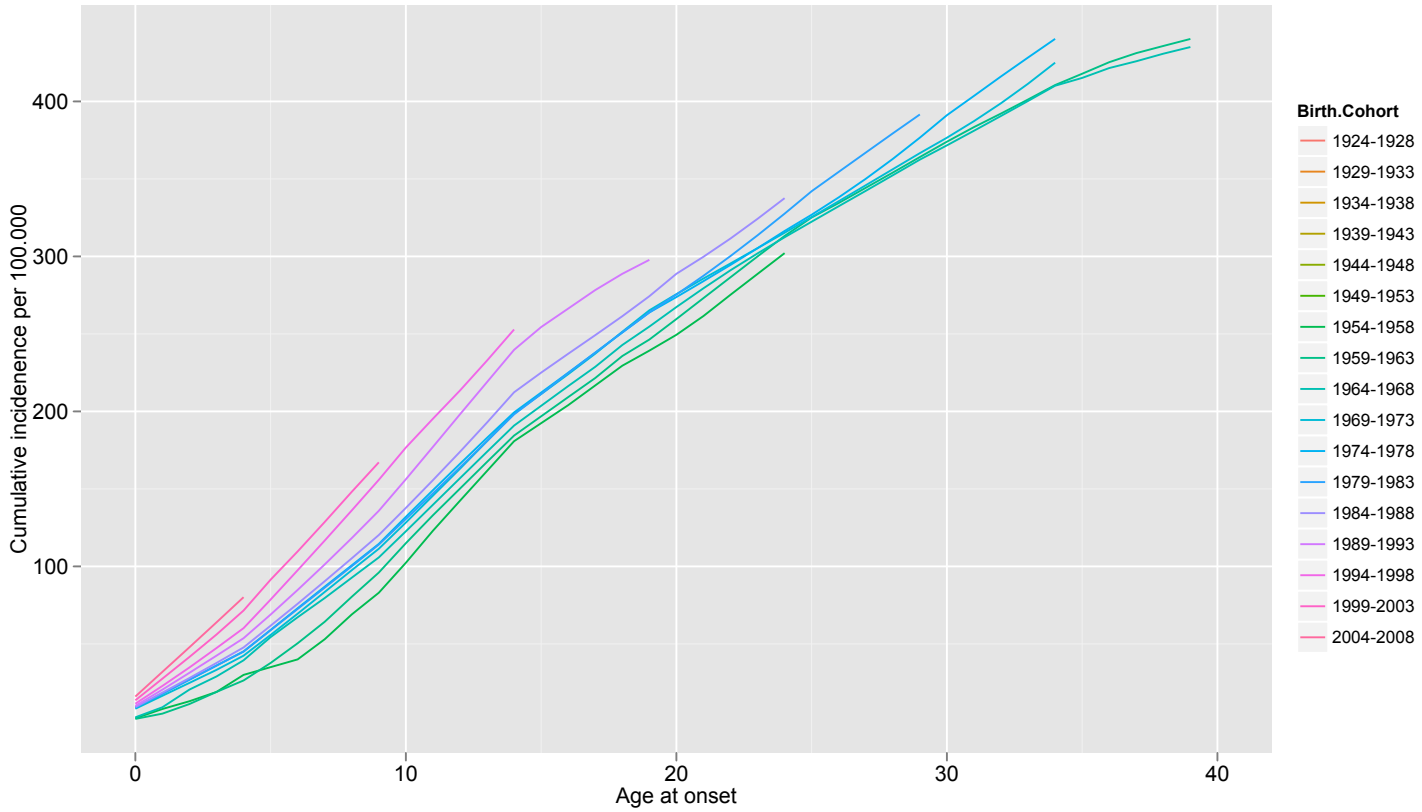
3.3.2.2 Findings

Cumulative incidence by birth cohorts dropped after 2004 in countries with very high incidence, and around 1994 in countries with intermediate, low and very low incidence of T1D. The **SI Figures 19-23** presented below show the increase in the incidence of T1D with successive birth cohorts; nevertheless, after the period 1994-1998, in countries with very high, intermediate and very low incidence levels, new cohorts exceed the previous cohort indicating a relative stabilization or a new tendency of T1D worldwide. The negative trend of T1D is persistent after stratification by country-incidence-level.

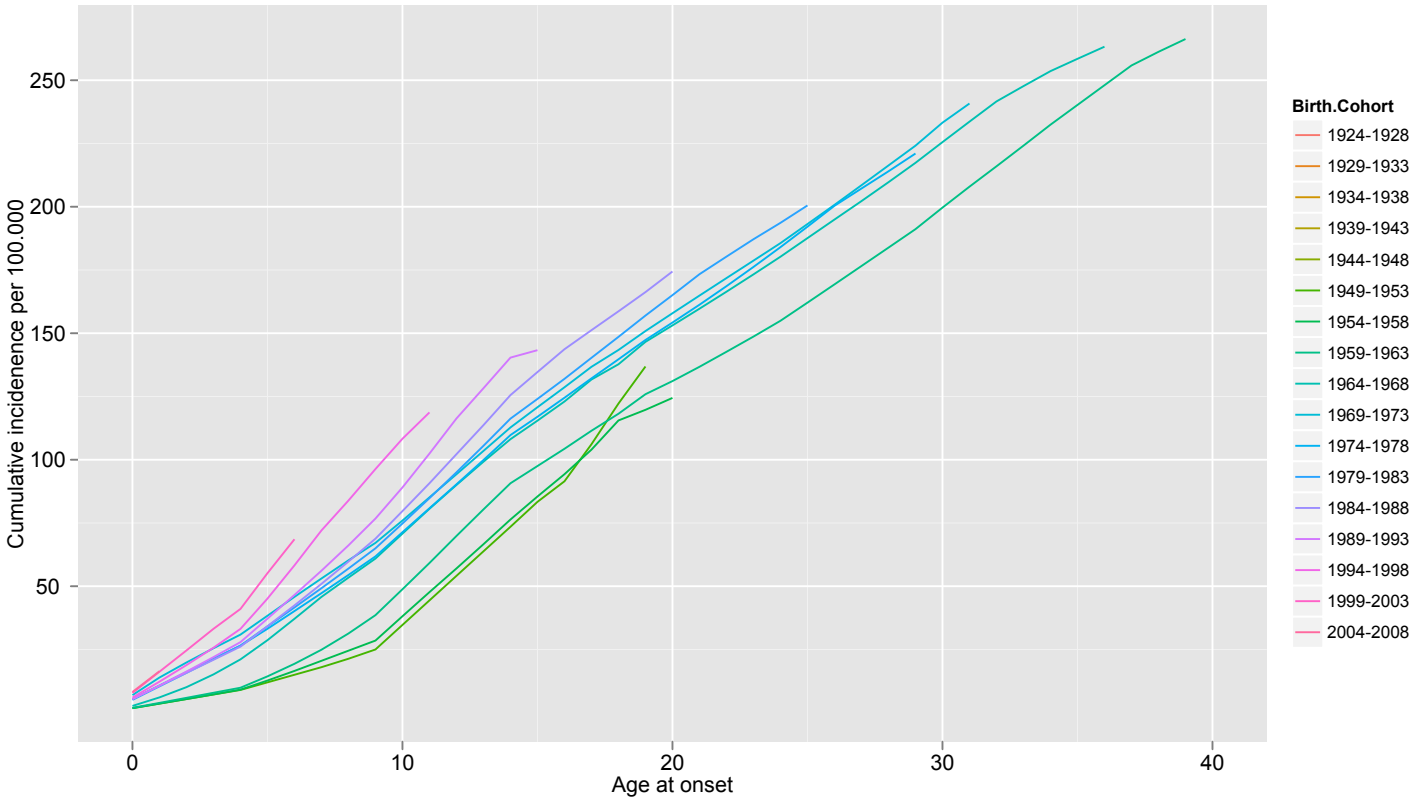
There are enormous variations in incidence trends of T1D in individuals aged 0-40 years after stratifying the analysis according to incidence-country-level. Maximum cumulative incidence of T1D per 100.000 persons was respectively, 649.5 for countries with very high-incidence level, 394.8 for high, 220.4 for intermediate, 56.2 for low, 10.3 for very low-incidence countries, and 486 after cumulating all countries.



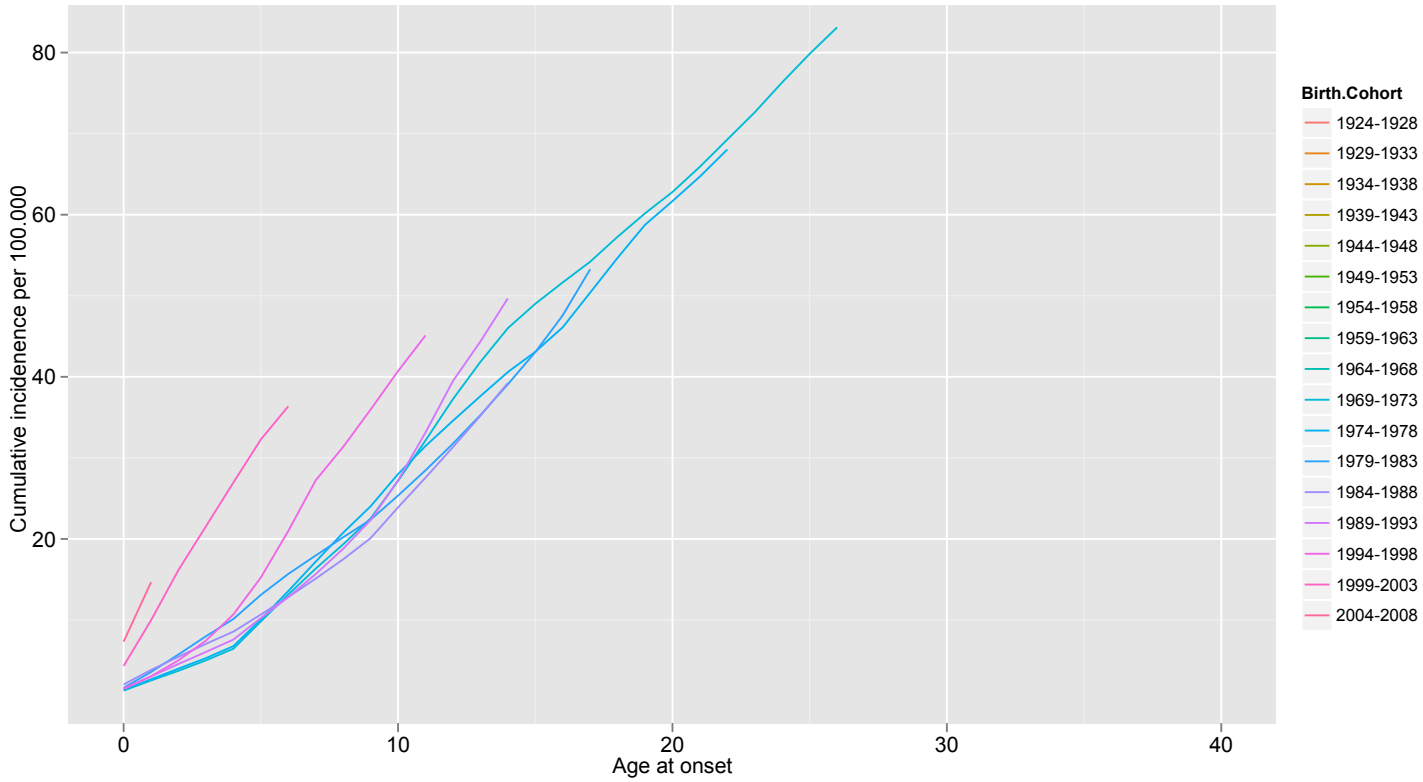
SI Figure 19: Cumulative incidence of T1D in very high-incidence countries very high: ≥ 20 cases per 100.000 individuals per year by birth cohorts (1924-2008)



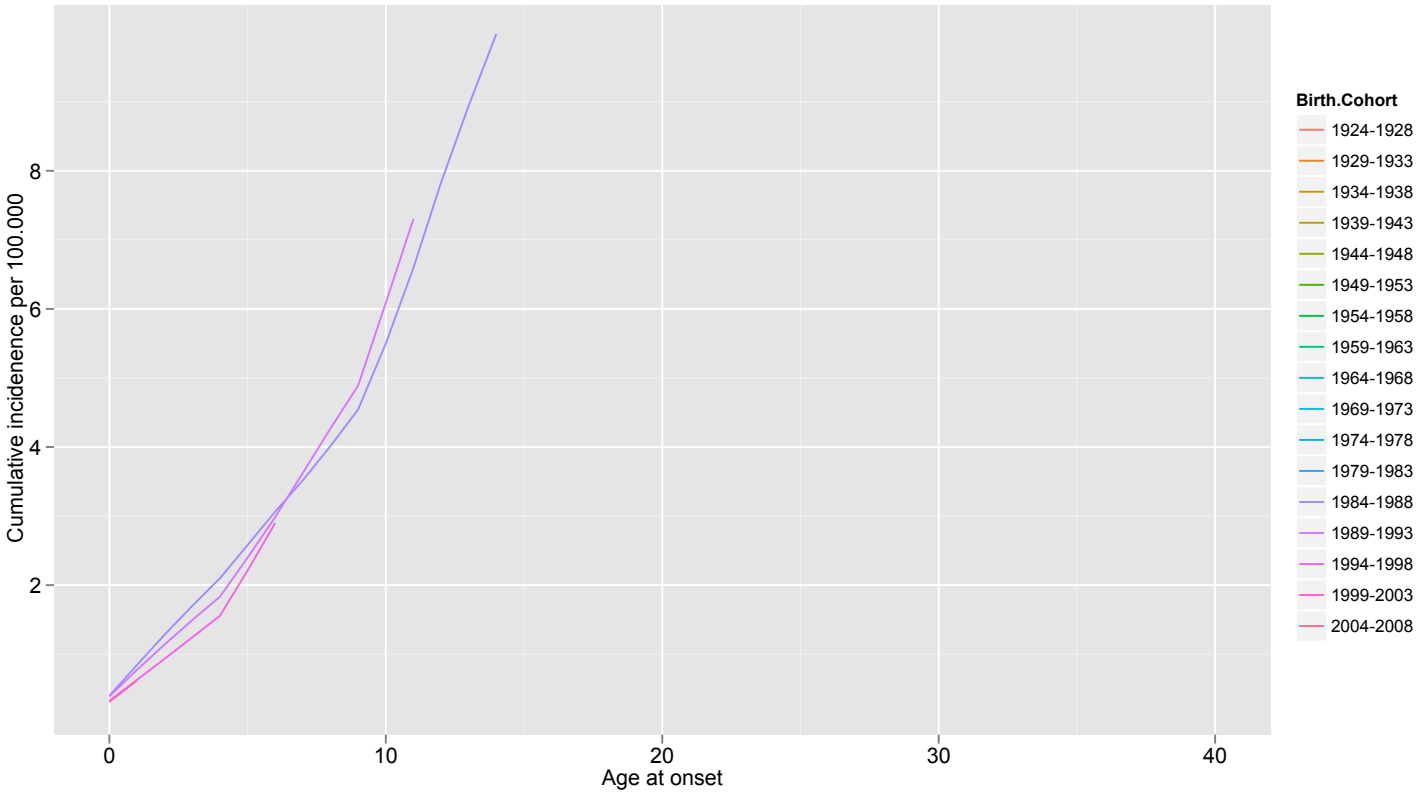
SI Figure 20: Cumulative incidence of T1D in high-incidence countries: 10-19.99 cases per 100.000 individuals per year by birth cohorts (1924-2008)



SI Figure 21: Cumulative incidence of T1D in intermediate-incidence countries: 5-9.99 cases per 100.000 individuals per year by birth cohorts (1924-2008)



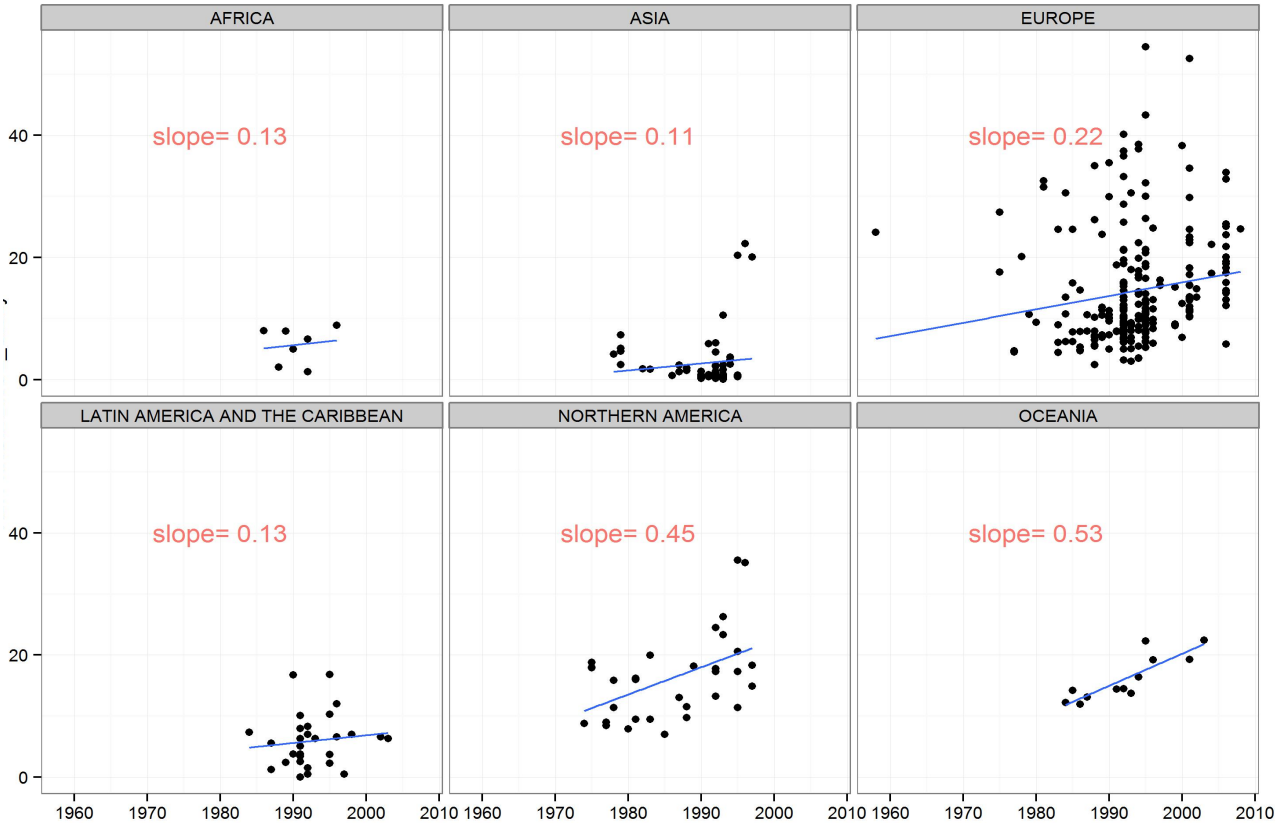
SI Figure 22: Cumulative incidence of T1D in low-incidence countries: 1-4. cases per 100.000 individuals per year by birth cohorts (1924-2008)



SI Figure 23: Cumulative incidence of T1D in very low-incidence countries: <1 case per 100.000 individuals per year by birth cohorts (1924-2008)

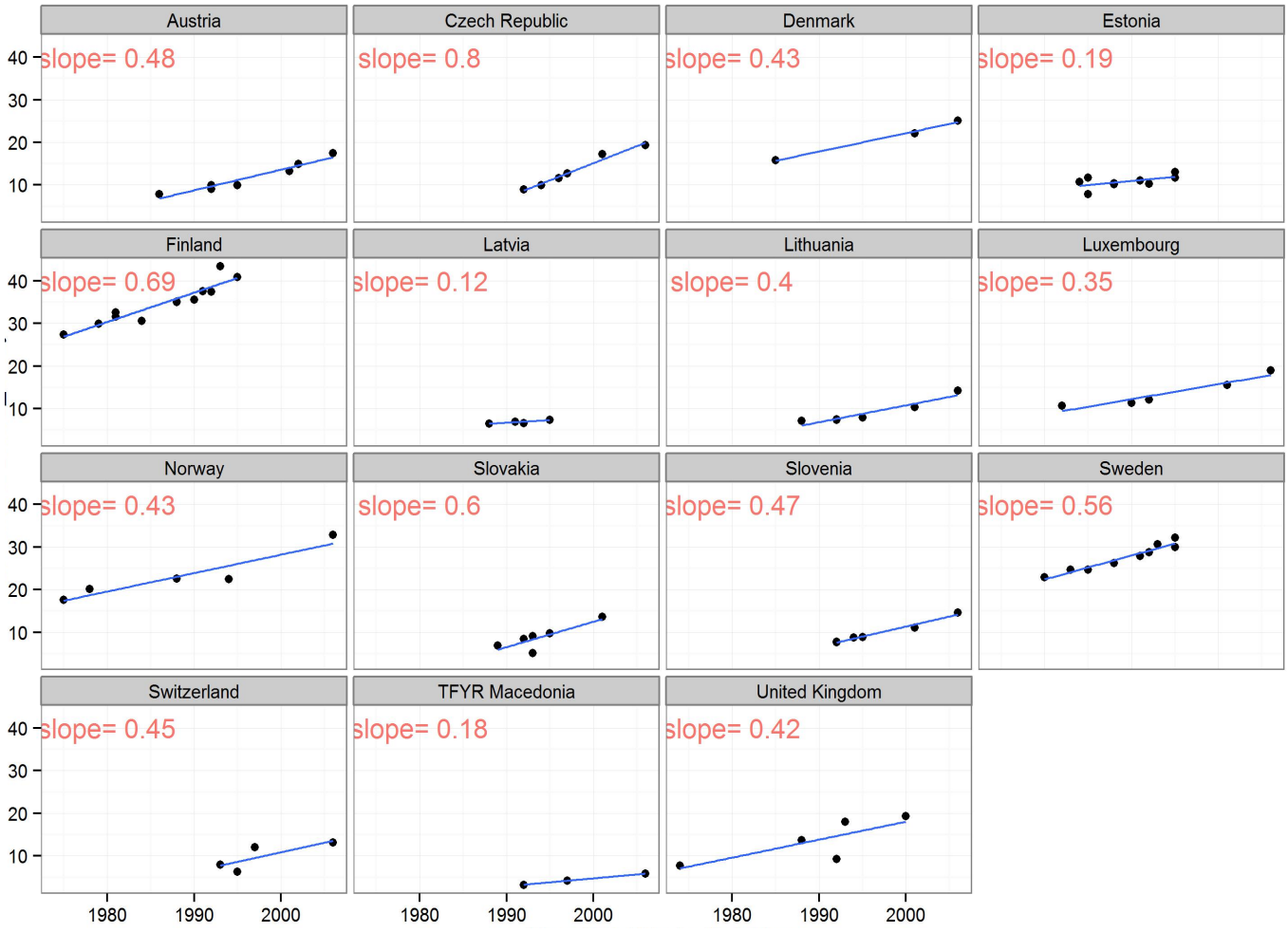
3.3.3 Worldwide Incidence trends of T1D

Independently of the initial level of incidence a positive slope is observed for all continents plotting data published from 1960 to 2010. Asia (incidence slope = 0.11 case per 100.000 individuals per year), Africa (incidence slope = 0.13 case per 100.000 individuals per year) and Latin America and the Caribbean (incidence slope = 0.13 case per 100.000 individuals per year) show the smallest increases, Europe (incidence slope = 0.22 case per 100.000 individuals per year) presents an intermediate increase, and North America (incidence slope = 0.45 case per 100.000 individuals per year) and Oceania (incidence slope = 0.53 case per 100.000 individuals per year) the largest. (**SI Figure 24**). Since 1980, the speed of the increase had varied depending on the country: comparing only nation-wide studies performed in Europe, the slope of the variation of incidence of T1D with time has varied from a incidence slope = 0.12 case per 100.000 individuals per year (Latvia) to a incidence slope = 0.8 case per 100.000 individuals per year (Czech Republic). (**SI Figure 25**).



The analysis of the variations of T1D incidence across continents is based on datasets for which the percent of ascertainment was reported. *Y*-axis: incidence of T1D per 100.000 individuals of both sexes (0-14 years old) per year. *X*-axis: time of the mean point of duration of each study. Circles represent each retrieved study.

SI Figure 24: T1D incidence trends in major UN areas among studies reporting ascertainment



The analysis of the variation of T1D incidence with time in European countries was restricted to nationwide studies having reported the percentage of ascertainment. *Y*-axis: incidence of T1D per 100.000 individuals of both sexes (0-14 years old) per year. *X*-axis: time of the mean point of duration of each study. Circles represent each retrieved study.

SI Figure 25: T1D incidence trends in Europe among nation-wide studies reporting ascertainment

3.3.4 Anticipation phenomenon in the age at onset of T1D

The increase in the global trends of T1D is clear, and this seems to be a global phenomenon independent of whether the risk of the population is low or high. Also, the variation in the age at onset of T1D in the last decades has been reported. Since 1955, a little variation of the incidence in the younger age groups in Oslo, Norway had been reported, in a remarkable longitudinal study of the population that was analyzed from data collected between 1925 and 1954 (357).

Today, even though the increase in T1D incidence apparently has affected all age groups worldwide, several research teams have been working on the epidemiology of T1D and have reported that apparently, the age at onset is decreasing, and in most studies the incidence of T1D increased in children between 0 and 14 years, and has been most pronounced in the youngest age group, among of children between 0 and 4 years of age. This is consistent with the greatest rate of increase in childhood onset of T1D incidence in the group of 0-4 years of age (224). This situation may be a reflection of a situation of "anticipation" in which individuals with susceptible genotypes may develop the disease at an earlier age than previously (118), a concept first proposed by Kurtz et al. in 1988 (175), by this time called "accelerated onset".

The reason for the continuous decline in the age at onset is unclear. Some authors affirm that the rising incidence of T1D is caused by an earlier clinical presentation rather than due to a global increase in the incidence of T1D in all age categories. Changes in the exposure to environmental factors may promote or accelerate the subclinical disease process in young subjects genetically predisposed to T1D (352), and a more permissive early life environment favorable to the development of T1D could also be implicated (344).

3.3.4.1 Epidemiological reports showing the change in incidence trend in the youngest age groups

Green et al. reported that in Europe during the period 1989-1998 the annual increase in the incidence of T1D was higher in the very young child group (0-4 years of age), than in the 5-9 or 10-14 years age group, 4.5% (CI 95% 3.8-5.9) versus 3.7% (CI 95% 2.9-4.5) and 2.1% (CI 95% 1.4-2.8) respectively (121). In the Eurodiab study, a particular finding was that the increase in incidence was particularly rapid in children under 5 years of age. The rates of increases were: 6.3% (CI 95% 4.1-8.5), 3.1% (CI 95% 1.5-4.8) and 2.4% (CI 95% 1.0-3.8) in children aged 0-4, 5-9 and 10-14 years respectively (90). Other multicenter prospective registration of European studies, published in 2007, evaluated the incidence trends in 20 population-based registers in 17 countries. As main finding, the annual incidence of T1D increased for all centers and was on average 3.9% (CI 95% 3.6-4.2), rising to 5.4% (CI 95% 4.8-6.1) in the group 0-4 years, 4.3% (CI 95% 3.8,4.8) to in the group 5-9 years, and to 2.9% (CI 95% 2.5-3.3) in the group 10-14 years of age (242).

The results of the European studies are consistent with the hypothesis of the decrease of the age at onset of childhood diabetes. Other unaggregated studies, conducted in Europe and North America provided similar results. An article published in 2008 in Germany, concluded that although the absolute incidence was highest in the group of 10-14 years of age, the age at onset of T1D has decreased, and the highest rise in incidence occurred in the group of 0-4 year-old patients (5.8%, CI 95% 2.5-9.3). In the group of 5-9 and 10-14 year-old patients, it was 3.4% (CI 95% 0.8-6.0) and 2.7% (CI 95% 0.3-5.1), respectively (85). Also in 2008, an article was published reporting that in Aquitaine, France, the annual increase of incidence was highest in the group of 0-4 years, 7.59% in comparison with the group of 5-9 (4.06%) and 10-14 years (1.28%) (28). In a Swedish study published in 2011, on 14.721 incident cases of T1D aged 0-14 years in the period 1978-2007, confirms that children aged 0-5 years are the most affected by T1D. This publication argues that the rise in the incidence of T1D is coincident with a birth cohort effect (33). Also, a Czech study published in 2000 registered that the age at onset of diabetes had presented a significant log-linear increasing trend in children (in those aged 0-4 years the increment was 6.9%, (p = 0.033) and in the group of 5-9 years it was 4.8% (p = 0.038)) (64).

In Colorado, USA, the incidence of T1D in children aged 0-4 years had increased more compared with the other age groups: 1.96 (CI 95% 1.6,2.4) in the 0-4 year-old group, 1.6 (CI 95% 1.3-1.8) in the 5-9 year-old group, 1.5 (CI 95% 1.3-1.7) in the 10-14 year-old group, and 1.6 (CI 95% 1.2-2.1) in the 15-17 year-old group (344).

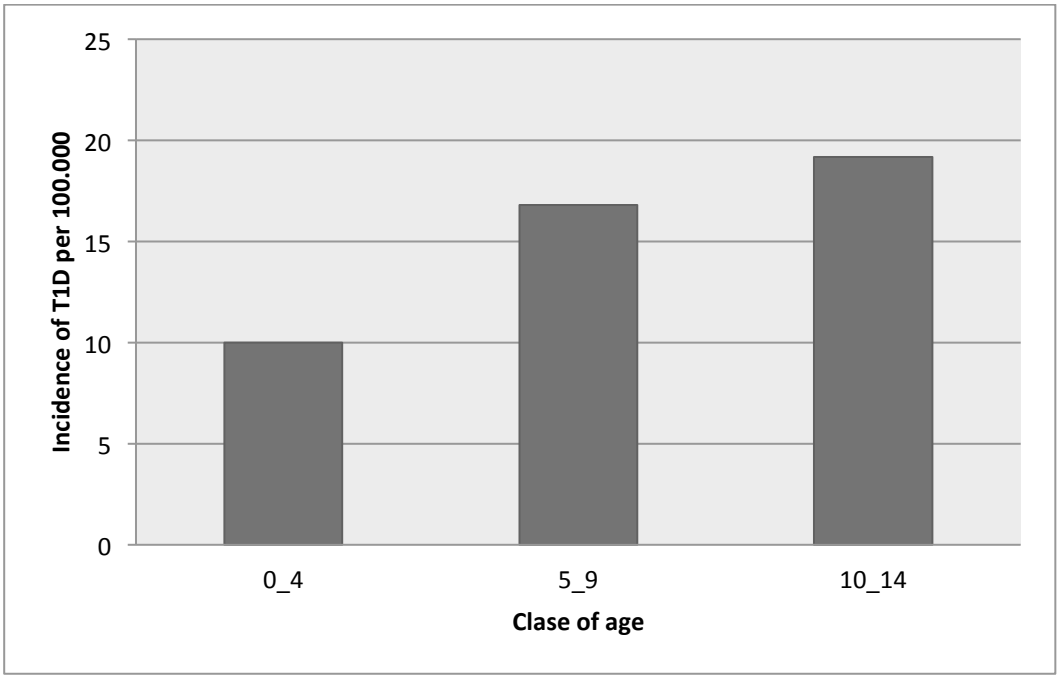
In Israel, the annual increase in incidence in the period 2000-2008 was 5.82% (CI 95% 1.80-9.98) and the group of children aged less than 5 years had the highest increase; it increased by 104%, from 5.41 (CI 95% 3.44-7.37) per 100.000 person years to 11.04 (CI 95% 8.27-13.81) per 100.000 person years in the periods 2000-2002 and 2006-2008 respectively. As a consequence, the age at onset of T1D decreased from 10.21 (SD 4.48) to 9.25 (SD 4.54) ($p = 0.07$) in this time interval (284).

In contrast with the above reports, others studies carried out in Italy (43), Finland (177) and Western Australian (130), observed an increase in T1D in all groups of age. These results are against of the observation of an earlier age of onset of T1D (40).

3.3.5 Median age at onset of T1D

In Aquitaine, Franc, the median age at onset of diabetes was 10.04 years (CI 95% 6.64-12.53) in the period 1988-1996 and 8.83 years (CI 95% 5.48,11.73) in the period 1997-2004 (28). In the study of Northern Italy, the incident cases were identified in the a majority of cases during puberty, and with respect to the group aged 0-4 years, the Relative Risk (RR) was 1.64 (CI 95% 1.41-1.91) (46).

Using data retrieved in this thesis, the distribution of the age at onset of T1D was explored among 1690 data reporting the incidence of T1D by classes of age: 0-4, 5-9 and 10-14 years. The analyses show that the mean incidence for the age group was 10.0 cases per 100.000 individuals per year in the age group 0-4, 16.8 cases per 100.000 individuals per year in the group 5-9, and 19.2 cases per 100.000 individuals per year in the group 10-14; **SI Figure 26**.



SI Figure 26: Mean incidence of T1D by class of age at onset retrieved in 1690 data

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Chapter 4

Incidence of Type 1 Diabetes in young and young adults

Contents

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4 Epidemiology of T1D in young adults and adults

This thesis was initially focused on the study of T1D in children only because one usually thinks that the so-called "juvenile" diabetes is a disease specific of the youngest age groups. Nevertheless, no limit of age at onset of T1D was detected during the data collection for this thesis, as mentioned in **chapter 1**. With time, interesting papers appeared reporting the incidence of T1D in older individuals in several countries, and then in preliminary analyses, we observed that cumulative incidence among individuals older than 15 years followed patterns similar to those observed in children, as mentioned in section 3.4 of **chapter 3**. It was then that we decided to study the epidemiology of T1D in adults as presented here.

All possible studies reporting T1D in people aged over 15 years and published in indexed databases by the time this thesis was undertaken, were searched. Special attention was focused on the diagnostic criteria used to define T1D in adults as well as on the use of autoantibodies and detection of the C-peptide, a sub-product of insulin, as criteria to define T1D.

Finally, even though the map of the epidemiology of T1D in children as described in **chapters 1** and **2** is as yet incomplete, we could see that this statement was even more valid for the epidemiology of T1D in adults, since available information was retrieved in only 17% (35 of 196) of the world countries. Moreover, interesting results were found, such as high correlation between incidences in children and adults, a same pattern of variability observed in children and a surprising male predominance of T1D among adults (82).

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4.1 Global epidemiology of T1D in young adults and adults: a systematic review

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Global epidemiology of type 1 diabetes in young adults and adults: a systematic review

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Abstract

Background: Although type 1 diabetes (T1D) can affect patients of all ages, most epidemiological studies of T1D focus on disease forms with clinical diagnosis during childhood and adolescence. Clinically, adult T1D is difficult to discriminate from certain forms of Type 2 Diabetes (T2D) and from Latent Autoimmune Diabetes in Adults (LADA). We searched the information available worldwide on the incidence of T1D among individuals over 15 years of age, and which diagnostic criteria should be used use to qualify T1D in adults. We then studied the variation of T1D incidence with age in adults, and compared it to the incidence in the <15 years-old.

Methods: A systematic review of the literature was performed to retrieve original papers in English, French and Spanish published up to November 6, 2014, reporting the incidence of T1D among individuals aged over 15 years. The study was carried out according to the PRISMA recommendations.

Results: We retrieved information reporting incidence of T1D among individuals aged more than 15 years in 35 countries, and published in 70 articles between 1982 and 2014. Specific anti-beta-cell proteins or C-peptide detection were performed in 14 of 70 articles (20%). The most frequent diagnostic criteria used were clinical symptoms and immediate insulin therapy. Country-to-country variations of incidence in those aged >15 years paralleled those of children in all age groups. T1D incidence was larger in males than in females in 44 of the 54 (81%) studies reporting incidence by sex in people >15 years of age. The overall mean male-to-female ratio in the review was 1.47 (95% CI = 1.33-1.60, SD = 0.49, n = 54, p = <0.0001). Overall, T1D incidence decreased in adulthood, after the age of 14 years.

Conclusions: Few studies on epidemiology of T1D in adults are available worldwide, as compared to those reporting on children with T1D. The geographical variations of T1D incidence in adults parallel those reported in children. As opposed to what is known in children, the incidence is generally larger in males than in females. There is an unmet need to evaluate the incidence of autoimmune T1D in adults, using specific autoantibody detection, and to better analyze epidemiological specificities – if any – of adult T1D.

PROSPERO registration number: CRD42012002369.

Keywords: Type 1 diabetes, Systematic review, Adults, Incidence, Epidemiology

Background

The worldwide epidemiology of childhood Type 1 diabetes (T1D) was extensively described in the 6th edition of the International Diabetes Federation (IDF) [1]. Data were retrieved in approximately 45% of the countries [1-4]. In contrast, we are unaware of a similar review on the worldwide epidemiology of adult T1D diabetes, although T1D is known to occur even late in adults [5-7]. A major limitation of the epidemiology of T1D in adults is certainly the difficulty there is to distinguish it from Type 2 diabetes (T2D) requiring insulin treatment or from Latent Autoimmune Diabetes in Adults (LADA), when specific markers of autoimmunity are not searched.

Here, our primary objective was to describe – through a systematic review of the literature – the available published information on adult T1D incidence, and the diagnostic criteria used for case definition. A secondary

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objective was to study how the variations of T1D incidence in adults mirrored those in children.

Methods

Literature review

A systematic review was conducted according to the PRISMA recommendations to retrieve original papers published in English, French and Spanish up to November 6th, 2014, in peer-reviewed journals reporting the incidence of T1D among individuals aged more than 15 years, in population-based studies (*i.e.* collected in a defined geographic area [8]) and reporting the diagnostic criteria used to define T1D.

The databases used for the literature search were Medline (PubMed), Google Scholar and Thomson Reuters (Web of Knowledge). The protocol of the search was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and is available on http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369 (Registration number: 2012:CRD42012002369). Figure 1 presents the flow diagram of the bibliographic search, Additional file 1 for the full electronic search strategy, and Additional file 2 for the PRISMA checklist.

Data collection

For each study, the following information was extracted:

- the identification of the study: authors, title, journal, publication year,
- the period and country of study. The country was categorized by its World Health Organization (WHO) region and economic level: high-income (HIGH) or low- and middle-income (LMIC) [9],

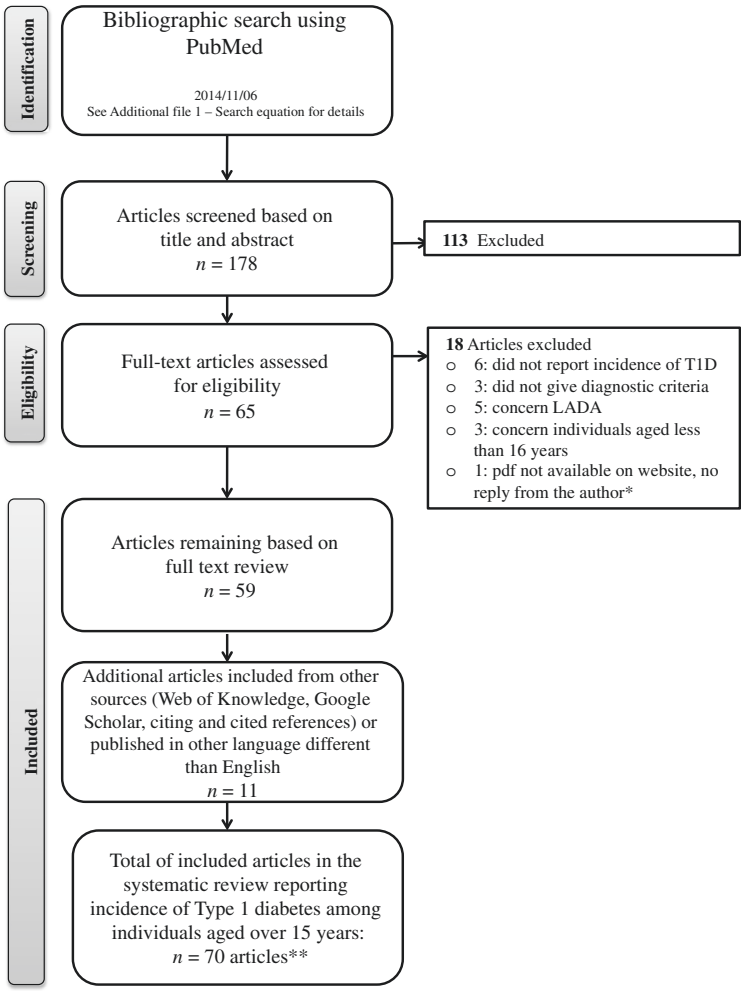

Figure 1 PRISMA Flow diagram bibliographic search strategies. * Kumar P, et al. Indian Med Assoc. 2008;106(11):708–711. ** The article: Radosevic B, et al. Pediatr Diabetes. 2013;14(4):273–4 gives information from two countries: 1) Bosnia and Herzegovina: Republic of Srpska and 2) Slovenia, Nationwide.

- the geographic coverage of the study: nationwide (when the study was performed in the entire nation) and local (when it was restricted to a given region, city, or a geographically defined population),
- the diagnostic criteria used to define T1D in adults: detection of autoantibodies against beta-cells (such as: islet cell antibody (ICA), insulin autoantibody (IAA), islet antigen-2 autoantibody (IA-2), anti-glutamic acid decarboxylase antibodies (GAD)), measurement of the fasting C-peptide level [7], need for permanent insulin therapy, time when the administration of insulin therapy was started, and clinical signals of T1D diabetes such as ketosis, ketonuria and weight loss,
- the sources of data/registers reporting T1D incidence in the studies, defined according to LaPorte et al. [10] as: *primary* source of information: a "well-established system of standardized registries for identifying new cases", for example national or regional registers, *secondary* source of information: other different sources of cases "that would provide a check on the degree of ascertainment", for example medical records or hospital discharges, and *tertiary* source of information: a third approach for identifying cases, for example, through surveillance system or death certificates,
- the reported percentage of completeness/ascertainment between sources of information reporting incidence [10],
- the incidence rates reported in the text, tables or graph (expressed as new cases per 100.000 persons/year) by sex and age classes,
- additional information such as those concerning rural/urban, or ethnic differences.

Data analyses

The country distribution of the T1D incidence information and the analysis of the diagnostic criteria used were performed on the entire set of articles retrieved. For the few papers for which the results were presented by ethnic origin, we estimated the mean value of the incidence for the given period in the countries/regions concerned.

Correlation between adult and children T1D incidences

In the geographical correlation analyses between children and adult incidences, we considered for each country the more recent nationwide study published, or if not available, the last published set of local studies retrieved from a given area in the country; in addition, we included all published papers reporting autoantibodies against beta-cells or C-peptide. To obtain an estimate of the incidence of T1D in children in the countries for which the adult incidence was available, we used the data provided by the same adult paper, when available. The incidence of T1D in children was not available in 9 of these papers included in the geographical correlation analyses. In this case, it was estimated through a separate systematic review focused on the corresponding countries and periods (see Additional file 3).

Statistics

Data were extracted from graphs using GraphClick [11].

The country-to-country co-variation of children and adult incidences was quantified by the Spearman correlation and a linear regression.

The R software (version 3.0.1) was used for statistical and graphic analyses [12].

Results

Description of the information obtained from the systematic review on adult T1D

Seventy articles reporting incidence of T1D in young adults and adults aged over than 15 years concerned one country, and one article concerning two countries were retrieved in this systematic review, resulting in a total of 71 studies covering 35 countries (Table 1). Twenty-four of the 71 studies were nationwide; 43 papers provided information on the T1D incidence in the age class 15–29 years, 26 in the age class 30–59 years, and 6 in the persons aged >60 years.

A *primary* source of information was reported in 99% (70 of 71) of the studies: among these reported sources, 60% (42 of 70) were from medical/hospital records, 36% (25 of 70) from national or regional registers, and 4% (3 of 70) from other sources, such as community-based surveys; a *secondary* source of information was reported in 90% (64 of 71) of the studies: among these reported sources, 58% (37 of 64) were from medical/hospital records, 16% (10 of 64) from associations of patients, 14% (9 of 64) from drug or supplies prescription registers, 8% (5 of 64) from national or regional registers, and 5% (3 of 64) from death certificates and schools registers; finally, a *tertiary* source of information was reported in 21% (15 of 71) of the studies: among these reported sources, 27% (4 of 15) were from national or regional registers, 27% (4 of 15) from associations of patients, 20% (3 of 15) from death certificates, 20% (3 of 15) from drug or supplies prescription registers, and 7% (1 of 15) from medical registers; see details in Table 1. Percentage of ascertainment (completeness) between sources of information was evaluated in 53 of 71 (75%) studies. The mean percentage of ascertainment of these 53 studies was 94% (Table 1).

In the group of young adults (15–19), the lowest incidence of T1D was reported in Mauritius, (1.1/100.000 persons/year) [13], and the highest in Estonia (39.9/100.000 persons/year) [19]. In the 70–79 year age group, the lowest incidence was reported in Navarra, Spain

Table 1 Systematic review of T1D in adults, diagnostic criteria and sources of information

Study information					T1D diagnosis criteria in adults and young adults						Source of information and validation of ascertainment between sources			
Country, area reported in the article	**First author, publication year**	**Ref**	**Age range**	**Period**	**Detect. AA/ C-Peptide**	**Need of insulin therapy**	**Administration insulin therapy**	**Clinical impression**	**Ketosis/ ketonuria**	**Weight loss**	**Primary**	**Secondary**	**Tertiary**	**% of ascertainment**
African Region, LMIC														
Mauritius: NW	Tuomileht J., 1993†	[13]	0-19	1986-1990	No	Yes	From diagnosis	Yes	NA	NA	Medical reports	Medical statistics	NA	95.0
United Republic of Tanzania: Dar es Salaam	Swai A. B., 1993†	[14]	0-19	1982-1991	No	Yes	From diagnosis	Yes	NA	NA	Medical reports	Hospital records	NA	NA
Eastern Mediterranean Region, LMIC														
Iran (Islamic Republic of): Fars	**Pishdad G. R., 2005†**	[15]	0-29	1990-1994	**Yes (a)**	Yes	From diagnosis	Yes	Yes	Yes	Medical reports from endocrinologists	Medical records	NA	100
Libyan Arab Jamahiriya: Benghazi	Kadiki O. A., 1996†	[16]	0-34	1981-1990	No	Yes	From diagnosis	NA	Yes	NA	National Diabetes Program	Hospital registers	NA	95.0
Tunisia: Beja, Monastir, Gafsa	Ben Khalifa F., 1998†	[17]	0-19	1990-1994	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	School health centers	NA	96.0
European Region, LMIC														
Croatia: Zagreb	Roglic G., 1995†	[18]	0- > 55	1988-1992	No	Yes	Within 1 week of diagnosis	Yes	Yes	NA	National Diabetes Program	Death certificates	Diabetes association	96.2
Estonia: NW	Kalits I., 1990†	[19]	0- > 50	1988-1988	No	Yes	From diagnosis	Yes	Yes	Yes	NA	NA	NA	NA
Lithuania: NW	Ostrauskas R., 2011†	[20]	15-34	1991-2008	No	Yes	Within 2 weeks of diagnosis	Yes	Yes	Yes	National Diabetes Program	Regional endocrinologist	Notes of patient insurance	86.8
Lithuania: NW	Pundziute-Lycka A., 2003	[21]	0-39	1991-2000	No	Yes	Within 2 weeks of diagnosis	Yes	Yes	NA	National Diabetes Program	Pediatrician and endocrinologist reports	Death certificates	91.2
Lithuania: NW	Ostrauskas R., 2000	[22]	15-39	1991-1997	No	Yes	Within 2 weeks of diagnosis	Yes	Yes	NA	National Diabetes Program	Pediatrician and endocrinologist reports	Death certificates	91.2
Poland: Bialystok	Kretowski A., 2001†	[23]	0-29	1994-1998	No	Yes	From diagnosis	Yes	Yes	Yes	Pediatric and Internal medicine records	Hospital discharge registers	NA	98.5
Poland: Province of Rzeszow	Sobel-Maruniak A., 2006†	[24]	0-29	1980-1999	No	Yes	From diagnosis	Yes	NA	NA	Pediatric and Internal medicine records	Others health care registers	NA	99.0
Poland: Province of Rzeszow	Grzywa M. A., 1995	[25]	0-29	1980-1992	No	Yes	From diagnosis	Yes	NA	NA	Pediatric and Internal medicine records	Others health care registers	NA	99.0

Table 1 Systematic review of T1D in adults, diagnostic criteria and sources of information *(Continued)*

Poland: Warsaw	Wysock M. J., 1992†	[26]	0-29	1983-1988	No	Yes	From diagnosis	Yes	NA	NA	Medical records from diabetic clinics	General practitioners and diabetologist registers	Death certificates	NA
Romania: Bucharest	Ionescu-Tirgoviste C., 1994†	[27]	0- ≥ 85	1981-1991	No	Yes	From diagnosis	Yes	Yes	NA	Bucharest Diabetes Registry	NA	NA	NA
Slovakia: NW	Kyvik K O, 2004†	[28]	15-29	1996-1997	No	Yes	From diagnosis	Yes	NA	NA	Pediatrician and endocrinologist reports	Other health care registers	NA	80.0
European Region, HIGH														
Austria: Upper	Rami B., 2001†	[29]	0-29	1994-1996	No	Yes	From diagnosis	Yes	NA	NA	Pediatricians and endocrinologists reports	Austrian Diabetes Association	NA	87.0
Belgium: Antwerp	**Weets I., 2007†**	[30]	0-39	1989-2003	**Yes**	Yes	From diagnosis	Yes	NA	NA	Pediatricians and endocrinologists reports	General practitioners and diabetes nurses reports	Diabetes associations and self-reporting	97.0
Belgium: Antwerp	**Weets I., 2002†**	[31]	0-39	1989-2000	**Yes**	Yes	From diagnosis	NA	NA	NA	Pediatrician and endocrinologist reports	General practitioner and diabetes nurse reports	Diabetes associations and self-reporting	93
Belgium: Antwerp	**Vandewalle C., 1997†**	[32]	0-39	1989-1995	**Yes**	Yes	From diagnosis	Yes	Yes	Yes	Pediatrician and endocrinologist reports	General practitioner and diabetes nurse reports	Diabetes associations and self-reporting	85
Bosnia and Herzegovina: Republic of Srpska	Radosevic B., 2013†	[33]	0-18	1998-2010	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	Insulin prescription registers	NA	100
Denmark: Copenhagen and Frederiksborg	**Molbak A. G., 1994†**	[34]	30-95	1973-1977	**Yes (b)**	Yes	From diagnosis	Yes	Yes	Yes	Hospital discharges	General practitioners and diabetologist registers and death certificates	Missing coding of T1D diagnosis in hospital admissions	99.0
Finland: NW	**Lammi N., 2007†**	[35]	15-39	1992-1996	**Yes**	Yes	From diagnosis	Yes	NA	NA	National Diabetes Program	Hospital discharge registers	Drug reimbursement registers	88.0
France: Aquitaine, Lorraine, Basse Normandie, Haute Normandie	Charkaluk M. L, 2002†	[36]	0-19	1988-1997	No	Yes	None declared	NA	NA	NA	Prospective registers	French Social Security registers	NA	96.0

Table 1 Systematic review of T1D in adults, diagnostic criteria and sources of information *(Continued)*

France: Aquitaine, Lorraine, Basse Normandie, Haute Normandie	Levy-Marchal, C., 1998	[37]	0-19	1988-1995	No	Yes	None declared	NA	NA	NA	Prospective registers	French Social Security registers	NA	96.0
Israel: NW	Blumenfeld O., 2014†	[38]	0-17	1997-2010	No	Yes	From diagnosis	Yes	NA	NA	Israel juvenile diabetes register	Israel Center for Disease Control	NA	NA
Israel: NW	Sella T., 2011	[39]	0-17	2000-2008	No	Yes	None declared	Yes	NA	NA	Israel juvenile diabetes register	Israel Center for Disease Control	NA	NA
Israel: NW	Koton S., 2007	[40]	0-17	1997-2003	No	Yes	From diagnosis	Yes	NA	NA	Israel juvenile diabetes register	NA	NA	NA
Italy: Lombardie	Garancini, P., 1991†	[41]	0-34	1981-1982	No	Yes	None declared	NA	NA	NA	Hospital discharge records	Hospital admission records	NA	85.7
Italy: Pavia	Tenconi M. T., 1995†	[42]	0-29	1988-1992	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	Drug registers	NA	100
Italy: Sardinia	Muntoni S, 1992†	[43]	0-29	1989-1990	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	Diabetes association	NA	92.8
Italy: Sardinia (Oristano)	Frongia O., 1997†	[44]	0-29	1993-1996	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	Drug registers	NA	100
Italy: Turin	**Bruno G., 2009†**	[45]	15-29	2000-2004	**Yes**	Yes	Within 6 months of diagnosis	NA	NA	NA	Hospital records	Drug registers	NA	NA
Italy: Turin	**Bruno G., 2005†**	[46]	30-49	1999-2001	**Yes**	Yes	Within 6 months of diagnosis	NA	Yes	NA	Diabetes clinics	Drug registers	NA	99.0
Italy: Turin	Bruno G., 1993	[47]	0-29	1984-1988	No	Yes	From diagnosis	NA	Yes	NA	Diabetic clinics records	Hospital discharge records	NA	97.0
Luxembourg: NW	De Beaufort C. E., 1988†	[48]	0-19	1977-1986	No	Yes	None declared	NA	NA	NA	Pediatric and Internal medicine records	Dutch Diabetes Association	NA	100
Malta: NW	Schranz A. G., 1989†	[49]	0-24	1980-1987	No	Yes	Within 3 moths of diagnosis	Yes	Yes	Yes	Medical reports	Diabetic clinic records	NA	NA
Netherlands: NW	Ruwaard D., 1994†	[50]	0-19	1988-1990	No	Yes	None declared	NA	NA	NA	Pediatric and Internal medicine records	NA	NA	81.0
Norway: NW	Joner G., 1991†	[51]	15-29	1978-1982	No	Yes	From diagnosis	NA	NA	NA	Pediatricians and endocrinologists reports	Hospital records	NA	90.0
Slovenia: NW	Radosevic B., 2013†	[33]	0-18	1998-2010	No	Yes	From diagnosis	Yes	NA	NA	Slovenian National Registry of Childhood diabetes	Insulin prescription registers	NA	100
Spain: Badajoz	Morales-Perez F. M., 2000†	[52]	0-29	1992-1996	No	Yes	From diagnosis	Yes	Yes	NA	Pediatricians and endocrinologists reports	Diabetic clinic records	NA	95.0

Table 1 Systematic review of T1D in adults, diagnostic criteria and sources of information *(Continued)*

Spain: Canarias Islands	Carrillo Dominguez, A., 2000†	[53]	0-30	1995-1996	No	Yes	None declared	Yes	NA	Yes	Hospital records and Endocrinologist reports	Diabetes association reports and sales on blood glucose monitors	NA	90.1
Spain: Catalonia	**Abellana R., 2009†**	[54]	0-29	1989-1998	**Yes (c)**	Yes	From diagnosis	Yes	Yes	NA	Catalan Registry of Type 1 Diabetes	Summer camps, associations, and prescription data	NA	90.0
Spain: Catalonia	Goday A., 1992	[55]	0-29	1987-1990	No	Yes	From diagnosis	Yes	NA	NA	Catalan Registry of Type 1 Diabetes	Summer camps, patient associations, and prescription data	NA	90.1
Spain: Navarra	**Forga L., 2014†**	[56]	0- > 45	2009-2012	**Yes**	Yes	Within 6 months of diagnosis	Yes	Yes	NA	Hospital records	Electronic medical records, diabetes associations	NA	98.4
Spain: Navarra	**Forga L., 2013†**	[57]	0-79	2009-2011	**Yes**	Yes	Within 6 months of diagnosis	Yes	Yes	NA	Hospital records	Electronic medical records, diabetes associations	NA	98.4
Sweden: NW	Dahlquist G. G., 2011†	[58]	0-34	1983-2007	No	Yes	From diagnosis	Yes	Yes	Yes	National Diabetes Program	Pediatricians and endocrinologist reports	NA	96.0
Sweden: NW	Östman J., 2008	[59]	15-34	1983-2002	No	Yes	From diagnosis	Yes	NA	NA	National Diabetes Program	Pediatrician and endocrinologist reports	Computer-based patient administrative register	82
Sweden: NW	Pundziute-Lycka A., 2002	[60]	0-34	1983-1998	No	Yes	From diagnosis	Yes	Yes	Yes	National Diabetes Program	Pediatrician and endocrinologist reports	Computer-based patient administrative register	91.2
Sweden: NW	Nyström L., 1992	[61]	0-34	1983-1987	No	Yes	None declared	NA	NA	NA	National Diabetes Program	Hospital admission and discharge registers	NA	89
Sweden: NW	Blohme G., 1992	[62]	15-34	1983-1987	No	Yes	From diagnosis	Yes	Yes	Yes	National Diabetes Program	Hospital admission and discharge registers	NA	NA
Sweden: Kronoberg	**Thunander M., 2008†**	[63]	0-100	1998-2001	**Yes**	Yes	Within 4 weeks of diagnosis	Yes	Yes	NA	Opportunistic screening of all adult patients in contact with the medical care system	Departments of ophthalmology	NA	98.0
United Kingdom: NW	Imkampe A. K., 2011†	[64]	0-34	1991-2008	No	Yes	Within 3 moths of diagnosis	Yes	NA	NA	National Diabetes Program	Pediatricians and endocrinologist reports	NA	NA
United Kingdom: Oxford region	Bingley P. J., 1989	[65]	0-21	1985-1986	No	Yes	From diagnosis	Yes	NA	NA	Medical reports from general practioners and pediatricians	Regional hospital records	NA	95.0

Table 1 Systematic review of T1D in adults, diagnostic criteria and sources of information *(Continued)*

Region of the Americas, LMIC														
Barbados: NW	Jordan O. W., 1994[†]	[66]	0-29	1982-1991	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	Others health care registers	NA	94.0
Region of the Americas, HIGH														
Canada: Quebec	Legault L., 2006[†]	[67]	0-18	2000	No	Yes	None declared	NA	NA	NA	Departmental program: Régie des Rentes du Québec program	NA	NA	NA
United States of America: Alabama (Jefferson County)	Wagenknecht L. E., 1991[†]	[68]	0-19	1979-1988	No	Yes	None declared	NA	NA	NA	Hospital records	Summer camps, patient associations, and prescription data	NA	NA
United States of America: Alabama (Jefferson County)	Wagenknecht L. E.,1989	[69]	0-19	1979-1985	No	Yes	From diagnosis	Yes	NA	NA	Hospital records	Association registers	NA	95.0
United States of America: Colorado	Vehik K., 2007[†]	[70]	0-17	2000-2004	No	Yes	Within 2 weeks of diagnosis	Yes	NA	NA	Pediatricians and endocrinologists reports	Other health care registers	The SEARCH Study	96.5
United States of America: Colorado	Kostraba J. N., 1992	[71]	0-17	1978-1988	No	Yes	Within 2 weeks of diagnosis	Yes	NA	NA	Pediatricians and endocrinologists reports	Hospital registers	NA	93.3
United States of America: Pennsylvania (Allegheny)	Libman I. M., 1998[†]	[72]	0-19	1990-1994	No	Yes	From diagnosis	Yes	NA	NA	Medical reports	General practitioners and diabetes nurses reports	NA	97.7
United States of America: Rhode Island	Fishbein H. A., 1982[†]	[73]	0-29	1979-1980	No	Yes	None declared	NA	NA	NA	Medical reports	Insulin prescription registers	NA	NA
United States of America: five areas [§]	**Bell R., 2009[†]**	[74]	0-19	2002-2005	**Yes**	Yes	From diagnosis	Yes	NA	NA	Medical reports	Other health care registers	The SEARCH Study	NA
United States of America: Wisconsin	Allen C., 1986[†]	[75]	0-29	1970-1979	No	Yes	From diagnosis	Yes	NA	NA	Hospital discharges	Pediatricians and endocrinologist reports	NA	90.0
United States of America: The United States Navy	Gorham C., 1993	[76]	17-34	1974-1988	No	NA*	None declared	Yes	NA	NA	Hospital discharges	NA	NA	NA
Western Pacific Region, HIGH														
Australia: New South Wales	Tran F., 2014[†]	[77]	10-18	2001-2008	No	Yes	NA	Yes	NA	Yes	Endocrine group diabetes register	National diabetes register	NA	96.0

Table 1 Systematic review of T1D in adults, diagnostic criteria and sources of information *(Continued)*

Australia: Sydney (Southern Metropolitan Health Region)	Sutton L., 1989[†]	[78]	0-19	1984-1987	No	Yes	From diagnosis	Yes	NA	NA	Medical reports from general practioners and pediatricians	Schools in the area	Syringe register	NA
Japan: Osaka	Sasaki A., 1992[†]	[79]	0-18	1978-1988	No	Yes	None declared	Yes	Yes	NA	Medical benefits system	NA	NA	NA
New Zealand: Canterbury	Scott, R. S., 1991[†]	[80]	0- ≥ 80	1981-1986	No	Yes	Within 1 year of diagnosis	Yes	NA	Yes	Community-based surveys administrated in pharmacies where diabetic patients acquired their insulin supplies	Hospital admission and discharge registers and diabetologist	NA	95.0
Other Regions currently non WHO														
Taiwan: NW	**Lin W.-H., 2013[†]**	[81]	0- ≥ 60	1999-2010	**Yes**	Yes	None declared	Yes	Yes	NA	National Health Insure register and Illness certificates	Random sample of a database used to reimbursements	NA	98.3
US Virgin Islands: NW	Washington R. E., 2013[†]	[82]	0-19	2001-2010	No	Yes	From diagnosis	Yes	Yes	Yes	Medical reports	Medical providers	NA	98.7

WHO Member States are divided into high-income (HIGH) or low- and middle-income (LMIC) states [30]. AA: autoantibodies, NW: Nation-wide study, NA: Unavailable data. (a) When there were diagnostic doubts, (b) Only for patients aged over 40 years at onset, (c) Not performed in all cases; the author of this study was contacted to confirm the proportion of these cases, but by the time of submission of this paper no answer was available. T1D: Type 1 Diabetes. Highlighted: reports of the systematic review using the autoantibodies/C-peptide as diagnosis criteria. ([†]) Studies used in the statistical analyses. (*) Data were not available but researchers assumed that patients have had T1D based on their average of age. ([§]) Ohio (8 counties), Washington State (5 counties), South Carolina, Colorado, California.

(0.8/100.000 persons/year) [57] and the highest in Kronoberg, Sweden (55/100.000 persons /year) [63]. The details of all retrieved incidence by study and age classes are in Additional file 4: Table S1.

Diagnostic criteria used to define T1D in adults reported in 71 epidemiological studies

Autoantibodies against beta-cell antigens or the C-peptide were included in the T1D diagnostic criteria in 14 studies [15,30-32,34,35,45,46,54,56,57,63,74,81], detection of ICAs was reported in 9 studies [15,30-32,34,45,46,54,63], IAA in 4 studies [30-32,54], IA2 in 5 studies [30-32,56,57], and GAD in 11 studies [30-32,35,45,46,56,57,63,74,81]. The C-peptide was measured in 7 studies. In one paper difference of auto-antibodies by age group (0–19) was explored but no significant differences were detected [74]. The other reported diagnostic criteria for T1D were the need for insulin therapy (reported in 70 of 71 studies), clinical symptoms of diabetes (reported in 56 of 71 studies), low or normal body weight (14 of 71 studies), and ketosis or ketonuria (26 of 71 studies). The details are shown in Table 1.

Comparison of adult and children T1D incidences

The variations of incidence of T1D in adults with country and age were studied in each area for which we retrieved information on a geographically defined population. This concerned 35 countries.

Variation of T1D incidence with age in adults

In 23 out of 35 (66%) countries (55 of 71 studies), the incidence of T1D was higher in the age range of 0–14 compared with 15–19 years. When restricted to the 14 reports for which the criteria of diagnosis of T1D were auto-antibodies against beta-cells or C-peptide detection, the variation of adult incidence with age showed a consistent decrease after the age of 14 years (Figure 2 and Additional file 4: Table S1).

Geographical correlation of adult and child T1D incidence

A significant geographical correlation, as measured by the Spearman correlation coefficient, was found between adult T1D incidence and 0–14 incidence in the age classes 15–19 years, 20–24 years, 25–29 years, 30–34 years

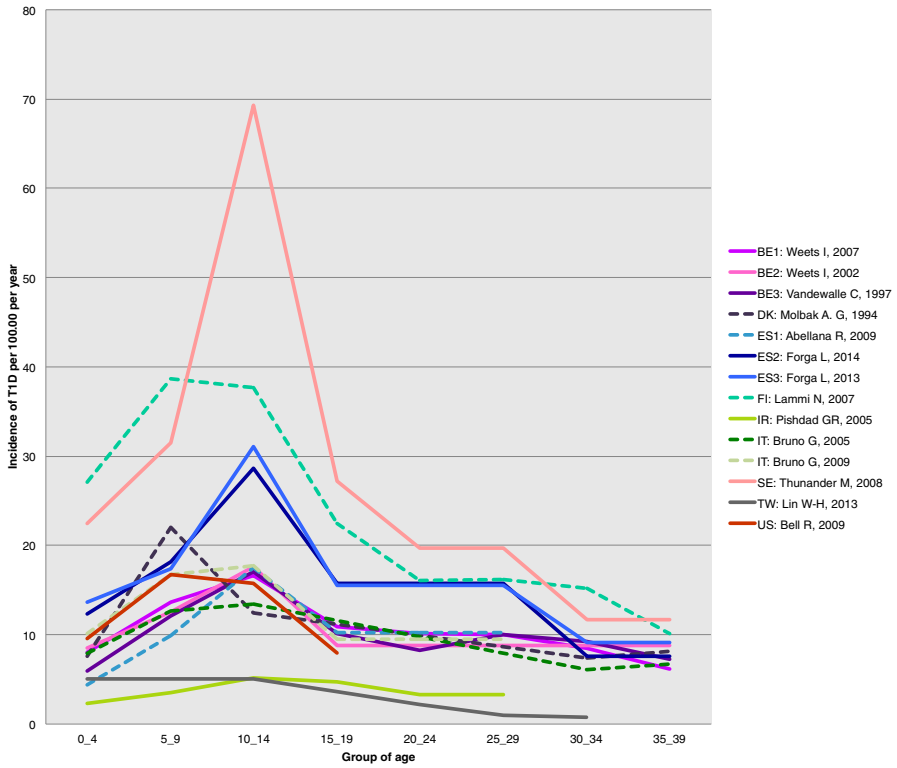

Figure 2 Age variation of incidence from childhood to adult age. On this figure, the adult estimates of incidence were taken from the 14 reports of the systematic review using the autoantibodies/C-peptide as diagnostic criteria. Full lines correspond to articles from which both child as well as adult information could be retrieved. The dotted lines are those for which the child information was searched in the same country as in the adult paper, but was from a different paper (see Additional file 3 for details on this literature search). The corresponding countries are shown as: BE1: Belgium (2007) [30]; BE2: Belgium (2002) [31]; BE3: Belgium (1997) [32]; DK: Denmark [34]; ES1: Spain, Catalonia [54]; ES2: Spain, Navarra (2014) [56]; ES3: Spain, Navarra (2013) [57]; FI: Finland [35]; IR: Iran (Islamic Republic of) [15]; IT: Italy [45,46]; SE: Sweden [63], TW: Taiwan [81]; US: United States of America [74].

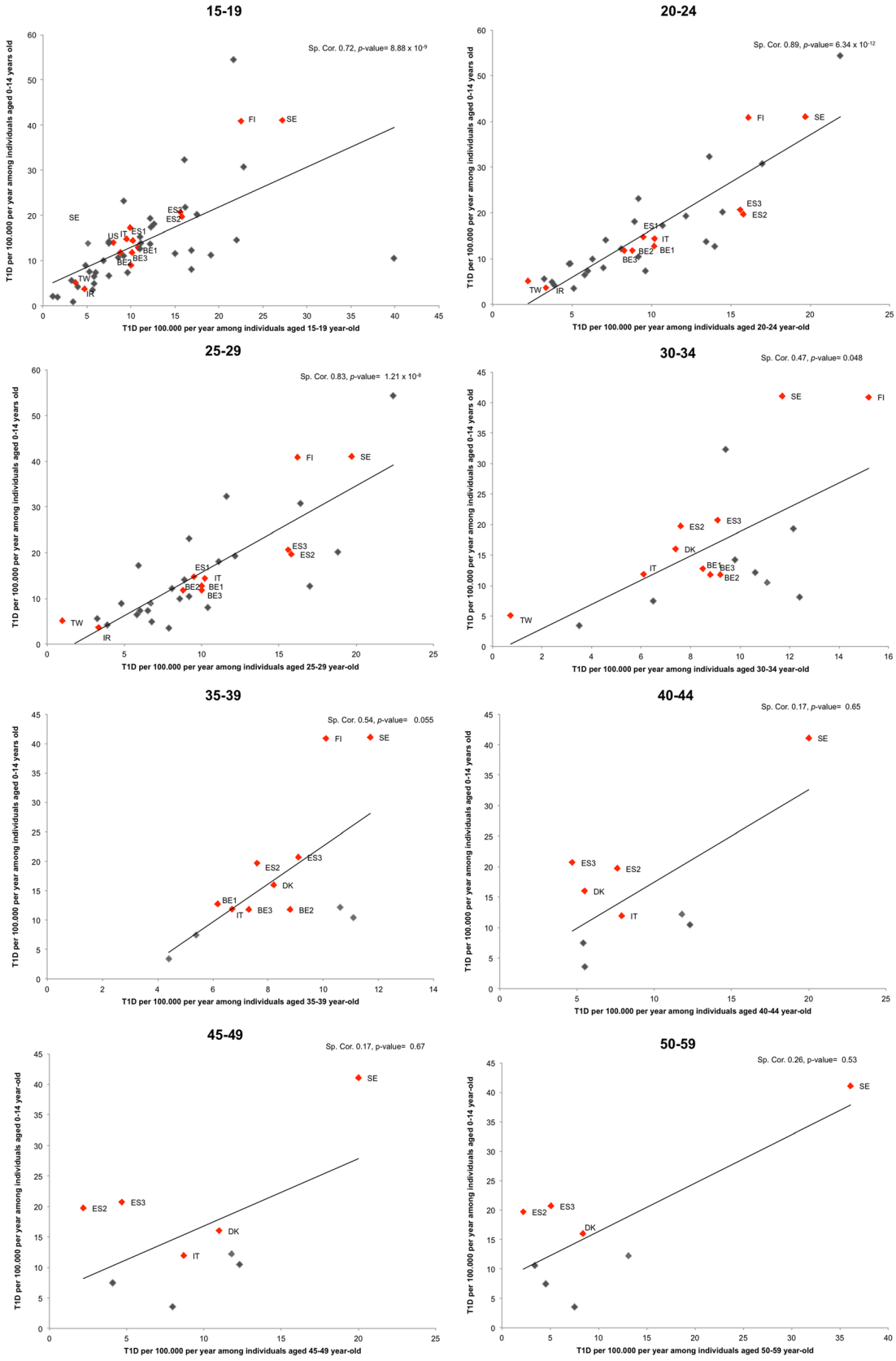

Figure 3 (See legend on next page.)

(See figure on previous page.)
Figure 3 Geographical correlation of T1D incidence between individuals aged 0–14 years and adults. Studies using autoantibodies/C-Peptide for T1D case definition are identified by Red diamonds. The corresponding countries are shown as: BE1: Belgium (2007) [30]; BE2: Belgium (2002) [31]; BE3: Belgium (1997) [32]; DK: Denmark [34]; ES1: Spain, Catalonia [54]; ES2: Spain, Navarra (2014) [56]; ES3: Spain, Navarra (2013) [57]; FI: Finland [35]; IR: Iran (Islamic Republic of) [15]; IT: Italy [45,46]; SE: Sweden [63], TW: Taiwan [81]; US: United States of America [74]. Sp. Cor: Spearman correlation.

and overall in the entire 15–60 group ($r = 0.75$, p-value: 5.7×10^{-10}). The correlation was not significant in the oldest class where sparse data were available, but the relation was similar (Figure 3).

Comparison of male and female T1D adult incidences

T1D incidence was larger in males aged 15 to 39 years than in females in 44 (81%) of the 54 studies reporting incidence by sex (Additional file 5: Table S2). The mean male-to-female ratio in our review was 1.47 (95% CI for mean 1.33-1.60, SD = 0.49, $n = 54$, $p = < 0.0001$).

Discussion

A first result of this systematic review is the paucity of data available on adult incidence of T1D as compared to those concerning children. The 71 studies retrieved provided information on adult T1D in only 35 countries, 40% of the 88 countries with primary childhood T1D incidence information in the 6th IDF atlas [1].

A second result is that only a small proportion ($n = 14$) of the 71 studies used detection of specific autoantibodies and/or dosage of C-peptide [83] as diagnostic criteria of adult T1D.

A third result was that in a majority of the retrieved studies, adult T1D incidence was greater in men than in women, which contrasts with incidence of T1D in children where sex ratio is around one [2,84]. Using comparative data, Karvonen et al. also described a male excess among young adults in the 15–39 years of age [85]. Sex differences in exposure to possible environmental triggers of T1D, in hormonal/genetic susceptibility, in lifestyle have been proposed as possible explanations for this difference [62].

A last striking observation of the current analysis is the strong geographical correlation of the incidences in adults and children. This correlation may be explained by the fact that adults with T1D share the gene alleles known to be associated to incidence of T1D in children, [86,87], and/or some predisposing environmental causes [4]. For example, in a previous study on incidence of T1D in children, a significant positive correlation was detected between the percentage of urban population and the incidence of T1D in children ($r = 0.41$ p-value: < 0.0001) [4]; in this review a significantly higher urban proportion of T1D incidence among adults was found in 4 of the 7 studies reporting differences between rural *vs* urban areas [15,21,42,75].

There was an overall decrease of incidence with age in adults and young adults after the age of 14. A second peak of T1D around the age of 50, as described by Krolewski et al. [88], was only reported in 7% (4 of 58) of the studies [18,63,80,89].

The paucity of data made it impossible to document an increase in adult T1D incidence that would parallel the dramatic increase observed in children [2,3,90]. Indeed, successive studies in the same region over different periods reporting incidence in people aged >30 years of age were only found for Belgium [30-32], Lithuania [20-22] and Sweden [58-62]. Similarly, this review did not dispose of sufficient data to document differences in the clinical presentation of T1D of adults and children as suggested elsewhere [32,40]; indeed only two of the 71 studies describe differences in clinical presentation of T1D between adults and children [89,91].

Improving the quantity and quality of information on adult T1D is not only useful to better understand the epidemiology and natural history of T1D, but can have practical consequences, as delay of T1D diagnosis may mean retardation in insulin treatment, lost opportunities for potential prevention of acute and chronic complications, and even death [92]: in Croatia [18], 14% of the incident cases were identified solely through death certificates, and high mortality was found in the newly-diagnosed T1D aged over 50.

Conclusions

Overall, the results of this systematic review should encourage the launching of epidemiological studies of adult T1D with specific diagnostic criteria.

Availability of supporting data

All the supporting data are included as additional files.

Additional files

Additional file 1: Search equation used for the bibliographic analysis.

Additional file 2: PRISMA checklist.

Additional file 3: List of selected papers reporting incidence of T1D in 0–14 year-olds in 9 countries.

Additional file 4: Table S1. Geographic repartition, and reported adult T1D incidences found in the systematic review. Incidence was per 100.000 persons per year. T1D: Type 1 Diabetes. NW: Nation-wide study. HIGH, LMIC: High, Low-Medium Income Level. Highlighted: reports of the systematic review using the autoantibodies/C-peptide as diagnosis

criteria. (a) 0–9 years of age, (b) 10–19 years of age, (c) 10–18 years of age, (d) 15–17 years of age, (e) 15–18 years of age, (–––): unavailable data. (*): Data was retrieved from a different study; for details see Additional file 3. (†) Studies used in the geographical correlation analyses. (‡) Special population. (§) The five areas were Ohio (8 counties), Washington State (5 counties), South Carolina, Colorado and California; the table presents the mean incidence calculated, retrieved from 5 populations: African American, Asian Pacific Islander, Navajo, Hispanic and non-Hispanic young.

Additional file 5: Table S2. T1D incidences by sex in young adults and adults found in the Systematic Review. Male-to-Female ratios >1 are highlighted. Ref: Reference. First author and publication year in reports of the systematic review using the autoantibodies/C-peptide as diagnosis criteria are highlighted. Inc: incidence per 100.000 persons per year. NW: Nation-wide study. HIGH, LMIC: High, Low-Medium Income Level. (†) Studies used for analyses. (§) The five areas were Ohio (8 counties), Washington State (5 counties), South Carolina, Colorado and California; the table presents the mean incidence calculated retrieved from 5 populations: African American, Asian Pacific Islander, Navajo, Hispanic and non-Hispanic young. Incidence was calculated as the mean of retrieved information: (a) in Jews and other non-Arabs and Arabs; (b) in White and Black populations; (c) in Non-Hispanic Whites and Hispanic Whites. (d) Study giving the total incidence by sex, not by age classes.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PAD-V conducted the data collection and analyses. PAD-V, PB and AJV, contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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4.1.1 Supporting Information

4.1.1.1 Search equation used for the bibliographic analysis of incidence of T1D in adults

We used the following equation to search the electronic database Medline on November 6th 2014:

"diabetes mellitus, type 1/epidemiology"[MAJR] AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND (adult[TIAB] OR adult[MeSH Terms]) AND "humans"[MeSH Terms]) AND (Journal Article[PT] NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Vascular Diseases" [MeSH Terms] OR "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms]) ➔ AND **English**[Lang]: 178 Retrieved articles[4].

Note 1. The last terms of the equation (after "Diabetic Neuropathies" were added to focus the bibliographic search on incidence papers by removing all those dealing, for example, with the incidence of complications of T1D.

Note 2: Through a general search, we searched in other languages than English. We identified 115 articles published in French and 70 in Spanish, from which we assessed full text for eligibility of 7 papers published in French and 14 in Spanish. At the end, one paper in French and two in Spanish were included in the analysis.

[4] *Glossary for PubMed search*: [MAJR]: MeSH Major Topic, a MeSH term that is one of the main topics discussed in the article; [MeSH]: MeSH Terms, the National Library of Medicine's controlled vocabulary of biomedical terms that is used to describe the subject of each indexed journal article in MEDLINE; [SH]: MeSH Subheadings; it describes more completely a particular aspect of a subject; [TIAB]: Title/Abstract, the search include words and numbers included in the title, abstract, and other abstract of a citation; [PT]: Publication Type, it describes the type of material the article represents (e.g., Review, Clinical Trial, Retracted Publication, Letter).

4.1.1.2 CONSORT PRISMA checklist

SI Table 14: CONSORT PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	116
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	116-117
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	117
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	117
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	117, 118
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	117, 118
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	117, 118
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	118, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	119, Figure 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	119
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	119, Additional files 4 and 5

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	119
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	119
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Additional files 4 and 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	120
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	120, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Additional files 4 and 5, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	129
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	129
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	129
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	130

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

4.1.1.3 List of additional papers used in the child-adult correlations

SI Table 15: List of selected papers reporting incidence of T1D in 0-14 year-olds in 9 countries

This list was obtained through a separate review focused on 9 countries considered (1st column). These values were used in the child-adult correlations.

Country, Area reported in the article	First Author, publication year	Mean TID incidence group of age 0-14 years	Period of study	Ref.
Australia: New South Wales	Diamond, 2006	**14.5**	1990-1993	(318)
Slovakia: NW	Diamond, 2006	**8.90**	1990-1999	(318)
Denmark: Copenhagen and Frederiksborg	Eurodiab, 2000	**16.00**	1989-1994	(90)
Finland: NW	Diamond, 2006	**40.90**	1990-1999	(318)
Italy: Turin	Bruno G, 2009	**11.86**	1984-2004	(46)
Italy: Turin	Bruno G, 2009	**14.8**	2000-2004	(46)
Norway: NW	Joner G, 1989	**20.22**	1973-1982	(150)
Lithuania: NW	Patterson CC, 2012	**14.20**	2004-2008	(243)
United States: Wisconsin	Allen C, 1986	**18.10**	1970-1979	(13)

NW: Nation-wide

4.1.1.4 Geographic repartition, and reported adult T1D incidences found in the SR

SI Table 16: Geographic repartition, and reported adult T1D incidences found in the SR

Country, Area	First Author, publication year	Ref	Age range	Period	0-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-59	60-69	70-79	80
African Region, LMIC																
Mauritius: NW	Tuomilehto J., 1993 †	(332)	0-19	1986-1990	2.1	1.1	---	---	---	---	---	---	---	---	---	
United Republic of Tanzania: Dar es Salaam	Swai A. B., 1993 †	(311)	0-19	1982-1991	0.9	3.4	---	---	---	---	---	---	---	---	---	
Eastern Mediterranean Region, LMIC																
Iran (Islamic Republic of): Fars	Pishdad G. R., 2005 †	(248)	0-29	1990-1994	3.7	4.7	3.4	3.3	---	---	---	---	---	---	---	
Libyan Arab Jamahiriya: Benghazi	Kadiki O. A., 1996 †	(153)	0-34	1981-1990	8.1	16.9	7.0	10.4	12.4	---	---	---	---	---	---	
Tunisia: Beja, Monastir, Gafsa	Ben Khalifa F., 1998 †	(32)	0-19	1990-1994	6.7	7.5	---	---	---	---	---	---	---	---	---	
European Reion, LMIC																
Croatia: Zagreb	Roglic G., 1995 †	(268)	0->55	1988-1992	7.4	9.6	9.6	6.5	6.5	5.4	5.4	4.1	4.5	---	---	
Estonia: NW	Kalits I., 1990 †	(157)	0->50	1988-1988	10.5	39.9	9.2	9.2	11.1	11.1	12.3	12.3	3.4	---	---	
Lithuania: NW	Ostrauskas R., 2011 †	(235)	15-34	1991-2008	14.2*	7.4	7.1	8.9	9.8		---	---	---	---	---	
Lithuania: NW	Pundziute-Lycka A., 2003	(254)	0-39	1991-2000	8.4[(a)]	11.1[(b)]	7.8	7.8	7.8	7.8	---	---	---	---	---	
Lithuania: NW	Ostrauskas R., 2000	(234)	15-39	1991-1997	---	6.9	6.9	5.5	8.8	7.8	---	---	---	---	---	
Poland: Bialystok	Kretowski A., 2001 †	(172)	0-29	1994-1998	7.3	6.0	6.0	6.0	---	---	---	---	---	---	---	
Poland: Province of Rzeszow	Sobel-Maruniak A., 2006 †	(296)	0-29	1980-1999	6.4	5.8	5.8	5.8	---	---	---	---	---	---	---	
Poland: Province of Rzeszow	Grzywa M. A., 1995	(123)	0-29	1980-1992	5.4	6.0	5.0	5.7	---	---	---	---	---	---	---	
Poland: Warsaw	Wysocki M. J.,	(366)	0-29	1983-1988	4.87	5.25	3.75	6.75	---	---	---	---	---	---	---	

Country, Area	First Author, publication year	Ref	Age range	Period	0-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-59	60-69	70-79	80
	1992 †															
Romania: Bucharest	Ionescu-Tirgoviste C., 1994 †	(143)	0-≥85	1981-1991	3.5	5.6	5.1	7.9	3.5	4.4	5.5	8.0	7.5	9.2	8.6	
Slovakia: NW	Kyvik K. O., 2004 †	(176)	15-29	1996-1997	8.9*	4.8	4.8	4.8	---	---	---	---	---	---	---	
European Region, HIGH																
Austria: Upper	Rami B., 2001 †	(259)	0-29	1994-1996	9.0	10.0	4.9	6.7	---	---	---	---	---	---	---	
Belgium: Antwerp	Weets I., 2007 †	(353)	0-39	1989-2003	12.8	10.9	10.2	10.0	8.5	6.2	---	---	---	---	---	
Belgium: Antwerp	Weets I., 2002 †	(352)	0-39	1989-2000	11.8	8.8	8.8	8.8	8.8	8.8						
Belgium: Antwerp	Vandewalle C., 1997 †	(341)	0-39	1989-1995	11.8	10.1	8.3	10.0	9.20	7.3	---	---	---	---	---	
Bosnia and Herzegovina: Republic of Srpska	Radosevic B., 2013 †	(256)	0-18	1998-2010	13.8	5.1 [(e)]	---	---	---	---	---	---	---	---	---	
Denmark: Copenhagen and Frederiksborg	Molbak A. G., 1994 †	(215)	30-95	1973-1977	16.0*	---	---	---	7.4	8.2	5.5	11.0	8.4	10.4	11.2	
Finland: NW	Lammi N., 2007 †	(177)	15-39	1992-1996	40.9*	22.5	16.1	16.2	15.2	10.1	---	---	---	---	---	
France: Aquitaine, Lorraine, Basse Normandie, Haute Normandie	Charkaluk M. L., 2002 †	(59)	0-19	1988-1997	8.9	6.1	---	---	---	---	---	---	---	---	---	
France: Aquitaine, Lorraine, Basse Normandie, Haute Normandie	Levy-Marchal C., 1998	(187)	0-19	1988-1995	7.6	5.3	---	---	---	---	---	---	---	---	---	
Israel: NW	Blumenfeld O., 2014 †	(39)	0-17	1997-2010	11.1	9.2[(d)]	---	---	---	---	---	---	---	---	---	
Israel: NW	Sella T., 2011	(284)	0-17	2000-2008	13.3	11.1[(d)]	---	---	---	---	---	---	---	---	---	
Israel: NW	Koton S., 2007	(171)	0-17	1997-2003	9.2	8.8 [(d)]	---	---	---	---	---	---	---	---	---	
Italy: Lombardie	Garancini P., 1991 †	(108)	0-34	1981-1982	4.2	3.8	3.7	3.0	5.0	---	---	---	---	---	---	
Italy: Pavia	Tenconi M. T., 1995 †	(317)	0-29	1988-1992	10.0	6.9	6.3	8.6	---	---	---	---	---	---	---	
Italy: Sardinia (Oristano)	Frongia O., 1997 †	(102)	0-29	1993-1996	54.4	21.6	21.9	22.4	---	---	---	---	---	---	---	
Italy: Sardinia	Muntoni S., 1992 †	(220)	0-29	1989-1990	30.7	22.8	17.0	16.4	---	---	---	---	---	---	---	
Italy: Turin	Bruno G., 2009 †		15-29	2000-2004	14.8*	9.5	9.5	9.5	---	---	---	---	---	---	---	
Italy: Turin	Bruno G., 2005 †	(47)	30-49	1999-2001	11.9*	---	---	---	6.1	6.7	7.9	8.7	---	---	---	
Italy: Turin	Bruno G., 1993	(45)	0-29	1984-1988	8.2	6.9	5.9	4.6	---	---	---	---	---	---	---	
Luxembourg: NW	De Beaufort C. E.,	(75)	0-19	1977-1986	10.7	8.5	---	---	---	---	---	---	---	---	---	

Country, Area	First Author, publication year	Ref	Age range	Period	0-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-59	60-69	70-79	80
	1988 †															
Malta: NW	Schranz A. G., 1989 †	(280)	0-24	1980-1987	13.8	12.2	13.5	---	---	---	---	---	---	---	---	
Netherlands: NW	Ruwaard D., 1994 †	(271)	0-19	1988-1990	11.5	15.0	---	---	---	---	---	---	---	---	---	
Norway: NW	Joner G., 1991 †	(149)	15-29	1978-1982	20.2*	17.5	14.5	18.8	---	---	---	---	---	---	---	
Slovenia: NW	Radosevic B., 2013 †	(256)	0-18	1998-2010	13.8	7.5 [(e)]	---	---	---	---	---	---	---	---	---	
Spain: Badajoz	Morales-Perez F. M., 2000 †	(218)	0-29	1992-1996	17.2	9.9	10.7	5.9	---	---	---	---	---	---	---	
Spain: Canarias Islands	Carrillo Dominguez A., 2000 †	(55)	0-30	1995-1996	23.2	9.2	9.2	9.2	---	---	---	---	---	---	---	
Spain: Catalonia	Abellana R., 2009 †	(5)	0-29	1989-1998	14.4	10.2	10.2	10.2	---	---	---	---	---	---	---	
Spain: Catalonia	Goday A. 1992	(112)	0-29	1987-1990	11.5	11.4	11.3	8.5	---	---	---	---	---	---	---	
Spain: Navarra	Forga L., 2014 †	(98)	0->45	2009-2012	19.7	15.8	15.8	15.8	7.6	7.6	7.6	2.2	2.2	2.2	2.2	
Spain: Navarra	Forga L., 2013 †	(97)	0-79	2009-2011	20.7	15.6	15.6	15.6	9.1	9.1	4.7	4.7	5.1	0.5	0.7	
Sweden: NW	Dahlquist G. G., 2011 †	(74)	0-34	1983-2007	32.3	16.1	13.6	11.6	9.4	---	---	---	---	---	---	
Sweden: NW	Östman J., 2008	(233)	15-34	1983-2002	---	14.8	13.9	12.5	9.8	---	---	---	---	---	---	
Sweden: NW	Pundziute-Lycka A., 2002	(252)	0-34	1983-1998	28.0	15.2	13.2	12.1	9.9	---	---	---	---	---	---	
Sweden: NW	Nyström L., 1992	(229)	0-34	1983-1987	25.9	14.7	12.8	11.7	9.7	---	---	---	---	---	---	
Sweden: NW	Blohme G., 1992	(37)	15-34	1983-1987	---	14.8	12.7	11.7	9.8	---	---	---	---	---	---	
Sweden: Kronoberg	Thunander M., 2008 †	(320)	0-100	1998-2001	41.1	27.2	19.7	19.7	11.7	11.7	20.0	20.0	36.1	35.3	55.0	
United Kingdom: NW	Imkampe A. K., 2011 †	(141)	0-34	1991-2008	19.3	12.2	12.2	12.2	12.2	---	---	---	---	---	---	
United Kingdom: Oxford region	Bingley P. J., 1989	(35)	0-21	1985-1986	15.7	16.2	---	---	---	---	---	---	---	---	---	
Region of the Americas, LMIC																
Barbados: NW	Jordan O. W., 1994 †	(152)	0-29	1982-1991	5.6	3.3	3.3	3.3	---	---	---	---	---	---	---	
Region of the Americas, HIGH																
Canada: Quebec	Legault L., 2006 †	(184)	0-18	2000	15.3	11.1 [(d)]	---	---	---	---	---	---	---	---	---	
United States of America:	Wagenknecht L. E.,	(350)	0-19	1979-1988	13.9	11.1	---	---	---	---	---	---	---	---	---	

Country, Area	First Author, publication year	Ref	Age range	Period	0-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-59	60-69	70-79	80
Alabama (Jefferson County)	1991 †															
United States of America: Alabama (Jefferson County)	Wagenknecht L. E., 1989	(349)	0-19	1979-1985	18.3	9.3	---	---	---	---	---	---	---	---	---	
United States of America: Colorado	Vehik K., 2007 †	(344)	0-17	2000-2004	21.8	16.1 (d)	---	---	---	---	---	---	---	---	---	
United States of America: Colorado	Kostraba J. N., 1992	(170)	0-17	1978-1988	12.8	8.7	---	---	---	---	---	---	---	---	---	
United States of America: Pennsylvania (Allegheny)	Libman I. M., 1998 †	(191)	0-19	1990-1994	17.4	12.3	---	---	---	---	---	---	---	---	---	
United States of America: Rhode Island	Fishbein H. A., 1982 †	(96)	0-29	1979-1980	12.7	11.0	14.0	17.0	---	---	---	---	---	---	---	
United States of America: five areas §	Bell R., 2009 †	(31)	0-19	2002-2005	14.0	8.0	---	---	---	---	---	---	---	---	---	
United States of America: Wisconsin	Allen C., 1986 †	(13)	0-29	1970-1979	18.1	12.7	9.0	11.1	---	---	---	---	---	---	---	
United States of America: The United States Navy	Gorham C., 1993 ‡	(117)	17-34	1974-1988	18.1	10.4	21.8	27.3	61.7	---	---	---	---	---	---	
Western Pacific Region, HIGH																
Australia: New South Wales	Tran F., 2014 †	(326)	10-18	2001-2008	14.5*	22.0(c)	---	---	---	---	---	---	---	---	---	
Australia: Sydney (Southern Metropolitan Heath Region)	Sutton L., 1989 †	(308)	0-19	1984-1987	12.91	10.78	---	---	---	---	---	---	---	---	---	
Japan: Osaka	Sasaki A., 1992 †	(275)	0-18	1978-1988	1.89	1.65(e)	---	---	---	---	---	---	---	---	---	
New Zealand: Canterbury	Scott, R. S., 1991†	(281)	0-≥80	1981-1986	12.2	16.9 (b)	8.1	8.1	10.6	10.6	11.8	11.8	13.1	18.6	21.7	
Other Regions currently non-WHO																
Taiwan: NW	Lin W. -H., 2013 †	(192)	0-≥60	1999-2010	5.1	3.68	2.23	0.98	0.73	---	---	---	---	---	---	
US Virgin Islands: NW	Washington R. E., 2013 †	(351)	0-19	2001-2010	11.2(a)	19.1(b)	---	---	---	---	---	---	---	---	---	

Incidence was per 100.000 persons per year. T1D: Type 1 Diabetes. NW: Nation-wide study. HIGH, LMIC: High, Low-Medium Income Level. Highlighted: reports of the systematic review using the autoantibodies/C-peptide as diagnosis criteria. (a) 0-9 years of age, (b) 10-19 years of age, (c) 10-18 years of age, (d) 15-17 years of age, (e) 15-18 years of age, (---): unavailable data. (*): Data was retrieved from a different study; for details see Additional file 3. (†) Studies used in the geographical correlation analyses. (‡) Special population. (§) The five areas were Ohio (8 counties), Washington State (5 counties), South Carolina, Colorado and California; the table presents the mean incidence calculated, retrieved from 5 populations: African American, Asian Pacific Islander, Navajo, Hispanic and non-Hispanic young.

4.1.1.5 Incidence of T1D by sex in young adults and adults

SI Table 17: T1D incidences by sex in young adults and adults found in the systematic review

Country, Area	First Author, publication year	Ref	Period	Age range	Inc. Men	Inc. Fem	Male/Fem ratio
African Region, LMIC							
Mauritius: NW	Tuomilehto J., 1993 †	(332)	1986-1990	15-19	0.4	1.7	0.24
Eastern Mediterranean Region, LMIC							
Iran (Islamic Republic of): Fars	**Pishdad G. R., 2005** †	(248)	1990-1994	15-29	2.7	4.0	0.68
Libyan Arab Jamahiriya: Benghazi	Kadiki O. A., 1996 †	(153)	1981-1990	15-34	14.2	9.0	**1.58**
Tunisia: Beja, Monastir, Gafsa	Ben Khalifa F., 1998 †	(32)	1990-1994	15-19	6.2	8.8	0.70
European Region, LMIC							
Estonia, NW	Kalits I., 1990 †	(157)	1988-1988	15-39	18.2	21.9	0.83
Lithuania, NW	Ostrauskas R., 2011 †	(235)	1991-2008	15-34	10.4	6.1	**1.71**
Lithuania, NW	Pundziute-Lycka A., 2003	(254)	1991-2000	20-39	10.2	5.4	**1.89**
Lithuania, NW	Ostrauskas R., 2000	(234)	1991-1997	15-39	9.7	5.7	**1.70**
Poland: Province of Rzeszow	Sobel-Maruniak A., 2006	(296)	1980-1999	15-29	6.8	4.7	**1.45**
Poland: Province of Rzeszow	Grzywa M. A., 1995 †	(123)	1980-1992	15-29	6.0	5.1	**1.16**
Poland: Warsaw	Wysocki M. J., 1992 †	(366)	1983-1988	15-29	6.5	4.4	**1.48**
Slovakia: NW	Kyvik K. O., 2004 †	(176)	1996-1997	25-29	5.8	3.9	**1.49**
European Region, HIGH							
Austria: Upper	Rami B., 2001 †	(259)	1994-1996	25-30	8.2	4.4	**1.86**
Belgium: Antwerp	**Weets I., 2002** †	(352)	1989-2000	15-39	7.0	10.6	0.66
Belgium: Antwerp	**Vandewalle C., 1997** †	(341)	1989-1995	15-39	11.0	6.9	**1.59**
Bosnia and Herzegovina: Republic of Srpska	Radosevic B., 2013 †	(256)	1998-2010	15-18	6.3	3.9	**1.62**
Denmark: Copenhagen and Frederiksborg	**Molbak A. G., 1994** †	(215)	1973-1977	>30	9.1	7.5	**1.21**
Finland: NW	**Lammi N., 2007** †	(177)	1992-1996	15-39	20.1	11.8	**1.70**
Israel: NW	Blumenfeld O., 2014 † (a)	(39)	1997-2010	15-17	11.0	7.4	**1.49**
Israel: NW	Koton S., 2007	(171)	1997-2003	15-17	10.6	7.1	**1.49**
Italy: Lombardie	Garancini P., 1991 †	(108)	1981-1982	15-34	4.9	2.9	**1.69**
Italy: Pavia	Tenconi M. T., 1995 †	(317)	1988-1992	15-29	6.9	6.9	**1.00**
Italy: Sardinia	Muntoni S., 1992 †	(220)	1989-1990	15-29	25.3	12.1	**2.09**
Italy: Sardinia (Oristano)	Frongia O., 1997 †	(102)	1993-1996	15-29	21.7	22.3	0.97
Italy: Turin	**Bruno G, 2009** †	(46)	2000-2004	15-29	8.2	5.9	**1.39**
Italy: Turin	**Bruno G, 2005** †	(47)	1999-2001	30-39	9.2	5.4	**1.70**
Italy: Turin	Bruno G., 1993	(45)	1984-1988	15-29	7.4	4.2	**1.75**
Malta: NW	Schranz A. G., 1989 †	(280)	1980-1987	15-24	13.3	12.2	**1.09**
Netherlands: NW	Ruwaard D., 1994 †	(271)	1988-1990	15-19	16.6	13.3	**1.25**
Norway: NW	Joner G., 1991 †	(149)	1978-1982	15-29	19.0	15.0	**1.27**
Slovenia: NW	Radosevic B., 2013 †	(256)	1998-2010	15-18	8.4	6.6	**1.27**
Spain: Badajoz	Morales-Perez F. M., 2000 †	(218)	1992-1996	15-29	10.2	7.3	**1.40**

Country, Area	First Author, publication year	Ref	Period	Age range	Inc. Men	Inc. Fem	Male/Fem ratio
Spain: Canarias Islands	Carrillo Dominguez A., 2000 †	(55)	1995-1996	15-29	12.2	6.2	**1.97**
Spain: Catalonia	**Abellana R., 2009** †	(5)	1989-1998	15-29	10.6	7.0	**1.51**
Spain: Catalonia	Goday A., 1992	(112)	1987-1990	15-29	12.6	7.2	**1.75**
Spain: Navarra	**Forga L., 2014** †	(98)	2009-2012	15-29	23.0	8.2	**2.80**
Spain: Navarra	**Forga L., 2013** †	(97)	2009-2011	15-29	22.4	8.3	**2.69**
Sweden: NW	Dahlquist G. G, 2011 †	(74)	1983-2007	15-34	18.9	9.2	**2.05**
Sweden: NW	Östman J., 2008	(233)	1983-2002	15-34	16.4	8.9	**1.84**
Sweden: NW	Pundziute-Lycka A., 2002	(252)	1983-1998	15-34	16.1	9.1	**1.77**
Sweden: NW	Nyström L., 1992	(229)	1983-1987	15-34	15.8	8.6	**1.85**
Sweden: NW	Blohme G., 1992	(37)	1983-1987	15-34	15.9	8.6	**1.85**
Sweden: Kronoberg	**Thunander M., 2008** †	(320)	1998-2001	20-39	21.6	9.4	**2.29**
United Kingdom: NW	Imkampe A. K., 2011 †	(141)	1991-2008	15-34	16.5	8.5	**1.94**
United Kingdom: Oxford region	Bingley P. J., 1989	(35)	1985-1986	15-19	16.0	16.5	0.97
Region of the Americas, HIGH							
United States of America: Alabama (Jefferson County)	Wagenknecht L. E., 1989 (b)	(349)	1979-1985	15-19	8.6	10.0	0.86
United States of America: Colorado	Vehik K., 2007 † (c)	(344)	2000-2004	15-17	10.7	8.2	**1.31**
United States of America: Colorado	Kostraba J. N., 1992	(170)	1978-1988	15-17	9.8	7.6	**1.30**
United States of America: five areas §	**Bell R., 2009** †	(31)	2002-2005	15-19	8.3	7.7	**1.08**
United States of America: Wisconsin	Allen C., 1986 †	(13)	1970-1979	15-29	11.7	8.3	**1.41**
United States of America: The United States Navy	Gorham C., 1993 (b)	(117)	1974-1988	17-34	24.4	24.9	0.98
Western Pacific Region, HIGH							
Japan: Osaka	Sasaki A., 1992 †	(275)	1978-1988	15-18	1.8	1.5	**1.21**
New Zealand: Canterbury	Scott, R. S., 1991†	(281)	1981-1986	20-39	11.4	7.3	**1.56**
Other Regions currently non-WHO							
Taiwan: NW	**Lin W. -H., 2013** †	(192)	1999-2010	15-29	3.2	4.1	0.77

No available information

African Region, LMIC							
United Republic of Tanzania: Dar es Salaam	Swai A. B., 1993 †	(311)	1982-1991	NA	NA	NA	NA
European Region, LMIC							
Croatia: Zagreb	Roglic G., 1995 †	(268)	1988-1992	NA	NA	NA	NA
Poland: Bialystok	Kretowski A., 2001 †	(172)	1994-1998	NA	NA	NA	NA
Romania: Bucharest	Ionescu-Tirgoviste C., 1994 †	(143)	1981-1991	NA	NA	NA	NA
European Region, HIGH							
Belgium: Antwerp	**Weets I., 2007** †	(353)	1989-2003	NA	NA	NA	NA
France: Aquitaine, Lorraine, Basse Normandie, Haute Normandie	Charkaluk M. L., 2002 †	(59)	1988-1997	NA	NA	NA	NA
France: Aquitaine, Lorraine, Haute-Normandie, and Basse-Normandie.	Levy-Marchal C., 1998	(187)	1988-1995	NA	NA	NA	NA
Israel: NW	Sella T., 2010 (d)	(284)	2000-2008	NA	NA	NA	NA

Country, Area	First Author, publication year	Ref	Period	Age range	Inc. Men	Inc. Fem	Male/Fem ratio
Luxembourg: NW	De Beaufort C. E., 1988 † (d)	(75)	1977-1986	NA	NA	NA	NA
Region of the Americas, HIGH							
Canada: Quebec	Legault L., 2006 †	(184)	2000	NA	NA	NA	NA
United States of America: Alabama (Jefferson County)	Wagenknecht L. E., 1991 † (d)	(350)	1979-1988	NA	NA	NA	NA
United States of America: Pennsylvania (Allegheny)	Libman I. M., 1998 † (d)	(191)	1990-1994	NA	NA	NA	NA
United States of America: Rhode Island	Fishbein H. A., 1982 † (d)	(96)	1979-1980	NA	NA	NA	NA
Region of the Americas, LMIC							
Barbados: NW	Jordan O. W., 1994 † (d)	(152)	1982-1991	NA	NA	NA	NA
Western Pacific Region, HIGH							
Australia: New South Wales	Tran F., 2014 †	(326)	2001-2008	NA	NA	NA	NA
Australia: Sydney (Southern Metropolitan Heath Region)	Sutton L., 1989 †	(308)	1984-1987	NA	NA	NA	NA
Other Regions currently non-WHO							
US Virgin Islands: NW	Washington R. E., 2013 †	(351)	2001-2010	NA	NA	NA	NA

Male-to-female ratios >1 are highlighted. Ref: Reference. First author and publication year in reports of the systematic review using the autoantibodies/C-peptide as diagnosis criteria are highlighted. Inc: incidence per 100.000 persons per year. NW: Nation-wide study. HIGH, LMIC: High, Low-Medium Income Level. (†) Studies used for analyses. (§) The five areas were Ohio (8 counties), Washington State (5 counties), South Carolina, Colorado and California; the table presents the mean incidence calculated retrieved from 5 populations: African American, Asian Pacific Islander, Navajo, Hispanic and non-Hispanic young. Incidence was calculated as the mean of retrieved information: (a) in Jews and other non-Arabs and Arabs; (b) in White and Black populations; (c) in Non-Hispanic Whites and Hispanic Whites. (d) Study giving the total incidence by sex, not by age classes.

4.2 Additional analyses of the study: Global epidemiology of T1D in young adults and adults: a systematic review

4.2.1 Ethnicity differences in T1D Incidence of T1D in Adults

Among 71 studies described in **chapter 3**, ethnicity differences were reported in 7 studies. In Mauritius, the incidence was similar among individuals of Asian Indian, Chinese or Creole origin (332). In Israel, a significant difference was found between Jews and Arabs (39, 171). In Unites States, in Pennsylvania, the incidence was higher in non-Whites than in Whites (191), in Alabama the opposite was found (349, 350), whereas, in Colorado no significant differences were found after exploring the incidence of T1D in different periods (344).

4.2.2 Rural-urban differences in T1D Incidence of T1D in Adults

Only ten percent (7 of the 71) of the studies explored the differences in the incidence of T1D in rural *vs* urban areas. A significantly higher urban proportion of the incidence of T1D among young adults and adults was found in 4 of these 7, (Iran (Fars) (248), Lithuania (nation-wide) (254), Italy (Pavia) (317), and United States of America (Wisconsin) (13)). In another study from Poland (Bialystok), a significantly rising incidence trend was found in the rural areas but not in the urban regions (172). In the Province of Rzeszow no differences were found between the rural and urban incidences (123), nor in Turin, Italy (45).

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Chapter 5

Incidence Trends of Type 1 Diabetes

Contents

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5 Global incidence trends of T1D

A classical epidemiological method to disentangle the possible effects of environmental factors influencing the incidence of T1D at different ages, at different periods and in different birth cohorts is the Age-Period-Cohort (APC) method, first proposed by Derrick in 1927 (77) in studies of mortality, then extended to other domains of public health such as social sciences, psychology, stomatology, ophthalmology, demography, and studies of environmental factors related with cancer (110).

The first part of this chapter briefly describes the model and gives some examples of the APC approaches used to answer different questions in the domain of public health.

The second part of this chapter presents the APC approach we used to explain the increase in the incidence of T1D worldwide, as documented in **chapters 1, 2** and **3**. In the APC model presented in this chapter included 2,327,604,529 person-years at risk and 192,741 cases retrieved from 265 worldwide studies published between 1975 and 2014, reporting T1D incidence among individuals aged 0-14 years and collected through a systematic review.

After performing the APC analyses among individuals aged 0-14 years, a clear and strong birth cohort effect was observed. In addition, a calendar period effect that has been changing over time was also observed. The highest rate of incidence was observed for those aged 10-14 years. Environmental factors are no doubt implicated.

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5.1 Early literature on the Age-Period-Cohort (APC) analyses

Derrick (1927) (77) first proposed the analyses of cohorts to study the effect of the birth cohort on mortality. The history of the first 30 years of the cohort analyses is presented in Case's (1956) (56) historical article: *"cohort analysis of mortality rates as a historical or narrative technique"*. With time, the APC models were improved with the introduction of the age (of death, in the case of mortality studies) and period (in which the death/event of interest was produced), as described by Gilg Soit Ilg in her doctoral thesis (1999), supervised by Professor Alain-Jacques Valleron: "*La méthode âge-période-cohorte, outil prévisionnel application au mesothéliome en France*" at the UPMC (ED 393) (110).

The Norman Ryder's classical article published in 1965 (272): "*The cohort as a concept in the study of social change*", argues that a cohort membership could determine behavior as other social structures such as socioeconomic status, and describes in the abstract, the cohort analysis as follows:

THE COHORT AS A CONCEPT IN THE STUDY OF SOCIAL CHANGE *

NORMAN B. RYDER
University of Wisconsin

Society persists despite the mortality of its individual members, through processes of demographic metabolism and particularly the annual infusion of birth cohorts. These may pose a threat to stability but they also provide the opportunity for societal transformation. Each birth cohort acquires coherence and continuity from the distinctive development of its constituents and from its own persistent macroanalyic feaures. Successive cohorts are differentiated by the changing content of formal education, by peer-group socialization, and by idiosyncratic historical experience. Young adults are prominent in war, revolution, immigration, urbanization and technological change. Since cohorts are used to achieve structural transformation and since they manifest its consequences in characteristic ways, it is proposed that research be designed to capitalize on the congruence of social change and cohort identification.

Later, in 1973, Mason et al. (206) specified the Age-Period-Cohort (APC) "identification problem" due to the linear relationship of the variables age, period and birth cohort in the model, in their classical article: "*Some methodological issues in cohort analysis of archival data";* see abstract below:

SOME METHODOLOGICAL ISSUES IN COHORT ANALYSIS OF ARCHIVAL DATA *

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American Sociological Review 1973, Vol. 38 (April):242–258

Cohort analyses in which the joint effects of aging, historical change and birth cohort membership are estimated for some dependent variable are often desirable on substantive grounds. Unless two of these three variables are viewed as indexing identical unmeasured causal factors, any analysis which makes estimates for only two of the three variables is subject to spurious results. But three-way cohort analysis is problematic because age, time period and birth cohort are linearly dependent on each other. Although this confounding makes estimation of some three-way cohort models impossible, this paper demonstrates that estimation is feasible in a number of such models. By exploring estimates derived for some of these models from hypothetical data for which the underlying effects are known, this paper also shows that meaningful three-way cohort analysis is difficult unless the researcher entertains relatively strong hypotheses about the nature of aging, period and cohort effects.

During the last years, several articles and replies about the methods on APC analyses were published and detailed by Kenneth C. Land in the seminar: "*Disentangling Age-Period-Cohort Effects: New Models, Methods, and Empirical Applications"* (178). Land argues that recent methodological contributions such as developments of statistics (such as mixed (fixed and random) effect models, Markov Chain Monte Carlo (MCMC) estimation of Bayesian models) 'can lead to better methods for APC analyses that can be applied by ordinary [social] scientists'.

Recommendations for the estimation of APC models include: a) graphic descriptive analysis of the model, b) model fitting procedures, and when the analyses suggest that all three dimensions (age, period and cohort) are operating in the model: c) the introduction of an external factor, (e.g., apply the procedure of the Intrinsic Estimator (IE)) (178).

However, in APC analyses based on repeated cross-section sample surveys or data registers, such as the data we collected on T1D in this thesis, individual-level data are not available, then other research designs have been recently proposed. These new approaches of the APC model can use a different temporal grouping for the age (A), period (P), and cohort (C) dimensions that breaks the linear dependency:

- Single year of *age*
- Time *periods* correspond to years in which the surveys are conducted
- *Cohorts* can be defined either by five- or ten-year intervals

On this last APC based on population data from surveys or registers, to assess the possibility that individuals within the same periods and cohorts could share unobserved random variances, and to determine if a period and/or cohort heterogeneity can be explained by the given period and/or cohort characteristics, the *Hierarchical Age-Period-Cohort* (HAPC*) Models* were proposed as an alternative solution. The HAPC models use as analytical methods: a) mixed (fixed and random) effect models or hierarchical linear models (HLM) and b) cross-classified random effect models (CCREM) (178).

In **chapter 6**, thanks to Professor Pierre-Yves Boëlle from the UPMC, HAPC-CCREM were proposed to explain the effect of the *age*, the *period* and the *cohort* in the study of T1D using Poisson regression models, and with a country-level random level intercept according the Holford method (133, 134).

5.1.1 Some examples of APC analyses used in public health

In spite of limitations of the APC models this method was used extensively in mortality analyses (mainly in cancer research), as well as in other domains of public health such as phycology, social sciences, psychology, stomatology, ophthalmology, and demography (110).

APC analysis has been proposed to answer fundamental questions the public health through different methodological approaches. As examples see the following studies:

- The study: "*Estimation of the past and future burden of mortality from mesothelioma in France" (*Gilg Soit Ilg et al. *1998)* (140), states and predicts the mortality due to mesothelioma in France using a classical approach of the APC models.
- The study: "*Intrinsic Estimator for Age-Period-Cohort analysis: what it is and how to use it",* (Yang et al. 2008) (368), addresses the problem of the APC analysis of age-by-time period tables of rates or proportions.

- The study: *"Aplicación del estimador intrínseco a tasas de mortalidad por cancer de mama",* (Arnesi and Hachuel, 2011) (19), contrasts the use Generalized Linear Models and IE in an APC analysis.
- The study: "*A mixed models approach to the age-period-cohort analysis of repeated cross-section surveys, with an application to data on trends in verbal test scores*", (Yang and Land, 2006) (370), uses HAPC-CCREM models applied to sociology.
- The study: *"Trends in smoking in Sweden from 1968 to 2002: Age, period, and cohort patterns"* (Ahacic, et al. 2008) (8), uses HAPC-CCREM models applied to the study of tobacco consumption.
- The study: *"Is old age depressing? Growth trajectories and cohort variations in late life depression",* (Yang, 2007) (369), uses APC approaches in psychology, applied to longitudinal data of an initial sample of individuals from a broad array of ages.

5.1.1.1 Examples of APC analyses used to study T1D trends

Few studies have used APC models to study incidence trends of T1D. Classical approaches of APC models from Denmark, the United Kingdom and Sweden, have described a *calendar period effect* in the incidence of T1D (119, 141, 217, 233, 310), observed when trends affect all age groups at the same time. In contrast, in other studies from Norway, Sweden and the United States a *birth cohort effect* (3, 74, 156) was described. Only two studies report the analyses of the three interrelated variables: age-period-cohort: the study: *"Age-Period-Cohort Analyses of 1990-2003 Incidence time trends of childhood diabetes in Italy, the RIDI Study"* From Italy, (Bruno et al. 2010) (43), in which neither period nor cohort effect was observed, and the study: *"Spatiotemporal trends and Age-Period-Cohort modeling of the incidence of Type 1 diabetes among children aged <15 years in Norway 1973-1982 and 1989-2003"* from Norway, (Aamodt et al. 2007)(3), in which a birth cohort effect was described.

5.2 APC analysis of the Global Incidence trends of Type 1 diabetes

P. A. Diaz-Valencia, P. Y. Boëlle, P. Bougnères, A. J. Valleron.

5.2.1 Abstract

Background: Type 1 Diabetes (T1D) has generally been increasing worldwide. In contrast, in Scandinavian countries, the decline in cumulative incidence in recent years reflects a possible break in the trend.

Objective: to disentangle the effect of age, calendar period, and birth cohort on the temporal trends of T1D incidence in children aged 0-14 years.

Methods: the incidence of T1D worldwide was retrieved through a systematic review of the literature. To model the effects of age, calendar time and birth cohorts on the variation of T1D incidence, a Hierarchical Age-Period-Cohort cross-classified Random Effects Model (HAPC-CCREM) was then proposed using Poisson regression.

Findings: Information on the incidence of T1D was retrieved in 89 countries worldwide and increase in the incidence of T1D with age was examined among those aged less than 14 years. Global trends of T1D increase with age show increasing incidence in successive birth cohorts over the period of analysis. After allowing a cohort effect, little change due to period was present.

Conclusions: The incidence of T1D increases over the 14 first years of life. During the last century, dynamic changes of the incidence trends of T1D were observed. Both calendar period and birth cohort effects were associated.

5.2.2 Background

The incidence of T1D has been studied in several countries worldwide showing an enormous variation in trends (90, 122, 241, 243, 300, 318), that is not explained by either genetic or social factors or by health care systems (81). In the 1980s, the increase of the T1D incidence was recognized (105) and calculated to be on average 3% per year (318).

T1D is a complex disease with multifactorial causes (338, 342, 343). In the etiology of the disease, genetic (89) factors are implicated as well as environmental factors (104, 306); in which autoimmune (338, 367) mechanisms are involved. Previous studies have described a *calendar period effect* in the incidence of T1D (119, 141, 217, 233, 310), observed when trends affect all age groups at the same time. In contrast, in other studies a *birth cohort effect* (3, 74, 156) was described, in which the increase of the incidence trends was observed in all age groups from the same birth cohort. The importance of clarifying whether increases in temporal trends of T1D are due to period or cohort effects is fundamental to better understand the etiology of this disease. A calendar period effect has been related with short or long-term changes and more stable increases in incidence, in which an abrupt exposition to an environmental trigger could reflect a non-linear patron, whereas a birth cohort effect has been related with long-term changes, in which rapid and unstable changes in the incidence are comparable to an epidemic pattern.

Evidence of the influence of age, period, or birth cohort effects affecting the incidence trends of T1D has been studied in some countries; nevertheless, very few studies report the analyses of these three interrelated variables: age-period-cohort (3, 43), in part because during short periods of time, only a limited number of observations are available in most countries and are also due to methodological issues, such as the linear dependence between the variables age, calendar period and birth cohort (232). Among the studies reporting an APC analysis, neither period nor cohort effects were observed in the Bruno study (43), whereas a birth cohort effect was found in the Aamodt study (3). Here, using a systematic review of the literature, we have generated a large database containing global information on the incidence of T1D; then using a methodological approach based on Mixed Poisson Regression Models (MPRM) and introducing a random effect by country, we were able to estimate the APC rates of the global incidence of T1D, considering all three variables: age, calendar period, and birth cohort.

5.2.3 Methods

5.2.3.1 Global incidence of T1D data

A systematic literature search was conducted to obtain data to model trends in T1D worldwide. The recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Group were followed (213) (**SI Table 19** - Checklist). The registration number in PROSPERO, the International Prospective Register of Systematic Reviews is: CRD42012002369 (available on http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369). We searched MEDLINE, Web of Science and *Google Scholar* for all relevant original papers published in English between 1975 and 2014 including the reviews Diamond (318) and Eurodiab studies (90, 242, 243), and the International Diabetes Federation (IDF) atlas (241, 300).

The search, conducted on 28/11/2011 and updated in November 2014 included the following terms: "diabetes mellitus, type 1/epidemiology" AND "incidence" AND "age" (OR "age distribution" OR "age factors" OR "age groups"). All abstracts were read for reports of T1D incidence. If present, the full-text was obtained and the article included in the analysis if it reported incidence data in the general population at a regional or country level. **Figure 27** shows the flow diagram of the bibliographic search. The complete search strategy is in: **Supporting information 5.2.5.1.** For the entire list of selected references see **SI Table 20.**

5.2.3.2 Data abstraction

T1D incidence rates or counts up to the age of 14 years were extracted from the texts, tables or graphs in the articles. We also extracted the country where the study had been performed, the period (calendar year) and the age or age class. When available, we also extracted the population at risk (in person years).

5.2.3.3 Preparation of data

We searched for duplications in the data extracted. When two papers presented the same data, we included the more detailed version (in age and period). When local studies were included in studies performed on a larger scale, only the largest, up to the country level

were included. Finally, the data was grouped in age classes of 5 years each (0-4, 5-9, 10-14) and in 5 years period classes (starting in 1935). In all cases, the data was converted back to number of cases and populations at risk. If the population was not available, we used estimates from the United Nation population (335), and otherwise we checked that the population sizes from these references agreed with those reported in the published articles. The final database is presented in **Appendix A: Database IV.**

The classification of incidence-country-level was arbitrarily proposed as: very low, low, intermediate, and high incidence level, corresponding to countries with incidence levels of: ≥2 to <6, ≥6 to <10, ≥10 to <42 and ≥ 42 cases per 100.000 persons per year.

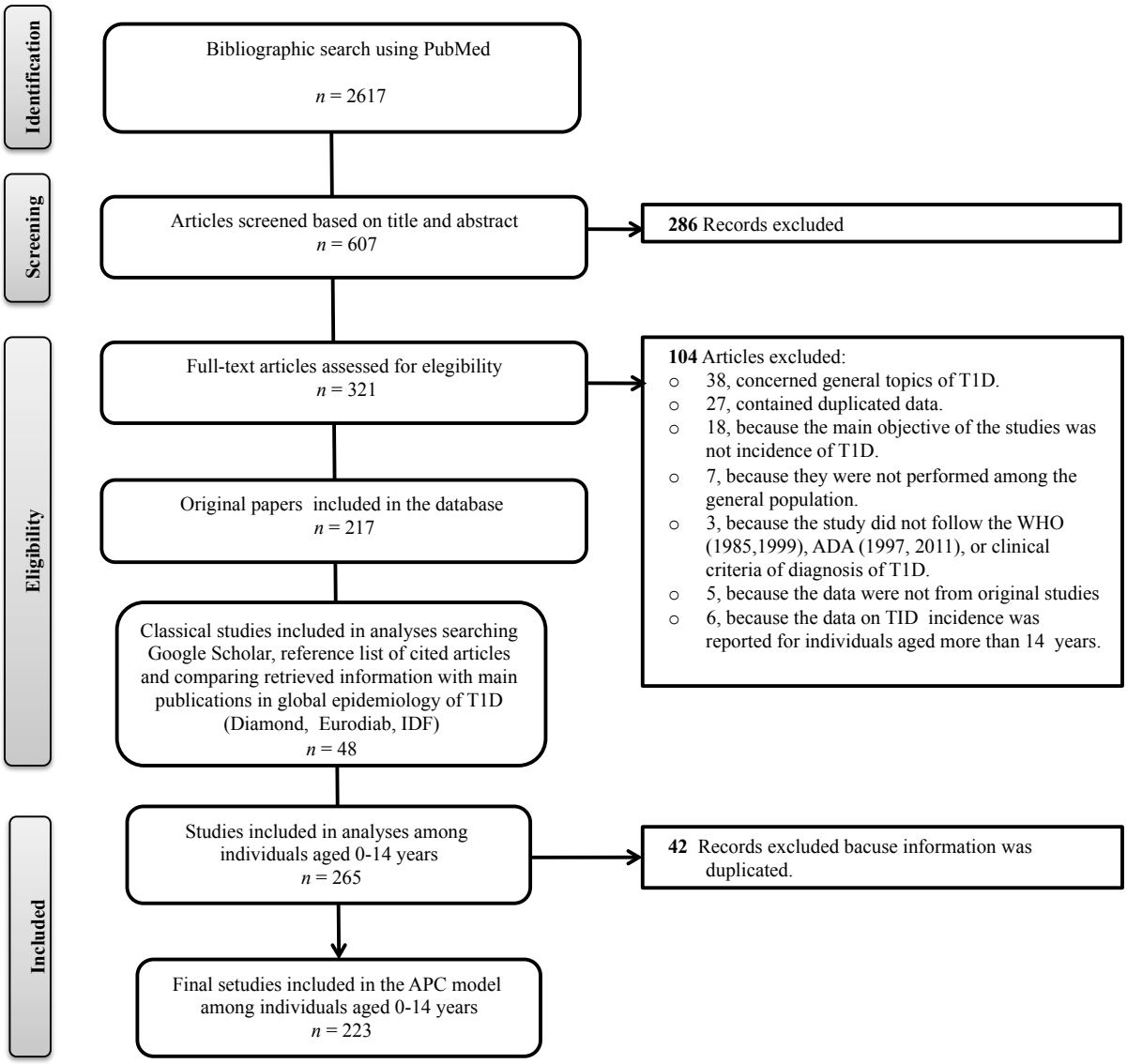


Figure 27: Flow diagram bibliographic search strategy

5.2.3.4 Analyses

We used an APC model, specifically a HAPC-CCREM using Poisson regression, to analyze the incidence rates over periods and ages. In the APC models, incidence is described as depending on age, calendar period, and birth cohort. Here *age* was the age at diagnosis of T1D - the year of the first insulin injection- reported by the studies, *calendar period* was the year of diagnosis, and *birth cohort* was the year of birth of the patient (obtained as period – age). To avoid over-parametrization, we used a 3-nodes linear spline to model the period and cohort components. We analyzed all data jointly, using a country-level random level intercept. More precisely, the model for analysis was:

$$\log E\left(\frac{D(a,p,c,y)}{N(a,p,c,y)}\right) = \alpha\, f_A(a) + \beta\, f_P(p) + \gamma\, f_C(c) + b_y$$

where D(*a,p,c,y*) was the number of incident cases at age *a*, period *p* and birth cohort *c* in country *y*, fA(*a*), fP(*p*) and fC(*c*) were the age, period and cohort components, N(*a,p,c*) the number of persons at risk and b_y a normally distributed country level effect with mean 0 and variance σ_Y^2.

The R software (version 3.0.1) was used for statistical and graphic analyses (255). Packages Epi, Splines, Lme4 and Grid were required.

5.2.3.5 Retrieved global information on T1D

Thanks to our systematic review, worldwide incidence trends of T1D were retrieved from 265 references (223 included in the APC model) between 1975 and 2014 that contained information of incident cases of T1D reported during the period 1938-2008 in individuals aged less than 14 years. There are enormous variations in incidence trends of T1D after stratification of the analysis according to incidence-country-level. Incidences varied widely between continents, countries, and regions. Among children aged 0-14 years, the lowest nationwide incidences (≤ 1 case per 100.000 individuals/year) were in Eastern Asia (China), South-Eastern Asia (Thailand), Melanesia Oceania (Papua New Guinea), and South America and the Caribbean (Saint Kitts and Nevis, Dominican Republic, and Paraguay). The highest nationwide incidences (≥ 30 cases per 100.000 individuals/year) were in Northern Europe

(Finland, Sweden, Norway). **SI Table 20** presents the variability of the incidences within a country, the duration of each study, the number of cases and the population at risk taken from the information used during these analyses.

5.2.3.6 APC analyses of the global incidence of T1D

The mean incidence of T1D was 13.7 cases (95% CI 13.1-14.2) per 100.000 persons per year. North America, Europe and Oceania are the regions with the highest incidences, in contrast Asia, Africa and Latin America and the Caribbean, showed the lowest incidences. Europe is the region in the world with most incidences registered: 147,220 cases and more person-years of following at risk: 1,048,075,945. See **Table 18.**

Table 18: Incidence rates of T1D among children aged 0-14 years retrieved from 89 countries during the years 1975-2014 by main geographical areas

	Incident cases (n)	Person-years at risk (n)	Mean Incidence per 100.000 person-years (95%CI)
Africa	1,372	30,084,343	5.9 (4.0-7.8)
Asia	12,169	934,989,765	4.0 (3.1-4.8)
Europe	147,220	1 048,075,945	15.6 (14.9-16.4)
Finland	6,048	15,302,876	43.9 (35.8-51.9)
Latin America and the Caribbean	5,961	152,894,342	7.2 (6.1-8.3)
Northern America	13,106	82,974,910	16.6 (15.4-17.8)
Oceania	12,914	78,585,224	14.7 (13.0-16.4)
All	**192,741**	**2,327,604,529**	**13.7 (13.1-14.2)**

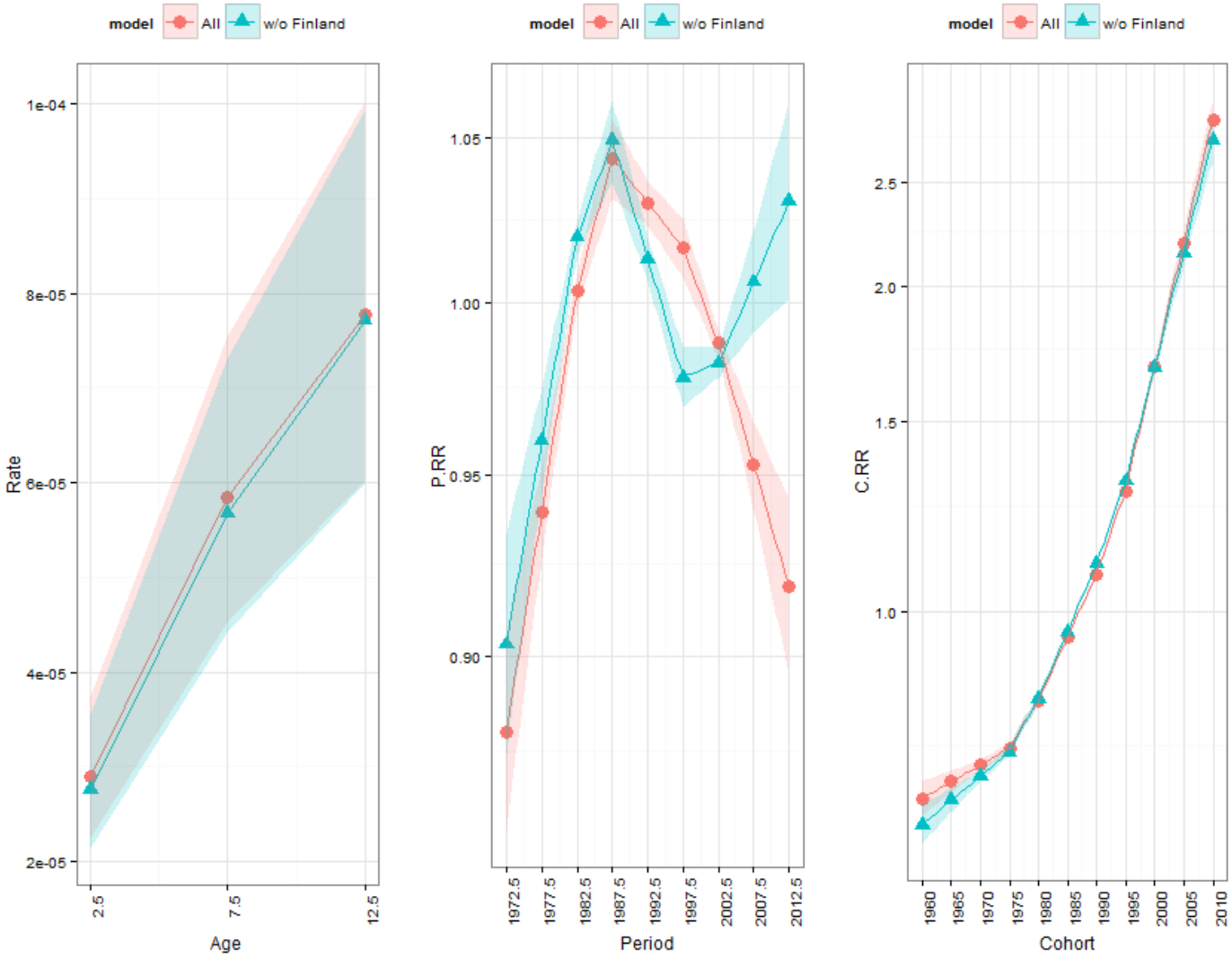
Retrieved datasets were predominantly from European countries (n = 2007), followed by North America (n = 527) and Asia (n = 499). 1989-1993 was the period reporting the largest number of datasets (n = 844); **Figure 28**.

Age (years) / Last year of the five-year period	1938	1943	1948	1953	1958	1963	1968	1973	1978	1983	1988	1993	1998	2003	2008	2013	Total
AFRICA										6	18	30	12	9	6		**81**
0 _ 4										2	6	10	4	3	2		27
5 _ 9										2	6	10	4	3	2		27
10 _14										2	6	10	4	3	2		27
ASIA								6	21	39	124	202	74	27	6		**499**
0 _ 4								2	7	13	43	68	25	9	2		169
5 _ 9								2	7	13	42	67	24	9	2		166
10 _14								2	7	13	39	67	25	9	2		164
EUROPE	6	15	15	18	18	21	36	73	136	215	309	459	389	201	81	15	**2007**
0 _ 4	2	5	5	6	6	7	12	24	45	71	102	152	129	66	27	5	664
5 _ 9	2	5	5	6	6	7	12	25	46	73	104	155	132	69	27	5	679
10 _14	2	5	5	6	6	7	12	24	45	71	103	152	128	66	27	5	664
LATIN AMERICA AND THE CARIBBEAN									3	36	108	93	30	36	12	3	**321**
0 _ 4									1	12	36	31	10	12	4	1	107
5 _ 9									1	12	36	31	10	12	4	1	107
10 _14									1	12	36	31	10	12	4	1	107
NORTH AMERICA						9	40	62	84	69	63	54	45	27	50	21	3	**527**
0 _ 4					9	25	22	20	23	21	18	15	9	16	7	1	186
5 _ 9						15	25	32	23	21	18	15	9	17	7	1	183
10 _14							15	32	23	21	18	15	9	17	7	1	158
OCEANIA							3	6	3	6	30	15	18	15	3		**99**
0 _ 4							1	2	1	2	10	5	6	5	1		33
5 _ 9							1	2	1	2	10	5	6	5	1		33
10 _14							1	2	1	2	10	5	6	5	1		33
Total	**6**	**15**	**15**	**18**	**27**	**61**	**101**	**169**	**232**	**365**	**643**	**844**	**550**	**338**	**129**	**21**	**3534**

Green-to-red gradient represents the number of datasets from the lower to the higher. Age is the mean for each age-class (0-4, 5-9, 10-14), each period correspond to 5 calendar years.

Figure 28: Distribution of information (datasets) used in the APC model by main geographical areas

The APC model presented in **Figure 29** corresponds to 2,327,604,529 person-years at risk and 192,741 cases retrieved from worldwide studies published between 1975 and 2014, reporting T1D incidence among individuals aged 0-14 years. A separate analysis of the APC model without Finland, the country with the highest reported worldwide incidence, is also presented in **Figure 29**.



On the *y*-axis: Rate: incidence rates of T1D per 100.000 individuals per year, P. RR: relative risk of the periods, C. RR: relative risk of the cohorts. *x*-axis: in years. w/o: without.

Figure 29: APC analyses using data groped in 5*5 groups

5.2.4 Discussion

The incidence of T1D is highly variable among the 89 countries and regions reporting information. Regarding incidence trends, the incidence of T1D increases with age; it presents the highest rate for those aged 10-14 years. In addition a birth cohort effect and a calendar period effect were observed. The curve representing the birth cohort effect shows a steady increase after 1975, been the RR = 1 in the 1980s and RR = 2.5 in the 2000s. Surprisingly, a decrease in the curve representing a calendar period effect appears after the peak in 1987; this tendency is strongly influenced by the effect of Finland, a very special country in which the epidemiology of T1D differs in genetic and maybe in environmental parameters and which provides a large amount of information, compared with other countries in this study.

In general, we observed that the incidence of T1D shows dynamic trends around the world. Large and sudden variations in the epidemiology over relatively short periods of time have also been described. Studying the ancient literature of T1D, Gale suggests that T1D showed a stable low incidence over the first half of the century (105). But in the 90s, collaborative studies such as Diamond (318) and Eurodiab (90, 242, 243) reported an increase in incidence trends of T1D worldwide. Our results are congruent with this finding and also with a nation-wide Swedish study, in which a reversed trend of cumulative incidence of T1D after 2000 ($p < 0.01$) was observed (33).

It is known that T1D is a multi-causal disease, and several hypotheses have been proposed as explanations. Nevertheless most authors agree with the theory that there is a strong influence of the environment among the causes of this disease. For example, Dahlquist (74) and Jaroz-Chobot (148) strongly support the idea that the most important promoters of the increase of T1D are the availability of fast food and the 'westernisation' of lifestyles (overweight, high growth rate, and having sedentary lifestyles), conditions that are associated with other environmental factors (e.g. enterovirus (314, 373)) and could be triggers in the initiation of the disease (probably by accelerating the beta-cell destructive process) due to a direct influence or to lack of protective agents (74, 148).

Our findings support the hypothesis that external factors including environmental risk determinants, and other non-genetic causes could be promoters or modifying factors implicated in the change of incidence trends of T1D worldwide. In a previous study,

significant predictors of T1D incidence were: UV radiation, mobile cellular subscriptions, health expenditure per capita, immunization against Hepatitis B and mean BMI (body mass index) (81). Nevertheless, more analyses of gene-environment as well as social determinants of health for T1D are still necessary.

Our study has several limitations. We found publications only in 46% (90 of 196) of the recognized countries. The variation of the duration of studies - between 1 and 40 years -, reflects enormous differences in surveillance and epidemiological reports of T1D worldwide. Few studies were carried out in Central and Latin America, Central Asia, and Sub-Saharan Africa, geographic regions where the epidemiological surveillance systems are concentrated in other priority concerns of health care systems or have under-developed data reports and registration systems. Nonetheless, part of the regional differences could also be due to different genetic (89) backgrounds of the populations not shown here. This could explain the extreme differences observed between and within countries, such as for example, the high incidence of Sardinia in Italy or in Newfoundland in Canada, and also the differences between ethnic groups, as for example Ashkenazi Jews, or non-Ashkenazi Jews in Israel, or among Hispanic or non-Hispanic populations in the United States.

To minimize the risk of bias, we only considered for the quantitative analyses performed here, references with population data-registers and in which an assessment of all included references at the study-level and outcome-level was rigorous; nevertheless, data plots and summarized results from heterogeneous populations could imply a bias. Also, to avoid duplications of the subject, we carefully selected the information to be entered in the analyses, excluding repetitions of data from a same region during a specific time period; however it is impossible to verify in all cases if any doubling exists. Similarly, we selected information reported for a given country or area during a specific period of time only once.

In addition, there are methodological issues of the APC models, here were treated the over-parametrization by introducing an external random factor, in our case the “country”. Using this method it was possible to present a separate analysis excluding Finland, the country with the highest incidence in the world. Also, data analyses were started in 1970, a period with more available information for most of the countries.

The birth cohort effect we show here should be explored. Researches focusing on pregnancy, and neonatal period are necessary to clarify causal factors of the birth cohort effect, for example, the implications of congenital infections as well as the absence of exposure to protective factors related to the way of delivery and the first moths of life of the newborns. Based on the period effect we report here, quick changes such as weight gain during early childhood (91) or adolescence could be risk factors of T1D and a manifestation of a calendar period effect.

Our results show that for children 0-14 years old, the global incidence of T1D increases with age, with a tendency of steady increase after the 1975 birth cohort. However, observing the period effect, after reaching a peak in 1987, the tendency shifted downwards, mainly influenced by the effect of information from Finland. Our remaining questions are if we are face a true slowdown in the tendency of T1D incidence; in this case, is it still necessary to understand the reasons why. Nevertheless, this apparent reversal trend could be due to miss or insufficient reporting of the disease in most countries during the last decades. Keeping the collection of standardized information, the collaborative studies performed worldwide and the promotion of public repositories with available data on the incidence of T1D remain valid and are still necessary to better understand the epidemiology of T1D.

5.2.5 Supporting Information

5.2.5.1 Search equation used for the bibliographic analysis

We used the following equation to search the electronic database Medline on November 6th 2014:

("diabetes mellitus, type 1/epidemiology"[MAJR]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND (age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] OR "age groups"[MeSH Terms]) AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Vascular Diseases" [MeSH Terms] OR "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms])[5].

Note 1. The last terms of the equation (after "Diabetic Neuropathies" were added to focus the bibliographic search on incidence papers by removing all those dealing, for example, with the incidence of complications of T1D.

[5] *Glossary for PubMed search*: [MAJR]: MeSH Major Topic, a MeSH term that is one of the main topics discussed in the article; [MeSH]: MeSH Terms, the National Library of Medicine's controlled vocabulary of biomedical terms that is used to describe the subject of each indexed journal article in MEDLINE; [SH]: MeSH Subheadings; it describes more completely a particular aspect of a subject; [TIAB]: Title/Abstract, the search include words and numbers included in the title, abstract, and other abstract of a citation; [PT]: Publication Type, it describes the type of material the article represents (e.g., Review, Clinical Trial, Retracted Publication, Letter).

5.2.5.2 CONSORT PRISMA checklist

SI Table 19: CONSORT PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	157
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	158
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	158
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3, 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	159
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	159
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	167
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	161, Figure 27
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	159, Figure 27
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	159
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	159

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	160
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	160
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	160
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 27
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Figure 29, Table 20
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 20
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	164
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	164
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	164
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

5.2.5.3 Selected papers reporting incidence of T1D in 0-14 year-olds

SI Table 20: List of selected countries and areas reporting incidence of T1D in 0-14 year-olds included in the APC model

Continent/Country	Area	First Author, publication year	Ref	Period	Mean T1D Inc.	SD	Population at risk	Number of cases	Asc. %
AFRICA									
Algeria	Oran	Diamond, 2006	(318)	1990-1999	8.60	NA	2441279	210	NA
Egypt	Alexandria, Damanhour	Arab M, 1992	(18)	1992-1992	8.00	NA	602535	48	NA
Ethiopia	Gondar	Alemu S, 2009	(12)	1995-2008	0.33	NA	1727076	6	NA
Ethiopia	Jimma	Alemu S, 2009	(12)	2002-2008	0.33	NA	5623928	19	NA
Libya	Benghazi	Kadiki O A, 2002	(154)	1991-2000	8.53	6.19	5860200	442	100
Libya	Benghazi	Kadiki O A, 1998	(155)	1991-1995	9.27	8.26	1564100	126	100
Mauritius	NW	Toumilehto J, 1993	(332)	1986-1990	2.07	0.96	1530250	32	95
Nigeria	Anambra	Afoke AO, 1992	(7)	1990-1990	1.96	NA	612245	12	NA
Sudan	Khartoum	Elamin A, 1992	(88)	1987-1990	7.93	1.72	4100000	325	95
Tunisia	Beja, Monastir, Gafsa	Ben Khalifa F, 1997	(32)	1990-1994	6.69	4.25	1713430	116	96
Tanzania (United Rep.)	Dar es Salaam	Swai A B, 1993	(311)	1982-1991	0.92	1.13	4309300	37	NA
ASIA									
China	23 local centers	Li X H, 2000	(189)	1988-1996	0.60	0.47	142560000	848	NA
China	22 centers	Yang Z, 2005	(371)	1988-1994	0.47	0.05	123929940	580	93
China	Harbin	Zhang H, 2008	(375)	1990-2000	0.74	0.49	14147694	103	98
China	North middle	Yang Z, 1998	(372)	1985-1994	0.58	0.19	65338202	418	94
China	Shanghai	Fu H, 1994	(103)	1980-1991	0.71	0.50	10221570	62	85
China	Shanghai	Shen S X , 1996	(291)	1989-1993	0.84	0.25	7008320	58	85
China	South middle	Yang Z, 1998	(372)	1985-1994	0.42	0.23	60126801	219	94
Georgia	NW	Amirkhanashvili K, 2000	(17)	1998-1999	3.30	1.68	5285667	171	NA
Hong Kong SAR	Hong Kong	Huen K F, 2000	(139)	1984-1996	1.37	0.42	16185143	224	100
Hong Kong SAR	Hong Kong	Wong G W K , 1993	(365)	1986-1990	1.93	1.03	1120030	22	94
India	Madras	Ramachandran A, 1996	(258)	1991-1994	11.00	1.70	1671170	184	90
Iran (Islamic Republic of)	Fars	Pishdad G R, 2005	(248)	1991-1996	3.68	1.45	9564000	298	100
Israel	NW	Koton S, 2007	(171)	1997-2003	10.38	5.09	12580033	1278	NA
Israel	NW	Laron Z V, 1985	(181)	1975-1980	4.20	2.74	7421790	295	95
Israel	NW	Shamis I , 1997	(289)	1965-1993	5.03	3.47	1992501	924	95
Japan	Hokkaido	Kawasaki E, 2006	(163)	1973-1996	1.89	1.22	3461452	69	NA
Japan	Hokkaido	Matsuura N, 1998	(207)	1973-1992	1.54	0.66	15909018	240	100
Japan	Kagoshima	Japan IDDM Epidemiology Study Group, 1993	(145)	1980-1989	1.77	0.30	533623	10	95
Japan	NW	Kawasaki E, 2006	(163)	1998-2001	2.35	0.70	73539756	1745	NA
Japan	NW	Kida K, 2000	(165)	1986-1990	1.46	0.75	103448508	1578	95
Japan	Osaka	Sasaki A, 1992	(275)	1978-1988	1.89	1.12	5987276	120	NA
Japan	Tokyo	Japan IDDM Epidemiology Study Group, 1993	(145)	1985-1989	1.62	0.43	11613492	192	95
Jordan	NW	Ajlouni K, 1999	(9)	1992-1996	3.33	2.10	8467045	275	95
Korea (Dem. People's Rep.)	Seoul	Diamond, 2006	(318)	1990-1991	1.10	NA	2369578	26	NA
Kuwait	Farwania	Abdul-Rasoul M, 2007	(4)	1995-1999	21.08	12.98	336745	68	98
Kuwait	NW	Shaltout A A, 2002	(288)	1992-1997	20.72	8.43	1811204	364	93
Oman	NW	Soliman A T, 1996	(297)	1993-1995	2.59	1.35	610175	15	96
Pakistan	Karachi	Staines A, 1997	(303)	1989-1993	1.03	0.59	34281426	337	NA

Continent/Country	Area	First Author, publication year	Ref	Period	Mean T1D Inc.	SD	Population at risk	Number of cases	Asc. %
Qatar	NW	Al-Zyoud M, 1997	(10)	1992-1994	11.40	NA	397497	45	NA
Saudi Arabia	Al-Madinah (North West)	Habeb A M, 2011	(125)	2004-2009	31.50	14.71	1519197	419	NA
Singapore	NW	Lee WW, 1998	(183)	1992-1994	2.42	1.50	2050302	47	92
Taiwan (Republic of China)	NW	Tseng CH, 2008	(327)	1992-1996	3.75	NA	4533333	170	NA
Thailand	Bangkok	Tuchinda C, 2002	(329)	1991-1995	1.65	0.93	244492	4	100
Thailand	Central	Tuchinda C, 2002	(329)	1991-1995	0.19	0.16	11454218	23	100
Thailand	Northestern	Panamonta O, 2000	(237)	1991-1995	0.30	0.04	25675073	76	NA
Thailand	Northestern	Panamonta O, 2011	(238)	1996-2005	0.64	0.42	53221307	339	NA
Thailand	Northeastern	Tuchinda C, 2002	(329)	1991-1995	0.30	0.04	40270354	120	100
Thailand	NW	Tuchinda C, 1992	(328)	1984-1985	0.17	0.04	36208676	60	NA
Thailand	Southern	Tuchinda C, 2002	(329)	1991-1995	0.42	0.10	9456906	40	100
Uzbekistan	NW	Rakhimova GGN, 2002	(257)	1989-1989	1.20	NA	8436250	101	NA
EUROPE									
Austria	NW	Schober E, 2008	(277)	1979-2005	10.02	3.83	35872193	3593	92
Austria	NW	Shober E, 2009	(278)	1997-2007	17.55	1.20	2788963	489	93
Belarus	Gomel	Martinucci M E, 2002	(205)	1976-1999	5.73	3.33	8591976	493	100
Belgium	Antwerp	Weets I, 2007	(353)	1989-2003	12.78	4.45	1217230	156	93
Bosnia and Herzegovina	Republic of Srpska	Radosevic B, 2013	(256)	1998-2010	8.13	2.67	3904151	320	100
Bosnia and Herzegovina	Tuzla Canton	Bratina N U, 2001	(42)	1990-1998	3.55	2.39	1142703	41	100
Bosnia and Herzegovina	Tuzla Canton	Tahirovic H, 2007	(312)	1995-2004	6.93	1.65	1120125	80	100
Bulgaria	Eastern	Tzaneva V, 1998	(334)	1974-1995	6.27	2.73	3186768	200	98
Croatia	NW	Stipancic G, 2012	(305)	1995-2003	8.90	2.76	7646381	692	97
Croatia	Zagreb	Roglic G, 1995	(268)	1988-1992	7.40	4.81	1003921	72	96
Cyprus	NW	Skordis N , 2012	(294)	1990-2009	12.34	3.46	3023124	371	100
Cyprus	NW	Toumba M, 2007	(325)	1990-2004	11.95	3.53	2327097	277	NA
Czech Republic	NW	Cinek O, 2000	(64)	1990-1997	9.94	3.41	15222265	1539	100
Czech Republic	NW	Cinek O, 2003	(65)	1990-2001	14.90	1.64	6905411	1026	99
Denmark	NW	Svensson J, 2002	(309)	1970-2000	14.32	6.11	12704194	1856	99
Denmark	NW	Svensson J, 2009	(310)	1996-2005	22.23	8.96	10149370	2276	NA
Estonia	NW	Teeaar T, 2010	(316)	1983-2006	13.09	5.15	6761392	843	98
Estonia	NW	Toumilehto J, 1991	(333)	1980-1988	10.90	2.51	990593	108	100
Estonia	NW	Podar T , 2001	(250)	1983-1998	6.93	2.78	8665396	601	NA
Finland	NW	Moltchanova E A, 2005	(216)	1965-1996	26.25	3.62	15976566	4160	100
Finland	NW	Harjutsalo V, 2008	(127)	1980-2005	42.93	11.52	24615936	10671	NA
Finland	NW	Harjutsalo V, 2013	(128)	2006-2011	62.42	9.05	5316126	3312	NA
France	4 countries (Aq,Lor,Nor B, Nor H)	Charkaluk M L, 2002	(59)	1988-1997	8.89	3.31	16076720	1456	95
France	4 countries (Aq,Lor,Nor B, Nor H)	Levy-Marchal C, 1990	(188)	1988-1988	7.17	3.04	1736066	124	90
France	Aquitaine	Barat P, 2008	(28)	1988-2004	11.70	4.42	3779331	443	95
France	Franche-Comté	Mauny F, 2005	(208)	1980-1998	7.01	1.36	4347369	308	81
Germany	Baden-Württemberg	Ehehalt S, 2008	(85)	1987-2003	14.06	2.80	28363640	4017	97
Germany	Baden-Württemberg	Neu A, 1997	(222)	1987-1993	10.63	3.74	11859042	1251	96
Germany	NW	Rosenbauer J, 1999	(270)	1993-1995	8.10	NA	12555556	1017	83
Germany	Saxony	Galler A, 2010	(107)	1999-2008	17.43	4.05	4831705	850	94
Greece	Crete	Mamoulakis D, 2003	(204)	1990-2001	5.98	1.93	1459728	89	98
Greece	NW	Dacou-Voutetakis C, 1995	(70)	1992-1992	6.03	3.94	1790691	115	NA

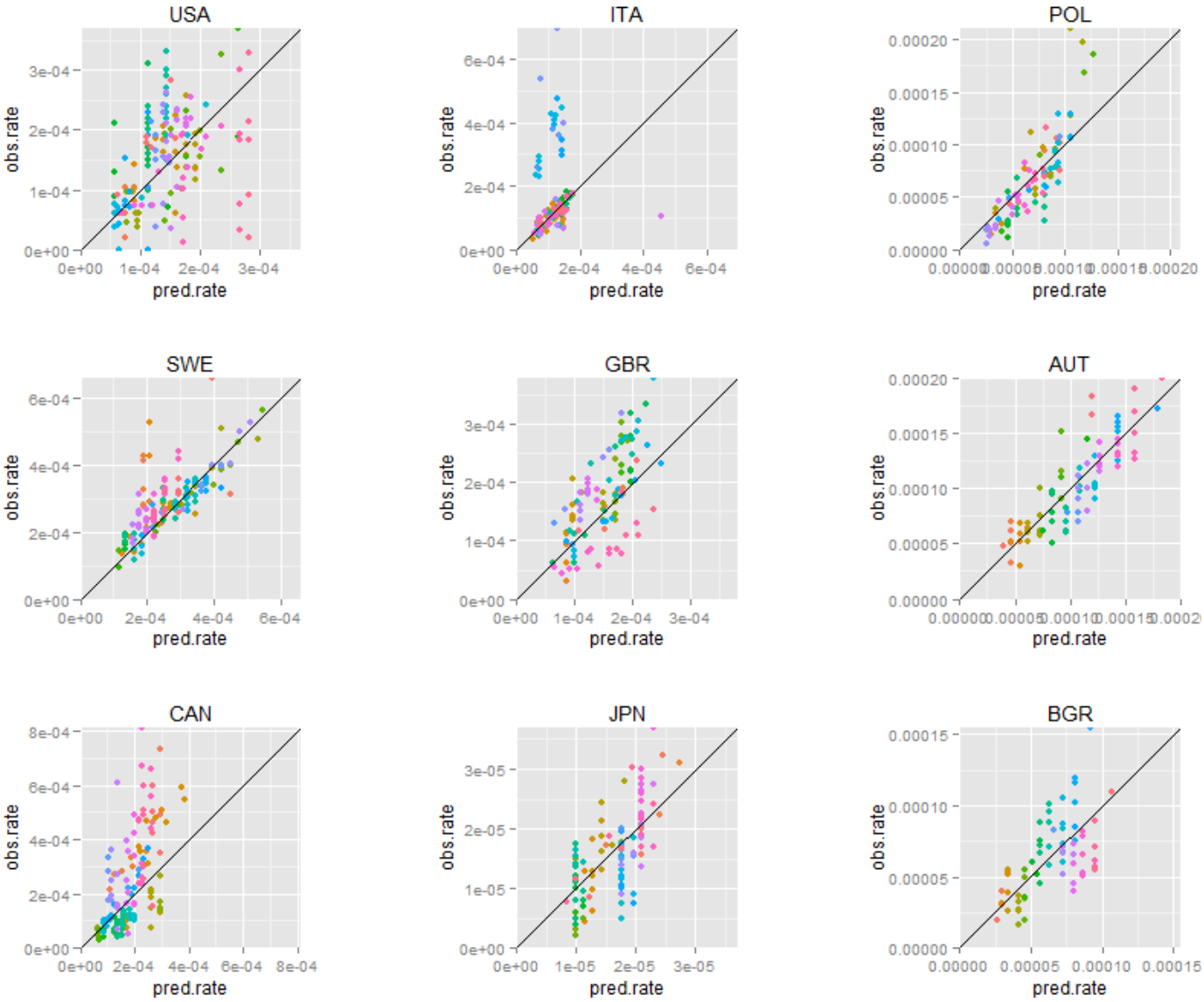
Continent/Country	Area	First Author, publication year	Ref	Period	Mean T1D Inc.	SD	Population at risk	Number of cases	Asc. %
Hungary	18 of 19 countries (less Budapest)	Gyurus EK, 2012	(124)	1989-2009	12.58	4.60	28487914	3610	96
Hungary	18 of 19 countries (less Budapest)	Soltesz G L, 1990	(299)	1978-1987	6.14	2.71	18763350	1166	96
Iceland	NW	Helgason T, 1992	(131)	1970-1989	9.40	1.98	1287610	121	100
Ireland	NW	Roche E F, 2002	(266)	1989-1994	16.37	5.28	844642	140	91
Italy	Abruzzo Region (L'Alquila, Chieti, Pescara, Teramo)	Altobelli E, 2002	(14)	1990-1995	9.31	1.73	1099400	102	98
Italy	Central Italy	Carle F, 2004	(53)	1990-1999	9.43	1.59	12239675	1161	98
Italy	Liguria	Cotellessa M, 2003	(67)	1989-1998	12.35	3.06	1754417	219	99
Italy	Liguria	Mazzella M, 1994	(209)	1987-1991	11.89	3.13	973499	118	99
Italy	Lombardia	Calori G, 1990	(50)	1983-1984	6.24	3.31	3555925	236	100
Italy	Marche Region	Cherubini V, 1994	(61)	1990-1992	7.97	3.41	647951	52	100
Italy	NW_39.7%	Bruno G, 2010	(43)	1990-2003	12.55	3.90	42209659	5180	NA
Italy	Pavia	Tenconi M T , 1995	(317)	1988-1992	10.03	5.38	291100	31	100
Italy	Piedmont	Bruno G, 2009	(46)	1984-2004	11.86	3.13	9536077	1135	NA
Italy	Rome and Lazio Region	Sebastiani L, 1996	(283)	1989-1993	7.87	1.78	5118966	403	85
Italy	Sardinia (Oristano)	Frongia O, 1997	(102)	1993-1996	54.43	14.76	101028	54	100
Italy	Sardinia	Casu A, 2004	(57)	1989-1999	38.63	8.32	3083065	1214	91
Italy	Sardinia	Karvonen M, 1998	(159)	1989-1992	33.83	8.18	1237440	425	91
Italy	Sardinia	Songini M , 1998	(302)	1989-1994	33.24	6.59	1376178	459	91
Italy	Sicily (Catania)	Arpi M, 2002	(20)	1989-1998	12.35	3.31	2205644	273	99
Italy	South Italy	Carle F, 2004	(53)	1990-1999	8.87	3.30	17171537	1354	98
Italy	Turin	Bruno G, 2001	(44)	1984-1996	9.75	2.47	4127879	401	98
Italy	Turin	Bruno G, 2009	(46)	1984-2004	11.33	3.71	2714027	305	NA
Italy	Veneto Region	Pinelli L, 1998	(247)	1993-1994	10.53	2.97	1210502	128	89
Lithuania	NW	Pundziute-Lycka A, 2004	(253)	1983-2000	7.50	3.05	13788189	1054	96
Luxembourg	NW	De Beaufort C E , 1988	(75)	1977-1986	10.67	3.11	637761	68	94
Macedonia (TFYR)	Skopje	Kocova M, 1993	(168)	1985-1991	2.49	0.97	4200000	105	100
Malta	NW	Formosa N, 2012	(100)	2006-2010	23.87	14.26	341480	81	100
Malta	NW	Schranz A G , 1989	(280)	1980-1987	13.75	6.13	697504	93	NA
Montenegro	NW	Samardzic M, 2010	(274)	1997-2006	13.53	5.04	1356619	184	100
Netherlands	NW	Ruwaard D, 1994	(271)	1988-1990	11.50	4.48	5435320	624	81
Norway	NW	Aamodt G, 2007	(3)	1973-2003	22.66	8.32	22151884	5031	NA
Norway	NW	Joner G, 2004	(151)	1989-1998	22.52	7.07	8549357	1905	98
Poland	Bialystok	Kretowski A, 2001	(172)	1994-1998	7.30	4.67	283912	25	99
Poland	Cracow Province	Dziatkowiak H, 2002	(83)	1987-1999	8.08	2.91	3377534	273	100
Poland	Midwestern	Rewers M, 1987	(264)	1970-1984	5.44	2.98	9071949	397	100
Poland	NW_35%	Jarosz-Chobot P, 2011	(148)	1989-2004	11.23	7.60	5540524	565	NA
Poland	Province of Rzeszow	Grzywa M A, 1995	(123)	1980-1992	5.39	1.53	2445781	130	99
Poland	Silesia	Jarosz-Chobot P, 2000	(147)	1989-1997	6.43	3.39	7928628	528	NA
Poland	Silesia	Jarosz-Chobot P, 2010	(146)	1989-2005	11.98	5.08	5824740	728	NA
Poland	Warsaw	Dziatkowiak H, 2002	(83)	1987-1999	7.58	2.98	3598612	273	100
Poland	Warsaw	Wysocki M J , 1992	(366)	1983-1988	4.87	1.66	1591171	77	90
Poland	Wielkopolska	Rewers M , 1989	(265)	1970-1985	4.74	2.65	10179406	478	90

Continent/Country	Area	First Author, publication year	Ref	Period	Mean T1D Inc.	SD	Population at risk	Number of cases	Asc. %
Poland	Wroclaw Province	Dziatkowiak H, 2002	(83)	1987-1999	6.29	1.71	3100903	195	100
Portugal	Algarve, Coimbra, Madeira Island, Portalegre	Diamond, 2006	(318)	1990-1994	14.60	NA	387332	57	87
Portugal	Coimbra	Diamond, 2006	(318)	1990-1999	9.60	NA	246302	24	100
Portugal	Madeira Island	Diamond, 2006	(318)	1990-1999	6.90	NA	459957	32	100
Portugal	Portalegre	Diamond, 2006	(318)	1990-1994	21.30	NA	21261	5	93
Romania	Bucharest	Ionescu-Tirgoviste C, 1994	(143)	1981-1991	3.47	1.88	5020730	176	NA
Romania	NW	Ionescu-Tirgoviste C, 2004	(142)	1988-1997	3.02	1.48	47040120	1487	100
Romania	NW	Serban V , 2001	(285)	1992-1995	3.71	2.29	19791336	706	94
Russian Federation	Moscow	Pronina E A, 2008	(251)	1996-2005	12.07	4.65	15784076	2031	94
Russian Federation	Novosibirsk	Podar T, 1993	(249)	1983-1989	4.73	3.20	2401787	112	NA
Serbia	Belgrade	Vlajinac H D, 1995	(347)	1982-1992	8.00	3.73	3196875	259	90
Slovakia	NW	Michalkova D, 2002	(211)	1985-2000	9.15	3.64	19477039	1776	99
Slovenia	NW	Battelino T, 1998	(30)	1988-1995	7.77	2.94	3148944	252	100
Slovenia	NW	Bratina N U, 2001	(42)	1990-1998	8.72	2.35	3343896	299	96
Slovenia	NW	Radosevic B, 2013	(256)	1998-2010	13.83	2.91	3872968	541	100
Spain	Badajoz	Morales-Perez F M, 2000	(218)	1992-1996	17.23	7.42	651020	115	95
Spain	Catalonia	Goday A, 1992	(112)	1987-1990	10.60	6.58	5029022	581	90
Spain	Caceres	Lora-Gomez R E, 2005	(198)	1988-1999	16.67	3.46	817104	137	99
Spain	Madrid	Serrano Rios M, 1990	(287)	1985-1988	10.60	0.24	4420972	469	90
Spain	Navarre	Bahíllo M, 2007	(27)	2003-2004	22.17	9.24	587206	130	100
Spain	Navarre	Chueca M, 1997	(63)	1975-1991	9.04	4.20	1894055	177	98
Sweden	Kronoberg	Thunander M, 2008	(320)	1998-2001	41.10	24.83	96474	40	100
Sweden	Northern	Hagglof B, 1982	(126)	1938-1977	24.12	11.39	7931274	1915	100
Sweden	NW	Berhan Y, 2011	(33)	1978-2007	30.65	10.73	47617789	14694	96
Sweden	NW	Dahlquist G G, 2000	(73)	1978-1997	26.32	7.77	31139774	8210	98
Sweden	NW	Dahlquist G G, 2011	(74)	1983-2007	39.24	11.32	15997395	6358	96
Sweden	South-eastern	Holmqvist B M, 2008	(135)	1977-2001	26.75	7.18	7002150	1873	NA
Sweden	Stockholm	Gopinath S, 2008	(116)	1990-2003	27.04	4.41	2664436	720	NA
Switzerland	NW	Schoenle E J, 2001	(279)	1991-1999	6.31	2.54	11860379	751	97
Ukraine	NW	Timchenko OI, 1996	(321)	1985-1992	8.10	NA	89099520	7217	NA
United Kingdom	Bradford	Feltbower R G, 2002	(93)	1978-1998	13.10	4.39	2211804	289	NA
United Kingdom	England - Oxford region	Gardner S G, 1997	(109)	1985-1996	18.82	7.27	5637500	1053	96
United Kingdom	England - Cornwall	Zhao H X, 1999	(376)	1975-1996	14.73	4.93	3269332	488	94
United Kingdom	Leicestershire	Burden A C , 1989	(48)	1951-1980	6.72	4.55	4963510	349	NA
United Kingdom	Leicestershire	Raymond N T , 2001	(261)	1989-1998	18.93	8.75	1718340	309	90
United Kingdom	Northern Ireland	Cardwell C, 2007	(52)	1989-2003	24.79	7.63	5741618	1433	99
United Kingdom	NW	Bloom A, 1975	(38)	1973-1974	7.67	0.75	29642000	2274	NA
United Kingdom	NW	Imkampe AK, 2011	(141)	1991-2008	19.32	5.17	7637391	1566	NA
United Kingdom	NW	Metcalfe M A , 1991	(210)	1988-1988	13.67	3.96	11803542	1600	NA
United Kingdom	NW	Wadsworth E, 1995	(348)	1992-1992	9.25	NA	4183784	387	99
United Kingdom	Scotland (Glasgow, Lanarkhire, Argyl and Clyde)	Barclay R P C, 1988	(29)	1976-1986	17.66	2.08	4983604	874	NA
United Kingdom	Scotland	Patterson C C , 1983	(245)	1968-1976	12.83	6.57	9752375	1283	NA
United Kingdom	Scotland	Patterson C C , 1988	(244)	1977-1983	19.83	6.31	6839304	1397	NA

Continent/Country	Area	First Author, publication year	Ref	Period	Mean T1D Inc.	SD	Population at risk	Number of cases	Asc. %
United Kingdom	Scotland	Rangasami J J, 1997	(260)	1984-1993	23.87	8.31	9728160	2326	99
United Kingdom	Yorkshire	Feltbower R G, 2003	(94)	1978-2000	8.32	3.17	31358793	2597	98
United Kingdom	Yorkshire	Harron KL, 2011	(129)	1978-2007	18.00	6.02	21533206	3911	98
LATIN AMERICA AND THE CARIBBEAN									
Argentina	Avellaneda	Sereday M S, 1994	(286)	1985-1989	6.67	0.77	481417	32	NA
Antigua and Barbuda	NW	Tull E S , 1997	(330)	1989-1993	3.45	NA	125935	4	100
Bahamas	NW	Peter SA, 2005	(246)	2001-2002	10.10	NA	89109	9	100
Barbados	NW	Jordan O W, 1994	(152)	1982-1991	5.56	2.56	642329	36	94
Brazil	Rio Grande do Sul (Passo Fundo)	Lisboa H R K , 1998	(197)	1996-1996	12.00	NA	50098	6	100
Brazil	São Paulo (Bauru)	Negrato C, 2010	(221)	1986-2006	10.40	3.96	1673132	176	NA
Brazil	São Paulo	Ferreira R G, 1993	(95)	1987-1991	7.73	2.46	714870	55	99
British Virgin Islands	British Virgin Islands (Tortola)	Tull E S , 1997	(330)	1989-1993	3.81	NA	21256	1	100
Chile	IX region	Larenas G, 1996	(180)	1980-1993	1.37	0.70	2571228	35	97
Chile	Santiago of Chile	Carrasco E, 1996	(54)	1986-1992	2.40	0.64	10698724	252	98
Chile	Santiago of Chile (Comunes of Metropolitan region)	Torres-Avilés F, 2010	(323)	2000-2005	6.30	1.11	9754547	613	100
Colombia	Bogota	Diamond, 2006	(318)	1990-1990	3.80	NA	1958529	74	97
Colombia	Cali	Diamond, 2006	(318)	1995-1999	0.50	NA	3294727	16	NA
Cuba	NW	Diamond, 2006	(318)	1990-1999	2.30	NA	24714580	568	63
Mexico	NW	Gomez-Diaz RA, 2012	(114)	2000-2010	6.13	2.70	33666691	2095	NA
Peru	Lima	Diamond, 2006	(318)	1990-1994	0.50	NA	10674410	53	68
Puerto Rico	NW	Frazer de Llado T E, 1998	(101)	1985-1994	16.72	1.77	9581239	1602	95
United States Virgin Islands	US Virgin Islands	Tull E S , 1991	(331)	1979-1988	7.38	8.12	336930	25	92
United States Virgin Islands	US Virgin Islands (Saint Croix)	Tull E S , 1997	(330)	1989-1993	8.22	2.65	181411	15	100
Uruguay	Montevideo	Diamond, 2006	(318)	1992-1992	8.30	NA	320157	27	97
NORTH AMERICA									
Canada	Alberta (Edmonton)	Toth E L, 1997	(324)	1990-1995	26.37	10.25	821729	217	84
Canada	Manitoba	Blanchard J F, 1997	(36)	1985-1993	20.33	7.94	2132163	434	95
Canada	Newfoundland	Newhook L, 2004	(223)	1987-2002	35.82	18.26	811466	293	95
Canada	Newfoundland and Labrador	Newhook LA, 2012	(225)	1987-2010	39.01	11.18	2471297	931	NA
Canada	Québec	Legault L, 2006	(184)	1989-2000	15.34	5.38	1312792	197	NA
Canada	Québec (Montreal)	Siemiatycki J, 1986	(292)	1971-1983	8.46	3.32	9445097	802	94
Canada	Québec (Montreal)	West R, 1979	(356)	1971-1977	8.76	1.63	2430829	213	98
United States	Alabama (Jefferson County)	Wagenknecht L E , 1991	(350)	1979-1988	13.85	5.46	1479075	207	NA
United States	California (San Diego)	Lorenzi M, 1985	(199)	1978-1981	7.30	2.08	835728	61	86
United States	Chicago	Lipton R, 1995	(196)	1985-1990	10.75	6.17	3109060	333	86
United States	Colorado	Vehik K, 2007	(344)	1978-1988	17.35	10.13	8937132	1675	97

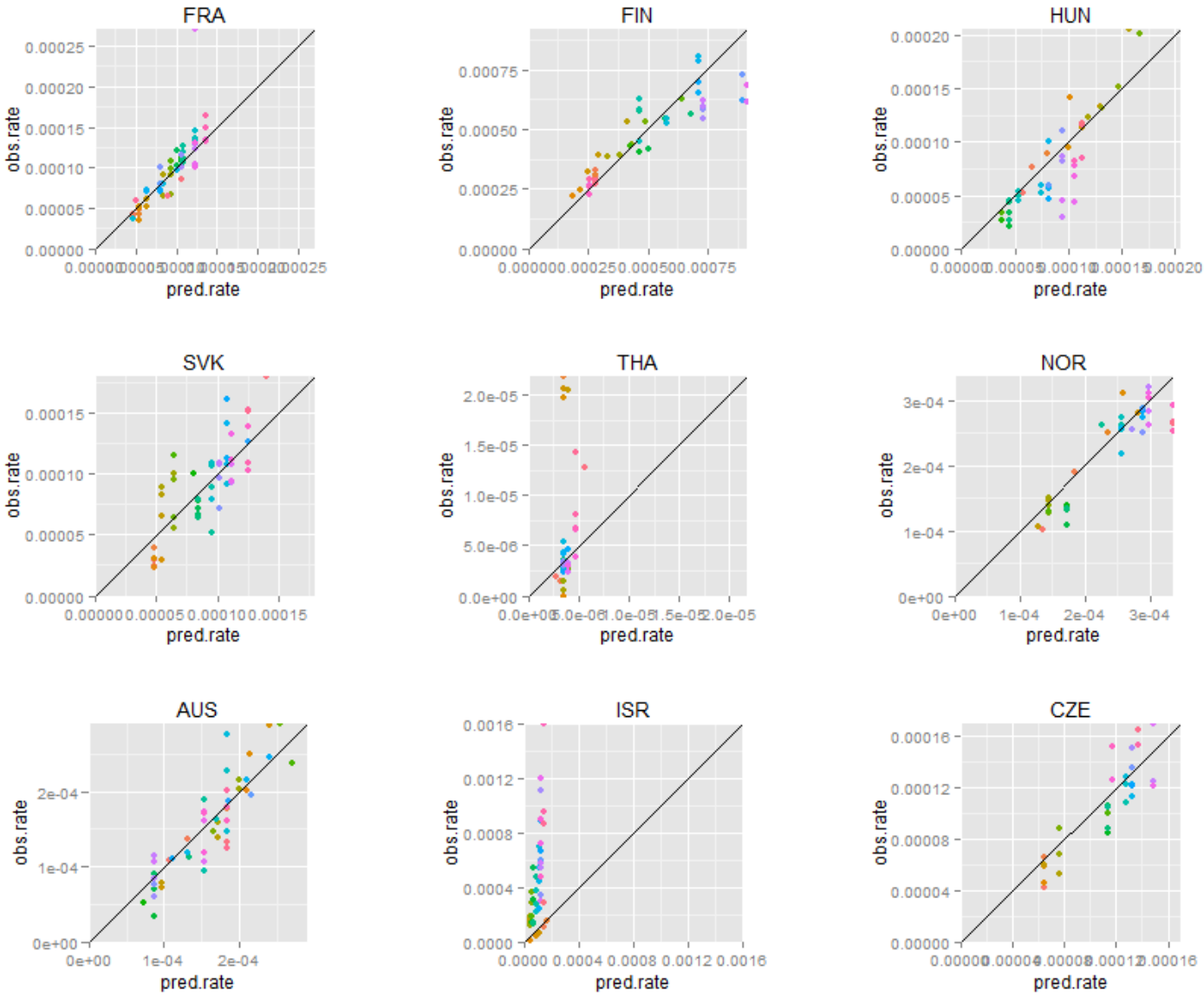
Continent/Country	Area	First Author, publication year	Ref	Period	Mean T1D Inc.	SD	Population at risk	Number of cases	Asc. %
United States	Hawaii (Oahu)	Patrick S L, 1997	(240)	1980-1990	7.04	NA	1605483	113	97
United States	Michigan	North F A , 1977	(228)	1958-1972	12.63	7.73	17884326	2262	NA
United States	Pennsylvania (Allegheny)	Libman I M, 1998	(191)	1990-1994	17.37	8.01	1215083	207	98
United States	Pennsylvania (Allegheny)	Rewers M , 1989	(265)	1970-1985	13.69	7.71	6775996	850	90
United States	Philadelphia	Lipman T H, 2002	(194)	1990-1994	13.30	5.76	1600755	209	96
United States	Philadelphia	Lipman T H, 2006	(195)	1995-1999	14.93	6.82	1600755	234	96
United States	Philadelphia	Lipman T H, 1993	(193)	1985-1989	13.14	5.57	1680113	212	93
United States	Rhode Island	Fishbein H A, 1982	(96)	1979-1980	12.67	6.51	197887	26	NA
United States	Seven areas	Bell R, 2009	(31)	2002-2005	14.01	9.82	14838874	3297	NA
United States	Wisconsin	Allen C, 1986	(13)	1970-1979	18.20	6.81	1789270	332	90
OCEANIA									
Australia	New South Wales	Taplin G E, 2005	(313)	1990-2002	19.35	6.75	16179667	3122	100
Australia	New South Wales	Verge C F, 1994	(345)	1990-1991	14.45	6.05	2419498	349	99
Australia	NW	Catanzarit L, 2009	(58)	2000-2006	22.50	7.18	28028715	6350	97
Australia	Sydney (Suthern Metropolitan Heath Region)	Sutton L, 1989	(308)	1984-1987	12.91	7.29	685476	90	NA
Australia	Victoria	Chong J W, 2007	(62)	1999-2002	19.33	6.69	3930965	767	99
Australia	Western Australia	Haynes A, 2004	(130)	1985-2002	16.47	4.75	6874359	1136	100
Australia	Western Australia	Kelly H A, 1992	(164)	1985-1989	13.16	4.16	2006600	265	99
New Zealand	Canterbury	Willis J A, 2002	(364)	1970-1999	14.19	5.81	2808234	398	100
New Zealand	NW	Crossley J R, 1980	(68)	1968-1972	8.85	NA	4826495	428	NA
Papua New Guinea	NW	Ogle G D, 2001	(230)	1996-2000	0.08	NA	10825215	9	NA

5.2.5.4 Observed vs predicted incidence of T1D by countries using an APC model



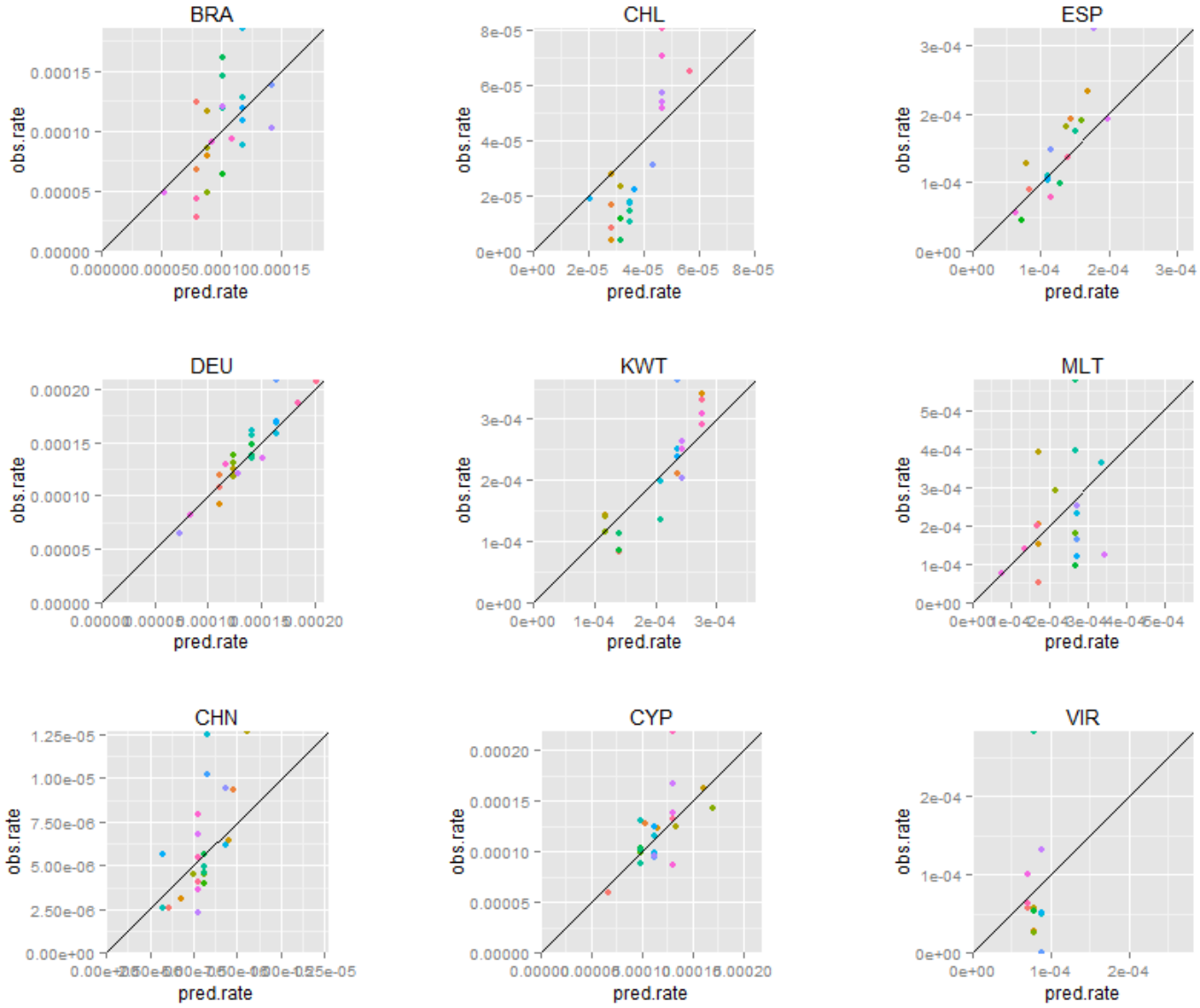
USA: United States of America; ITA: Italy; POL: Poland; SWE: Sweden; GBR: United Kingdom; AUT: Austria; CAN: Canada; JPN: Japan; BGR: Bulgaria. For each country there are several studies, dots represent these studies. Information from a particular study are in the same color in each country, color through different countries are independent.

SI Figure 30: Observed vs predicted incidence of T1D in countries with large incidence rates using an APC mode



FRA: France; FIN: Finland; HUN: Hungary; SVK: Slovakia; THA: Thailand; NOR: Norway; AUS: Australia, ISR: Israel; CZE: Czech Republic. For each country there are several studies, dots represent these studies. Information from a particular study are in the same color in each country, color through different countries are independent.

SI Figure 31: Observed vs predicted incidence of T1D by countries with medium incidence rates using an APC mode



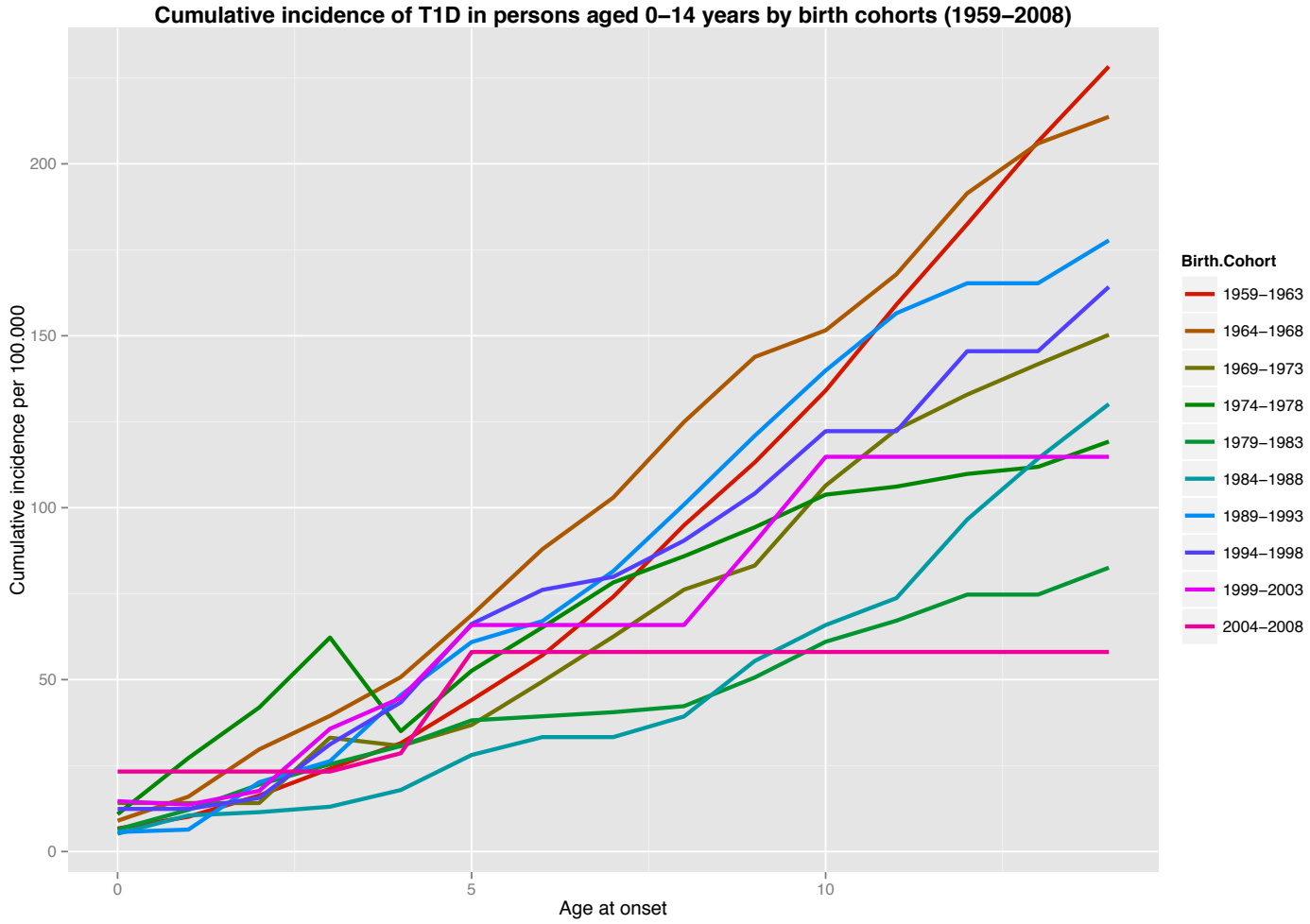
BRA: Brazil; CHL: Chile; ESP: Spain; DEU: Germany; KWT: Kuwait; MLT: Malta; CHN: China; CYP: Cyprus; VIR: United States Virgin Islands.

SI Figure 32: Observed vs predicted incidence of T1D by countries with small incidence rates using an APC mode

5.3 Additional analyses of the global incidence trends of T1D

5.3.1.1 Cumulative incidence of T1D by birth cohorts

Cumulative incidence of T1D was calculated for the birth cohorts 1959-2008 of the studies included in the APC model, where cohort = period-age.

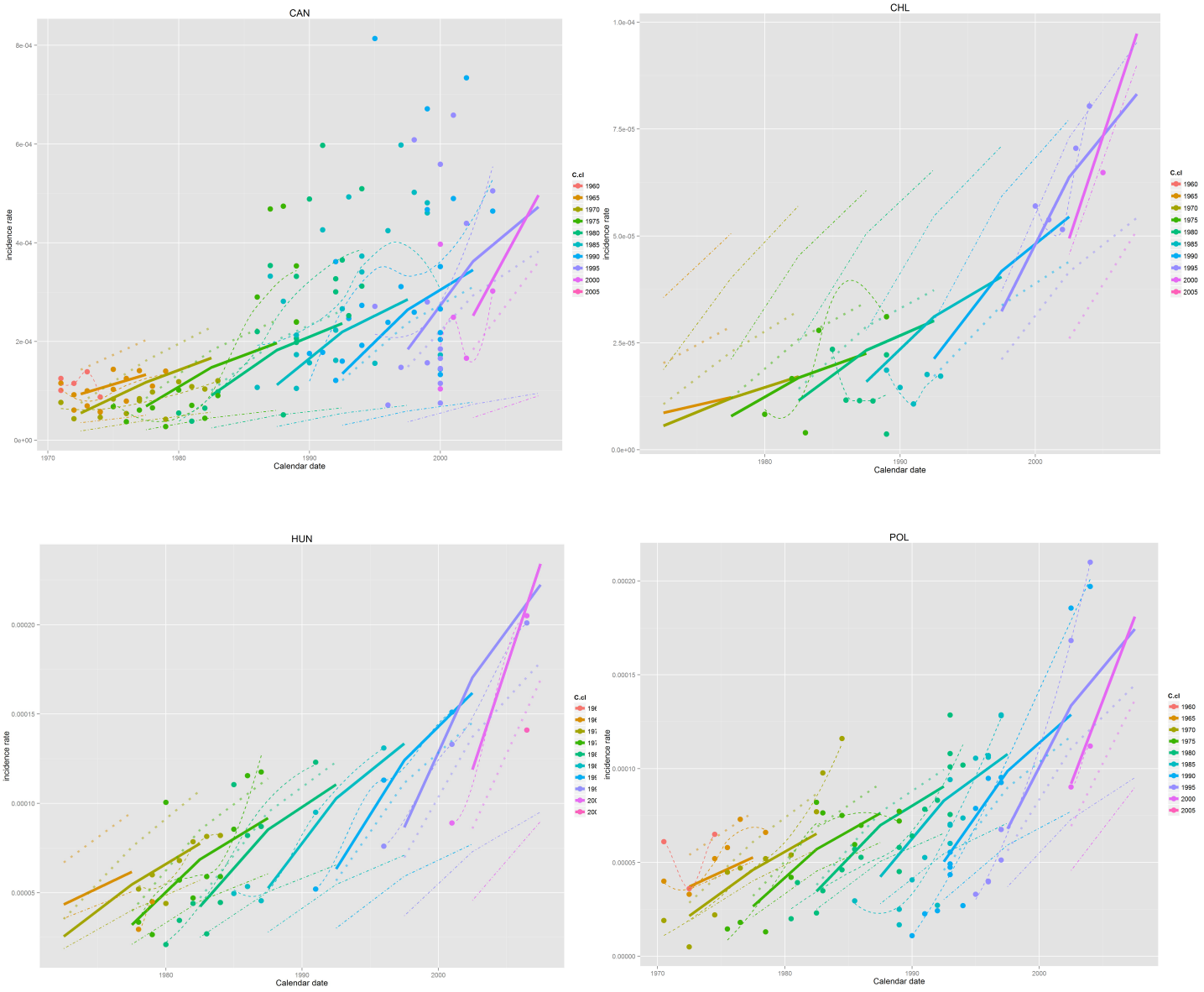


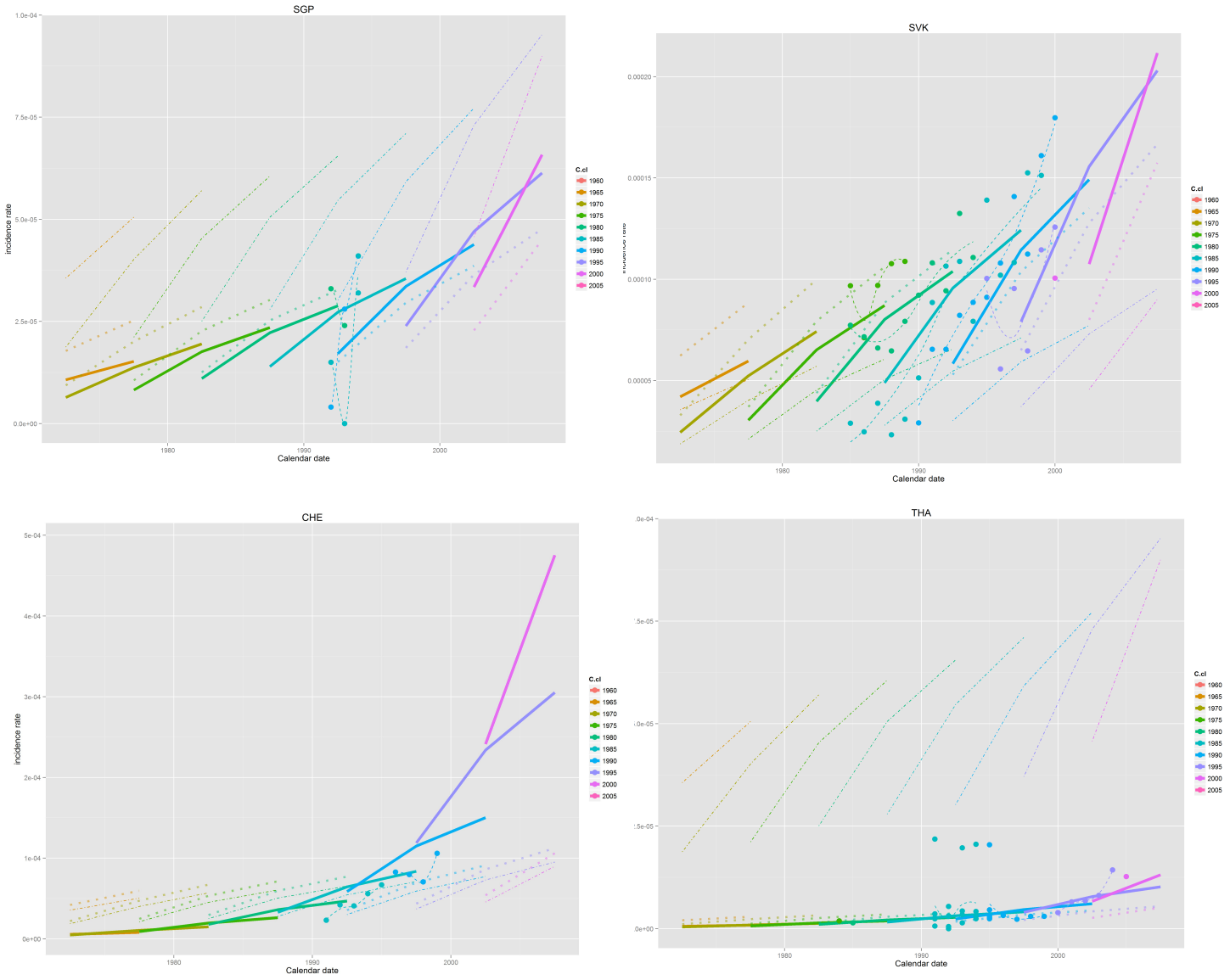
SI Figure 33: Cumulative incidence of T1D in persons aged 0-14 years by birth cohorts 1959- 2008

5.3.1.2 Incidence trends of T1D and temporal changes on the economic growth of countries

In an exploratory analysis, temporal trends of T1D incidence by each one of the 89 countries were analyzed. Comparing the resulting drift of each country allows to distinguish differences in the evolution of the T1D by birth cohort in each country.

The following figures show the results retrieved for the countries with a higher incidence growth with respect to countries with an average growth: Canada (CAN), Chile (CHL), Hungary (HUN), Poland (POL), Singapore (SGP), Slovakia (SVK), Switzerland (CHE), and Thailand (THA).

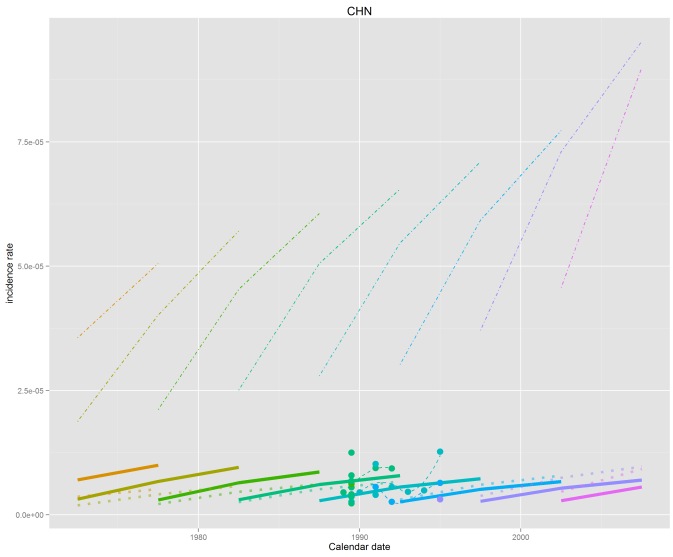


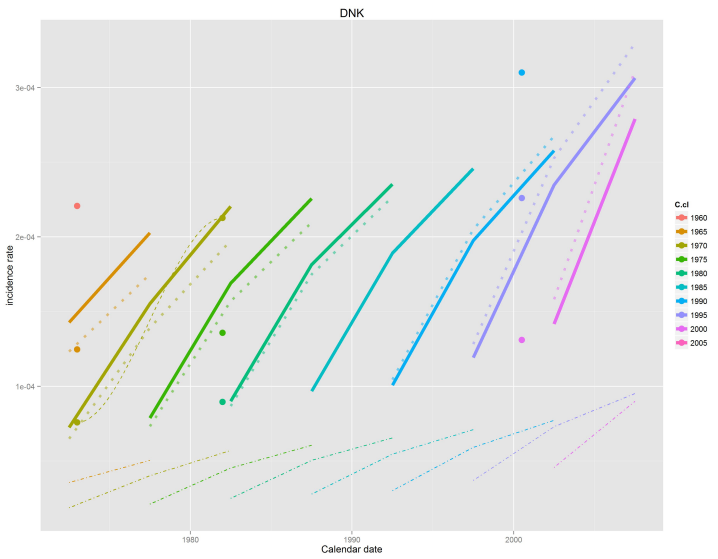


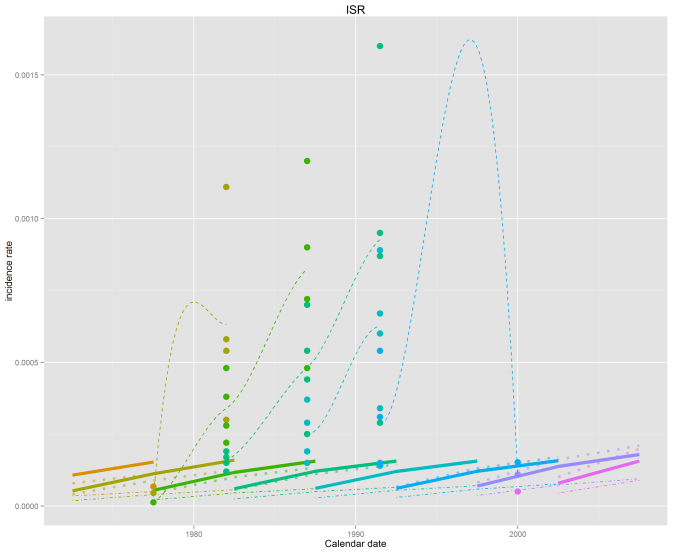
CAN: Canada, CHL: Chile, HUN: Hungary, POL: Poland, SGP: Singapore, SVK: Slovakia, CHE: Switzerland, and THA: Thailand.

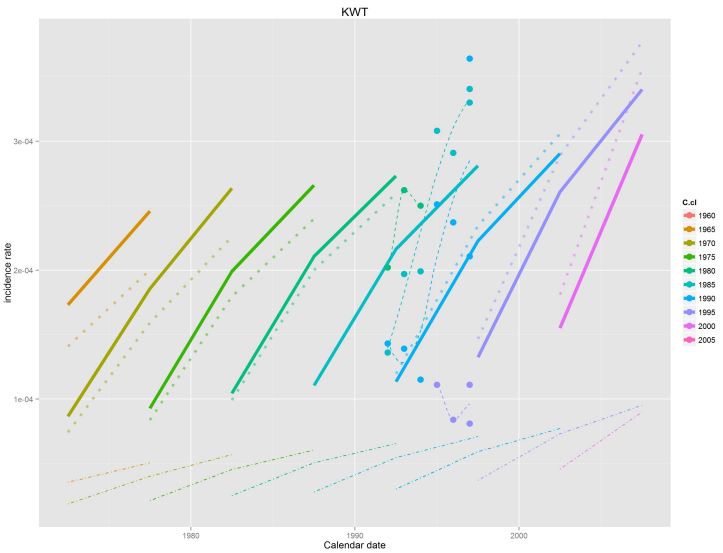
SI Figure 34: Countries with a higher incidence growth respect to countries with an average growth

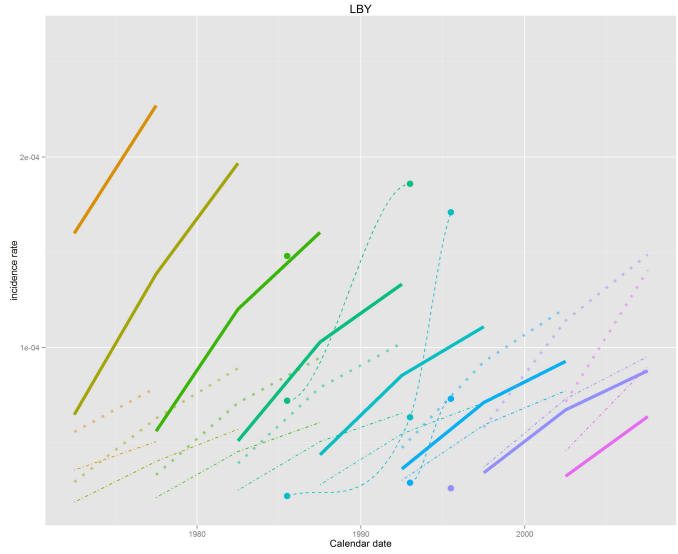
The following figures show the results retrieved for the countries with a lower incidence growth respect to countries with an average growth: China (CHN), Denmark (DNK), Israel (ISR), Kuwait (KWT), Libya (LBY), Norway (NOR), and Romania (ROU).

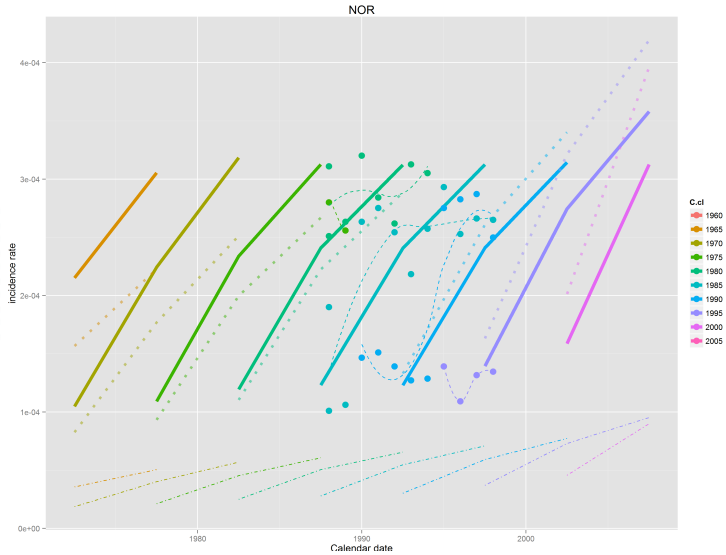

CHN
incidence rate
7.5e-05
5.0e-05
2.5e-05
0.0e+00
1980
1990
2000
Calendar date
C.cl
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005

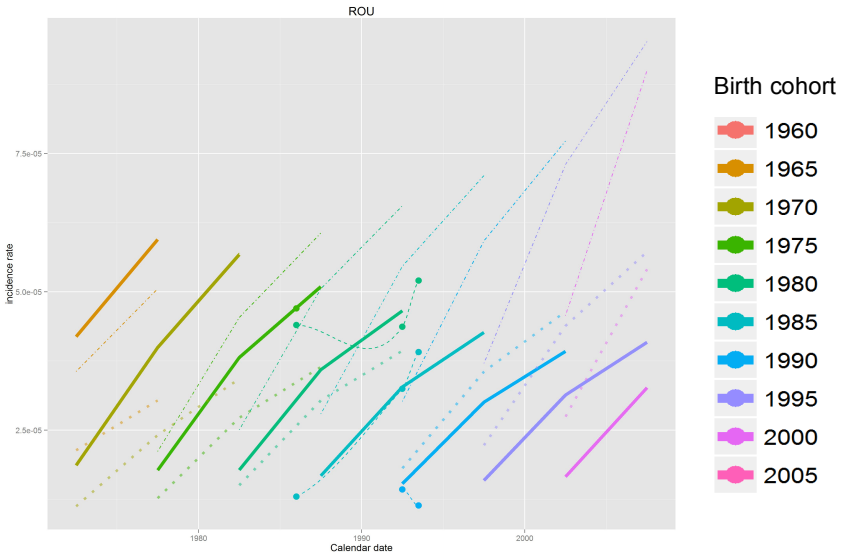

DNK
incidence rate
3e-04
2e-04
1e-04
1980
1990
2000
Calendar date
C.cl
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005


ISR
incidence rate
0.0015
0.0010
0.0005
0.0000
1980
1990
2000
Calendar date
C.cl
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005


KWT
incidence rate
3e-04
2e-04
1e-04
1980
1990
2000
Calendar date
C.cl
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005


LBY
incidence rate
2e-04
1e-04
1980
1990
2000
Calendar date
C.cl
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005


NOR
incidence rate
4e-04
3e-04
2e-04
1e-04
0e+00
1980
1990
2000
Calendar date
C.cl
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005

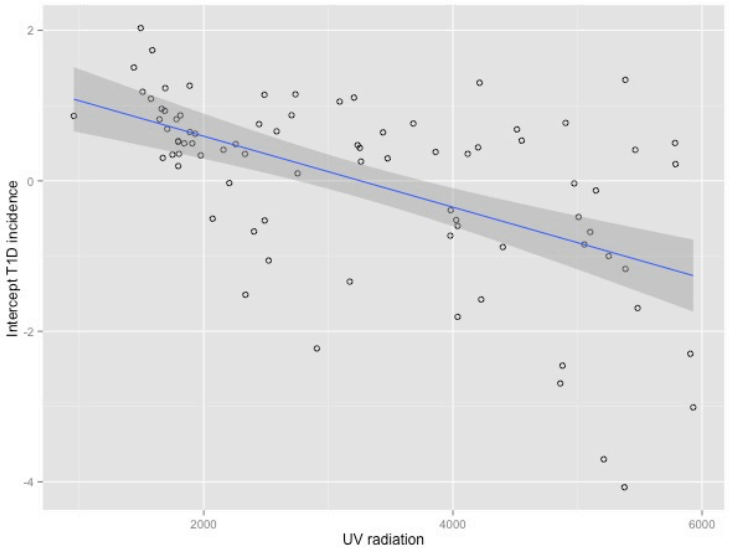


CHN: China, DNK: Denmark, ISR: Israel, KWT: Kuwait, LBY: Libya, NOR: Norway, and ROU: Romania.

SI Figure 35: Countries with a lower per capita GDP respect to countries with an average growth

5.3.1.3 Correlations between incidence of T1D predicted in the APC model and environmental indicators

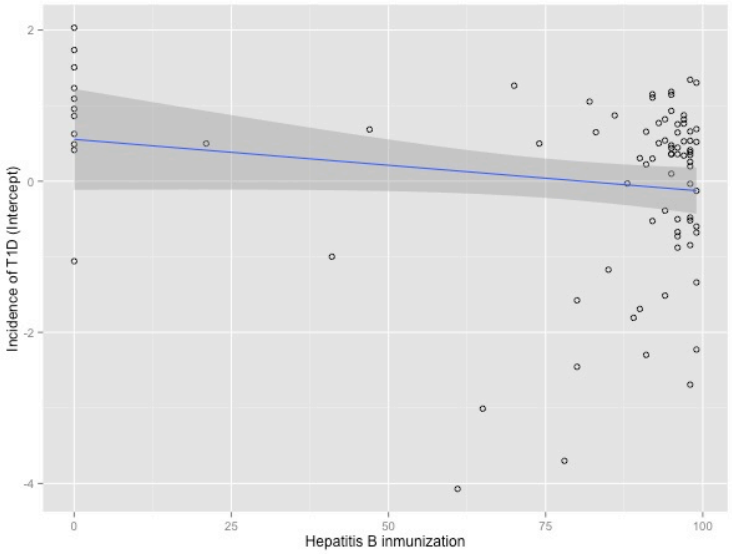
Five significant predictors of the country-to-country variation of T1D incidence, retrieved in a previous study (81), were correlated with the retrieved intercept of the predicted T1D, after perform an APC model. **SI Figures: 36 to 40**.



Sp. cor. = -0.56
p-value = 4.44 x 10^{-07}

The shaded region indicates 95% CI

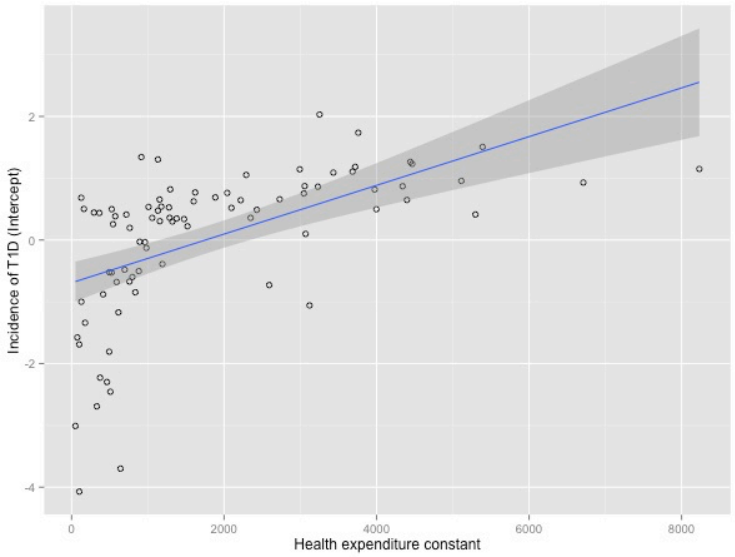
SI Figure 36: Predicted incidence of T1D and UV radiation (J/mt2, 2004)



Sp. cor. = -0.16
p-value = 0.155

The shaded region indicates 95% CI

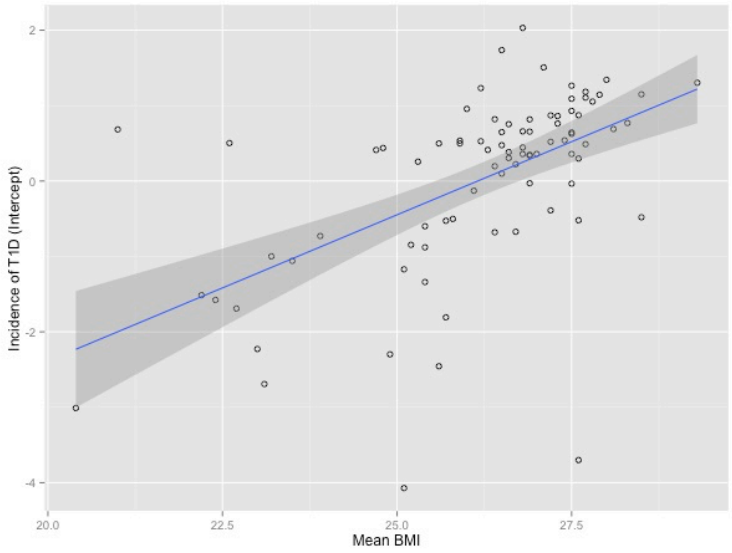
SI Figure 37: Predicted incidence of T1D and Hepatitis B (HepB3) immunization



Sp. cor. = 0.72
p-value = < 2.27 x 10^{-13}

The shaded region indicates 95% CI

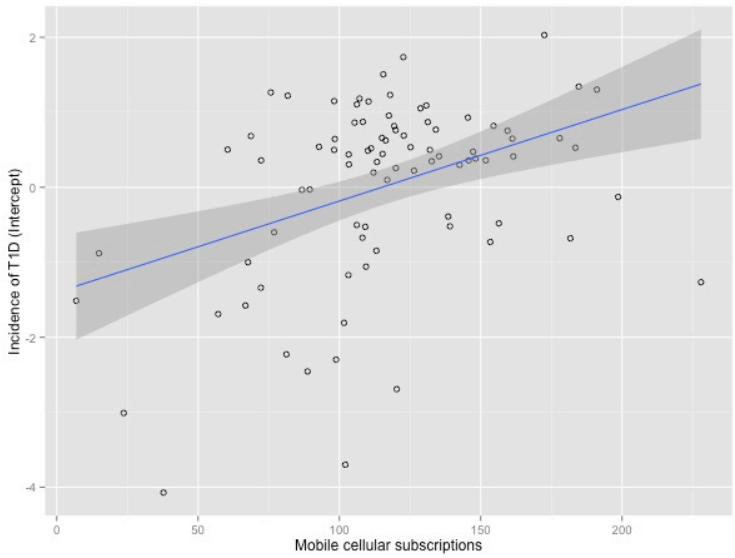
SI Figure 38: Predicted incidence of T1D and Health expenditure per capita (constant 2005 international $)



Sp. cor. = 0.57
p-value = 4.47 x 10^{-08}

The shaded region indicates 95% CI

SI Figure 39: Predicted incidence of T1D and Mean BMI (kg/m2) Male >20 yr.



Sp. cor. = 0.32
p-value = 0.002

The shaded region indicates 95% CI

SI Figure 40: Predicted incidence of T1D and Mobile cellular subscriptions (per 100 people)

5.3.1.4 Comparison of environmental correlations using the intercept of the T1D incidence retrieved in the APC model and the incidence of T1D retrieved in the systematic review

Table 21 compare the retrieved intercept of the incidence of T1D retrieved using the APC model presented above, in which the age, the period and the birth cohort of the retrieved incidences were adjusted, and the incidence retrieved in our systematic review and described in **chapter 3** (81).

SI Table 21: Comparison environmental correlations and incidence of T1D by countries, adjusted using am APC model and crudes

Category/ Cod.		Variable	Intercept of incidence of T1D in the APC model					Incidence of T1D in the review (81)					Reference
			Countries with available info. (n of 89)	Spearman Correlation		Mean	SD	Countries with available info. (n of 80)	Spearman Correlation		Mean	SD	
				Estimate (rho)	p-value				Estimate (rho)	p-value			
Climate and environment	**Agriculture**												
	CA_1	Agricultural land (% of land area)	86	0.03	8.19E-01	37	21	80	0.07	5.29E-01	37	21	WB
	CA_2	Arable land (% of land area)	86	0.00	9.82E-01	17	14	80	0.10	3.96E-01	17	14	WB
	CA_3	Cereal production (metric tons)	82	-0.03	7.94E-01	25999771	77463855	79	-0.03	8.02E-01	27600000	80200000	WB
	CA_4	Cereal yield (kg per hectare)	82	0.30	5.92E-03	4291	2077	78	0.33	2.77E-03	4419	2079	WB
	CA_5	Fertilizer consumption (kilograms per hectare of arable land)	80	0.11	3.23E-01	219	472	76	0.02	8.63E-01	233	488	WB
	CA_6	Forest area (% of land area)	86	-0.08	4.41E-01	30	20	80	-0.06	5.85E-01	29	19	WB
	CA_7	Permanent cropland (% of land area)	85	-0.32	3.00E-03	2	4	79	-0.36	1.08E-03	2	3	WB
	Environment												
	CE_8	Annual precipitation by country: values in millimeters. (Mean 1961-1999)	80	-0.19	9.44E-02	885	601	77	-0.16	1.71E-01	846	583	WB
	CE_9	Annual temperatures by country: values in degrees Celsius. (Mean 1961-1999)	80	-0.33	2.48E-03	14	9	77	-0.44	**5.45E-05**	14	8	WB
	CE_10	CO2 emissions (metric tons per capita)	85	0.62	**3.62E-10**	7	6	80	0.61	**1.38E-09**	7	7	WB
	CE_11	Latitude	89	0.49	**1.31E-06**	29	25	80	0.56	**5.31E-08**	30	26	Google Maps
	CE_12	Longitude	89	-0.12	2.60E-01	12	61	80	-0.14	2.15E-01	15	59	Google Maps
	CE_13	Methane emissions (kt of CO2 equivalent)	77	-0.08	5.01E-01	79231	215420	75	-0.18	1.32E-01	81100	219000	WB

Category/ Cod.		Variable	Intercept of incidence of T1D in the APC model					Incidence of T1D in the review (81)					Reference
			Countries with available info. (n of 89)	Spearman Correlation		Mean	SD	Countries with available info. (n of 80)	Spearman Correlation		Mean	SD	
				Estimate (rho)	p-value				Estimate (rho)	p-value			
	CE_14	Nitrous oxide emissions (thousand metric tons of CO2 equivalent)	77	0.48	**-8.16E-02**	29914	77690	75	-0.15	1.94E-01	30500	79200	WB
	CE_15	Nitrous oxide emissions in industrial and energy processes (% of total nitrous oxide emissions)	77	0.29	1.08E-02	18	12	75	0.32	5.69E-03	18	12	WB
	CE_16	Outdoor air pollution (Annual PM10 [ug/m3])	81	-0.37	6.53E-04	52	39	77	-0.42	**1.38E-04**	52	40	WHO
	CE_17	PM10, country level (micrograms per cubic meter)	81	-0.29	9.53E-03	32	26	76	-0.32	5.25E-03	33	27	WB
	CE_18	UV radiation (J/mt2, 2004)	82	-0.56	**4.44E-08**	3254	1432	80	-0.63	**6.68E-10**	3153	1395	WHO
Demography													
	DD_19	Adolescent fertility rate (births per 1,000 women ages 15-19)	84	-0.35	1.07E-03	28	27	80	-0.47	**1.06E-05**	27	26	WB
	DD_20	Female mean age of childbearing (years)	85	0.36	8.47E-04	29	2	80	0.44	**3.62E-05**	29	2	UN
	DD_21	Fertility rate, total (births per woman)	84	-0.13	2.48E-01	2	1	80	-0.25	2.65E-02	2	1	WB
	DD_22	Life expectancy at birth, female (years)	84	0.52	**4.43E-07**	78	6	80	0.58	**1.94E-08**	79	6	WB
	DD_23	Life expectancy at birth, male (years)	84	0.57	**1.69E-08**	73	6	80	0.60	**3.53E-09**	73	6	WB
	DD_24	Life expectancy at birth, total (years)	84	0.55	**6.25E-08**	76	6	80	0.60	**2.92E-09**	76	6	WB
	DD_25	Population ages 0-14 (% of total)	85	-0.30	5.11E-03	21	8	80	-0.42	**1.10E-04**	21	8	WB
	DD_26	Population 15-64 years of age (% of total)	85	0.00	9.90E-01	67	5	80	0.07	5.29E-01	67	5	WB
	DD_27	Population ages 65 and above (% of total)	85	0.44	**3.13E-05**	12	6	80	0.51	**1.52E-06**	12	6	WB
	DD_28	Population growth (annual %)	87	-0.19	8.52E-02	1	1	80	-0.20	8.05E-02	1	2	WB
	DD_29	Population, female (% of total)	85	0.08	4.77E-01	50	4	80	0.14	2.15E-01	50	4	WB
	DD_30	Probability of dying between birth and the age of 40 years (both sexes combined) (deaths under age 40 per 1,000 live births)	85	-0.56	**2.16E-08**	54	55	80	-0.65	**9.91E-11**	52	48	UN
	DD_31	Rural population (% of total population)	87	-0.45	**1.51E-05**	31	21	80	-0.41	**1.46E-04**	30	20	WB
	DD_32	Total population 0-14 years (both sexes combined)	85	-0.25	2.23E-02	14825	48326	80	-0.32	4.16E-03	15200	49900	UN
	DD_33	Urban population (% of total population)	87	0.45	**1.50E-05**	69	21	80	0.41	**1.45E-04**	70	20	WB
Economic factors	**Country Economy**												
	EC_33	GDP growth (annual %)	85	-0.48	**3.08E-06**	3	4	79	-0.47	**1.07E-05**	3	4	WB
	EC_34	GDP per capita (constant 2005 US$)	85	0.68	**1.04E-12**	17207	17402	79	0.72	**9.05E-14**	17800	17900	WB
	EC_35	GDP per capita, PPP (constant 2005 international $)	83	0.65	**3.04E-11**	19687	14333	78	0.71	**5.24E-13**	20100	14500	WB
	Development												
	ED_36	Adjusted savings: education expenditure (% of GNI)	80	0.49	**4.43E-06**	5	2	75	0.45	**5.56E-05**	5	2	WB
	ED_37	Improved sanitation facilities (% of population with access)	84	0.66	**1.29E-11**	88	21	78	0.67	**2.08E-11**	88	21	WB
	ED_38	Improved water source (% of population with access)	83	0.66	**7.52E-12**	93	13	79	0.67	**1.60E-11**	94	13	WB
	ED_39	Energy use (kg of oil equivalent per capita)	84	0.68	**9.28E-13**	3151	2963	79	0.69	**1.22E-12**	3303	3045	WB
	ED_40	Energy use (kg of oil equivalent) per $1,000 GDP (constant	82	-0.06	5.94E-01	181	114	77	-0.14	2.13E-01	184	114	WB

Category/ Cod.		Variable	Intercept of incidence of T1D in the APC model					Incidence of T1D in the review (81)					Reference
			Countries with available info. (n of 89)	Spearman Correlation		Mean	SD	Countries with available info. (n of 80)	Spearman Correlation		Mean	SD	
				Estimate (rho)	p-value				Estimate (rho)	p-value			
		2005 PPP)											
	ED_41	Mobile cellular subscriptions (per 100 people)	86	0.32	2.41E-03	116	39	80	0.44	**4.93E-05**	113	36	WB
	ED_42	Population using solid fuels (Total population: urban + Rural)	84	-0.52	**3.87E-07**	13	24	80	-0.50	**2.68E-06**	11	23	WHO
	Health Economy												
	EH_43	External resources for health (% of total expenditure on health)	83	-0.59	**5.25E-09**	2	7	79	-0.62	**7.62E-10**	2	7	WB
	EH_44	Health expenditure per capita (current US$)	83	0.71	**6.12E-14**	1838	2150	79	0.73	**1.62E-14**	1942	2198	WB
	EH_45	Health expenditure per capita, PPP (constant 2005 international $)	83	0.72	**2.27E-14**	1843	1685	79	0.75	**2.32E-15**	1924	1721	WB
Health conditions	**Risk Factors for Non-Communicable Diseases**												
	HR_46	Mean BMI (kg/m2) (age-standardized estimate) Female +20	84	0.15	1.66E-01	26	2	80	0.11	3.32E-01	26	2	WHO
	HR_47	Mean BMI (kg/m2) (age-standardized estimate) Male +20	84	0.59	**4.47E-09**	26	2	80	0.63	**2.58E-10**	26	2	WHO
	HR_48	Mean systolic blood pressure in mm Hg (age-standardized estimate) Female +25	84	-0.24	2.56E-02	125	4	80	-0.18	1.19E-01	125	4	WHO
	HR_49	Mean systolic blood pressure in mm Hg (age-standardized estimate) Male +25	84	0.09	4.38E-01	131	4	80	0.19	8.41E-02	131	4	WHO
	HR_50	Mean Total Cholesterol in mmol/l (age-standardized estimate) Female+25	84	0.60	**1.94E-09**	5	0	80	0.62	**1.25E-09**	5	0	WHO
	HR_51	Mean Total Cholesterol in mmol/l (age-standardized estimate) Male +25	84	0.65	**3.43E-11**	5	0	80	0.70	**5.18E-13**	5	0	WHO
	HR_52	Obesity: % of defined population with a BMI ≥ 30 kg/m2 (age-standardized estimate) Both Sexes +20	84	0.31	3.88E-03	21	8	80	0.33	3.06E-03	21	8	WHO
	HR_53	Overweight: % population with a BMI ≥ 25 kg/m2 (age-standardized estimate) Both Sexes +20	84	0.37	**6.16E-04**	53	14	80	0.37	7.49E-04	53	14	WHO
	HR_54	Preterm birth rate (per 100 live births)	82	-0.24	3.00E-02	9	2	79	-0.27	1.44E-02	8	2	WHO
	HR_55	Prevalence of undernourishment (% of population)	79	-0.58	**1.74E-08**	8	8	75	-0.59	**2.41E-08**	8	8	WB
	HR_56	Total alcohol in litres of pure alcohol per capita consumption, estimation for 2008, Both Sexes +15	83	0.34	1.83E-03	9	5	79	0.44	**4.38E-05**	9	5	WHO
	Infectious Diseases and Immunization												
	HI_57	Diphtheria tetanus toxoid and pertussis (DTP3) immunization coverage among 1-year-olds (%)	84	0.17	1.24E-01	93	9	80	0.24	3.00E-02	94	7	WHO
	HI_58	Haemophilus influenzae type B vaccine (Hib3) immunization coverage among 1-year-olds (%)	84	0.38	**3.40E-04**	82	30	80	0.48	**5.20E-06**	82	30	WHO
	HI_59	Hepatitis B (HepB3) immunization coverage among 1-year-olds (%)	84	-0.16	1.55E-01	78	33	80	-0.18	1.07E-01	78	34	WHO

Category/ Cod.	Variable	Intercept of incidence of T1D in the APC model					Incidence of T1D in the review (81)					Reference
		Countries with available info. (n of 89)	Spearman Correlation		Mean	SD	Countries with available info. (n of 80)	Spearman Correlation		Mean	SD	
			Estimate (rho)	p-value				Estimate (rho)	p-value			
HI_60	Incidence of tuberculosis (per 100,000 people)	87	-0.60	**1.15E-09**	48	70	80	-0.61	**1.91E-09**	49	72	WB
HI_61	Measles - number of reported cases (standardized using population 0-14 years, per 100,000 people)	82	0.09	4.17E-01	1873	12117	80	0.05	6.91E-01	1754	12200	WHO
HI_62	Measles (MCV) immunization coverage among 1-year-olds (%)	84	-0.01	9.47E-01	93	9	80	0.02	8.28E-01	93	7	WHO
HI_63	Measles immunization coverage among children ages 12-23 months (%)	83	-0.06	6.08E-01	93	8	79	-0.03	7.70E-01	93	8	WB
HI_64	Pertussis - number of reported cases (standardized using population 0-14 years, per 100,000 people)	77	0.12	2.94E-01	2085	15988	76	0.08	4.91E-01	2113	16093	WHO
HI_65	Polio (Pol3) immunization coverage among 1-year-olds (%)	84	0.16	1.48E-01	93	8	80	0.23	4.46E-02	94	7	WHO
Deaths from Non-Communicable Diseases												
HD_66	Cancers, deaths per 100,000 (age-standardized estimate) Female	84	0.12	2.79E-01	96	17	80	0.22	4.60E-02	94	16	WHO
HD_67	Cancers, deaths per 100,000 (age-standardized estimate) Male	84	0.21	5.41E-02	147	44	80	0.28	1.26E-02	146	44	WHO
HD_68	Cardiovascular diseases and diabetes, deaths per 100,000 (age-standardized estimate) Female	84	-0.51	**8.98E-07**	239	126	80	-0.50	**2.77E-06**	230	125	WHO
HD_69	Cardiovascular diseases and diabetes, deaths per 100,000 (age-standardized estimate) Male	84	-0.41	**9.45E-05**	330	166	80	-0.39	**3.10E-04**	326	170	WHO
HD_70	Chronic respiratory diseases, deaths per 100,000 (age-standardized estimate) Female	84	-0.25	2.08E-02	23	21	80	-0.34	1.99E-03	23	21	WHO
HD_71	Chronic respiratory diseases, deaths per 100,000 (age-standardized estimate) Male	84	-0.27	1.15E-02	42	31	80	-0.37	7.89E-04	42	30	WHO
HD_72	NCD deaths under age 60 (% of all non communicable diseases deaths) Both Sexes	84	-0.54	**1.41E-07**	21	11	80	-0.58	**1.31E-08**	21	11	WHO
HD_73	Probability of dying between exact ages 30 and 70 from any of cardiovascular disease, cancer, diabetes, or chronic respiratory disease (%)	84	-0.45	**1.76E-05**	19	6	80	-0.44	**3.98E-05**	19	7	WHO
Infant and Maternal Mortality Rates												
HM_75	Infant mortality rate (probability of dying between birth and age 1 per 1000 live births) Both sexes	84	-0.62	**2.40E-10**	12	14	80	-0.66	**2.01E-11**	11	13	WHO
HM_76	Maternal mortality ratio (modeled estimate, per 100,000 live births)	82	-0.57	**2.57E-08**	61	124	80	-0.62	**1.12E-09**	56	109	WB
HM_77	Mortality rate, under-5 (per 1,000 live births) (probability of dying by age 5 per 1000 live births)	84	-0.63	**1.08E-10**	15	20	80	-0.67	**7.57E-12**	14	17	WB

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Chapter 6

Genetic Determinants of Type 1 Diabetes

Contents

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6 Genetic determinants of T1D

In **chapter 3**, we describe the covariation of T1D incidence worldwide in children with environmental factors that could be retrieved thanks to public databases. We found that 51% of the variation of T1D incidence could be accounted for by country-to-country variation in environmental factors.

T1D has an important genetic component. HLA (Human Leukocyte Antigen) which is the best known and best studied locus and alone explains the 40-50% inheritable T1D risk (212) was the main subject of this chapter.

Here, we assessed the proportion of the variability of T1D incidence that could be explained by the country-to-country variation of the frequency of susceptible and protective HLA alleles and haplotypes identified as T1D determinants. We relied on the *Allele Frequency Net* at http://www.allelefrequencies.net/ (115), a public electronic repository that provided 1007 gene/allele HLA and 370 haplotype data for 1025 worldwide populations. In this website, we searched for the frequency of susceptible and protective HLA alleles and haplotypes and validated based on different populations around the world by the *Type 1 Diabetes Genetics Consortium Families* report (2008) (89); we then compared the retrieved data with the incidence of T1D retrieved throughout the systematic review using methods similar to those presented in **chapter 3**.

After Stepwise Multiple Linear Regression (MLR), the significant variables were the susceptible alleles: DRB1*04:01 (p = 0.0001) and DRB1*08:01 (p = 0.003). Only the protective allele DQB1*06:02 had a significant positive correlation with the geographical repartition of T1D incidence. The adjusted % of variance explained (R^2) in the model was 61% and 30% after 10-fold cross validation. Correlation coefficient on partial correlations between the incidence of T1D and HLA alleles after controlling environmental variables dropped in most cases. A combination of genetic predisposition and environmental factors is required to produce the clinical manifestation of T1D.

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6.1 Geographical covariation of T1D incidence and genetic markers

P. A. Diaz-Valencia, Sophie Le Fur, P. Bougnères, A. J. Valleron.

6.1.1 Abstract

Background: The incidence of Type 1 Diabetes (T1D) in children varies dramatically between countries and has increased during the last decades.

Methods: Information on the incidence on T1D and on country characteristics were searched for the 194 WHO member countries. T1D incidence was extracted from a systematic literature review of all papers published between 1975 and 2014, including the 2013 update from the International Diabetes Federation, and was estimated for 80 WHO countries. The frequency of the major HLA (Human Leukocyte Antigen) haplotype determinants to T1D was searched for those countries where incidence was retrieved was searched in the *Allele Frequency Net*.

Bivariate and multivariate analyses were used to determine the correlations between the incidence of T1D and selected independent predictors of the geographical variation of T1D within each domain and overall.

Findings: The frequency of documented susceptible and protector HLA haplotypes was investigated. We found heterogeneity in the effect of some haplotypes, conferring protection or susceptibility among different study populations. Seven significant correlations were detected in 21 alleles tested (12 conferring susceptibility to T1D and 9 conferring protection). After Stepwise Multiple Linear regression the significant variables were the susceptible alleles: DRB1*04:01 ($p = 0.0001$) and DRB1*08:01 ($p = 0.003$). Only the protective allele DQB1*06:02 had a significant positive correlation with the geographical repartition of T1D incidence.

Conclusions: The frequency of susceptible and protective haplotypes toward T1D was highly variable around the world. Susceptible HLA alleles to T1D are frequent that protective

alleles; among 21 alleles studied, DRB1 04:01 and DRB1 08:01 alleles are determinant in the risk of T1D.

PROSPERO Registration number: CRD42012002369

6.1.2 Background

It has long been noticed that the incidence of Type 1 Diabetes (T1D) is highly variable from one country to another (81). For example, the 62.42 per 100.000/ per year incidence found in Finland (128) was 780-fold larger than the 0.08 per 100.000/ per year incidence in Papua New Guinea (230); the variability of T1D incidence is even visible within countries; for example, in Italy, T1D incidence varied between 54.4 per 100.000/ per year (Sardinia (102)) 4.4 per 100.000/ per year in Lombardia (108). The reason for these differences is not precisely known, but is most unlikely due to classification bias, as the disease cannot go untreated, and the diagnosis was relative easy to perform in children, at least before the recent rise in obesity rates (263). Moreover there are also differences in incidence within countries where the health care systems are comparable. Environmental factors have been implicated either in addition or as cofactors to genetic determinants. In a previous study we reviewed 77 independent variables; significant environmental predictors of the country-to-country variation of T1D incidence included UV radiation, number of mobile cell-phone subscriptions in the country, health expenditure per capita, hepatitis B immunization and mean body mass index (BMI) (81). The country-to-country T1D variability may be partly explained by genetic variations.

The major and most studied loci of susceptibility are located in HLAs (Human Leukocyte Antigens) in the major histocompatibility complex (MHC) on chromosome 6p21, that encodes immune response proteins. HLAs alone contribute by 40-50% of the family clustering observed in T1D (inheritable T1D risk) (212). Among the three classes of HLAs, class II HLAs DR and DQ haplotypes have been associated with a genetic risk of T1D or the protection profile within different populations (89).

One could indeed expect that in this age of information, the country-to-country covariations of T1D incidence could be readily correlated with a variety of genetic

characteristics, insofar as several global organizations collect such data, and provide them free to researchers, with easy interface on the Internet.

6.1.3 Methods

6.1.3.1 Incidence of T1D data by country

The T1D incidence value per 100.000 persons/year for individuals in the age group 0-14 years for both sexes used here for 80 countries worldwide was obtained through a systematic review following the PRISMA recommendations (213). All relevant original papers published in English between 1975 and 2014 including reviews (Diamond (318) and Eurodiab studies (90, 242, 243), the International Diabetes Federation (IDF) atlas (241, 300)) were analyzed and described in detail elsewhere (81).

6.1.3.2 HLA DQ/DA haplotype frequencies by country

Thanks to the report of the *Type 1 Diabetes Genetics Consortium Families* (2008) (89), that collects and analyzes samples of families with T1D from various populations around the world, the most susceptible and protective haplotype determinants of T1D have been identified.

To retrieve global information of the frequency of these haplotypes, we explored the *Allele Frequency Net* at http://www.allelefrequencies.net/ (115), a public electronic repository that stores allele frequency of worldwide populations. For HLAs, on 11/20/2014 this website contained data from 1025 population studies, 1007 gene/allele data and 370 haplotype data. Using the tool "haplotype frequency search" we examined the frequency in all populations of the most susceptible haplotypes reported by the T1D Genetics Consortium Families: DRB1*0301-DQA1*0501-DQB1*0201 (OR 3.64), DRB1*0405-DQA1*0301-DQB1*0302 (OR 11.37), DRB1*0401-DQA1*0301-DQB*0302 (OR 8.39), DRB1*0402-DQA1*0301-DQB1*0302 (OR 3.63), DRB1*0404-DQA1*0301-DQB1*0302 (OR 1.59), DRB1*0801-DQA1*0401-DQB1*0402 (OR 1.25) and of the most protective haplotypes: DRB1*1501-DQA1*0102-DQB1*0602 (OR 0.03), DRB1*1401-DQA1*0101-DQB1*0503 (OR 0.02) and DRB1*0701-DQA1*0201-DQB1*0303 (OR 0.02) (89), (**Appendix A: Database V**). In the website *Allele Frequency Net* all haplotype frequencies were calculated

taking the total number of copies of the haplotype in the population sample (haplotypes/2n) and reported in percentages (%).

In addition, using the tool "allele frequency search" we examined the four-digit resolution (high resolution four subtyping *i.e.* DRx/DQx*xx00) of each of the alleles contained in the haplotypes mentioned above. After retrieve a database containing 6867 lines, we then analyzed information from the 80 geographical regions for which we retrieved information on T1D incidence as follows. 1) For each of the 80 countries, only one population reporting the HLA allele frequency was selected among all those reported in the *Allele Frequency Net*; the same population was used across all the alleles explored. The population selected was the one for which we retrieved information for most of the alleles studied (12 susceptible and 9 protective HLA alleles related to T1D; 21 alleles in total). 2) When for a given country, more than one population was retrieved informing in a similar among of alleles, the selected population was the one with the highest sample size and less among of "0" values. 3) If no information was available for a given country, this country was excluded from the analyses. See **Appendix A: Database VI** for the final HLA alleles frequency database.

6.1.4 Statistics

Spearman correlation was used to compute the correlation between the 21 alleles and the T1D incidence.

Stepwise Multiple Linear Regression model (MLR) methods were used to select the best HLA alleles independent predictors of T1D incidence. We started with all variables for which the *p* value tested the correlation whose incidence was smaller than 0.05, and we successively removed the variables until the maximum value of the adjusted R^2 was obtained. When a couple of variables was correlated with $r > 0.80$, only one variable was used in the regression analysis to avoid the computational issues associated with colinearity. Model assumptions for linear models were checked. 10-Fold Cross-validation after bootstrapping (273) was used to evaluate the predictive value of the final model. Graphic representation used the DAAG package (203).

Partial correlations were used to evaluate the effect of genetic factors controlled by environmental factors. The first-order partial correlations *rXY.Z* for the three intercorrelated variables were calculated using the application First-Order Partial Correlations at the VassarStats website available at: http://vassarstats.net/par.html (2). The R software was used for statistical and graphic analyses (255).

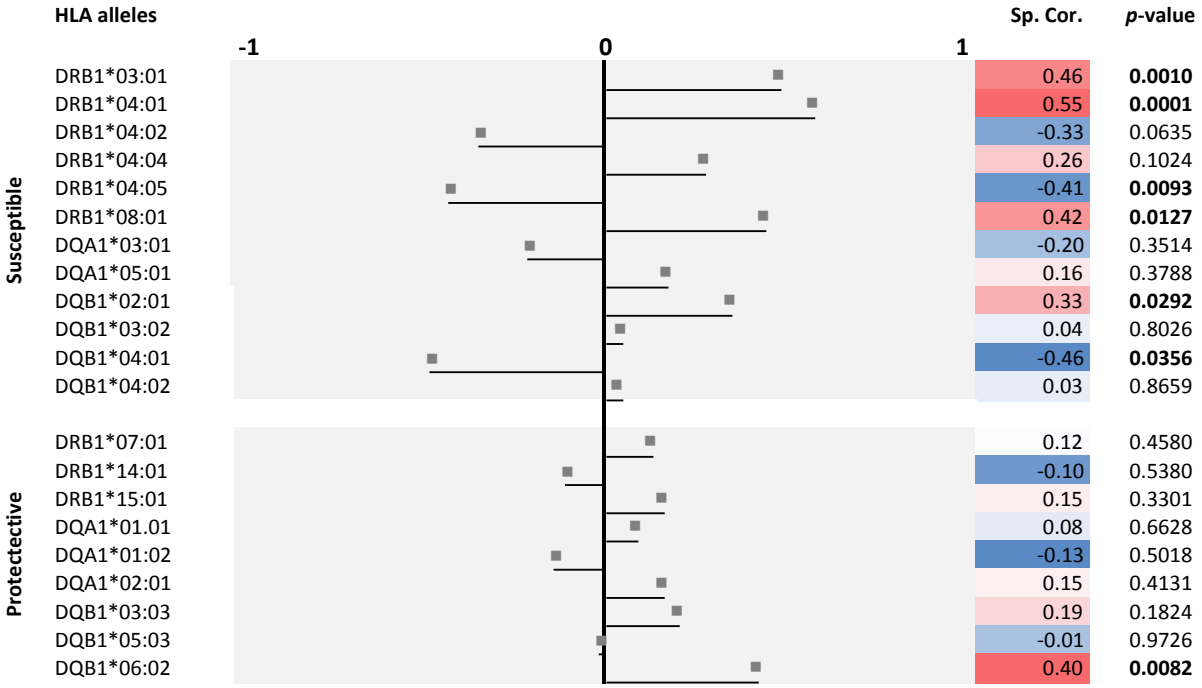
6.1.5 Results

6.1.5.1 HLA frequency haplotype determinants of T1D

T1D genetic variation of HLAs haplotypes found are in **Appendix A: Database V**. With the little information available, it was only possible to perform the correlation between the incidence of T1D and the susceptible haplotype: DRB1*0301-DQA1*0501-DQB1*0201 (OR 3.64, Spearman correlation (Sp. Cor.) = 0.18, p = 0.71, n = 7), and the protective haplotypes DRB1*15:01-DQA1*01:02-DQB1*06:02 (OR 0.03, Sp. Cor = 0.48, p = 0.36, n = 6), DRB1*1401 - DQA1*0101 - DQB1*0503 (OR 0.02, Sp. Cor = 0.66, p = 0.18, n = 6), and DRB1*0701-DQA1*0201-DQB1*0303 (OR 0.02, Sp. Cor = 0.40, p = 0.75, n = 4); **SI Table 23, SI Figure 42-43**.

6.1.5.2 HLA frequency Alleles related with T1D

For 56 countries it was possible correlate the 21 alleles contained in the DR-DQ haplotypes associated with T1D and the incidence of T1D retrieved in this review (**Appendix A: Database VI**). For susceptible haplotypes, significant positive correlations were found for the alleles, DRB1*03:01, DRB1*04:01, DRB1*08:01 and DQB1*02:01, and significant negative correlations for the alleles, DRB1*04:05 and DQB1*04:01. For protective alleles, only the allele DQB1*06:02 shows a significant (positive) correlation with incidence of T1D. **Figure 41** and **SI Figure 44-47** for graphs of retrieved correlations.



The correlations were computed in the 56 WHO countries where the incidence of T1D and the frequency of HLA haplotypes could be estimated. Significant correlations at *p*-value <0.05 are highlighted. See supporting information: **Database VI** for the database of the frequency of the HLA alleles.

Figure 41: Correlations between T1D incidence in 56 countries and susceptible/protective HLA alleles with respect to T1D

Seven of the 21 HLA alleles (6 susceptible and 2 protective) qualified to be entered in the model, after the Stepwise MLR selection the five selected variables were: DRB1*03:01, DRB1*04:01, DRB1*04:05, DRB1*08:01 and DQB1*04:01. Then, checking for colinearity, DQB1*04:01 was excluded because it was highly correlated with DRB1*08:01 (r = 0.99 *p*-value = <0.01). In the final model, the significant independent predictors were: DRB1*04:01 and DRB1*08:01. The adjusted % of variance explained (R^2) in the model was 61% (see model in **Table 22**, the details in **SI Table 24 -26**, the backward selection process in **AP Table 34,** and the graphic validation of the model in **AP Figure 71-72**). 10-fold cross-validation indicated that the fraction of the variability of the global incidence of T1D was estimated to be 30% (**SI Figure 48**). See **Appendix F** for the validation of the model.

Table 22: Final Stepwise MLR model

Coefficients of HLA alleles	Estimate	Std. Error	*p* -Value
(Intercept)	6.81	2.48	0.0110
DRB1*03:01	-8.90	24.97	0.7245
DRB1*04:01	115.62	25.79	0.0001
DRB1*04:05	-36.55	37.15	0.3346
DRB1*08:01	92.62	28.41	0.0032

6.1.5.3 Partial correlations between incidence of T1D and HLA alleles controlling environmental factors

Partial correlations between incidences of T1D and selected HLA alleles after adjustment, controlling on independent environmental predictors were established; **Appendix A: Database VII, SI Table 27-30**.

The incidence of T1D retrieved from 56 countries reporting information on HLA alleles and five independent predictors found in a previous study (81) were: UV radiation, number of mobile cell-phone subscriptions in the country, health expenditure per capita, hepatitis B immunization and mean body mass index (BMI). The selected HLA alleles were those of the four alleles that qualified to be included in the final model after checking for colinearity: DRB1*03:01, DRB1*04:01, DRB1*04:05, DRB1*08:01.

Partial correlations between incidence of T1D and HLA alleles, and level of statistical significance, at the *p*-value <0.05, dropped after controlling for environmental variables for the allele DRB1*03:01 controlling for: UV radiation, number of mobile cell-phone subscriptions in the country, health expenditure per capita and BMI; only controlling for hepatitis B immunization the correlation coefficient increase in 1% (p = 0.0003).

For the alleles DRB1*04:01 and DRB1*04:05 the correlation coefficient at the *p*-value <0.05 dropped, after controlling for all five environmental predictors for: mobile cell-phone subscriptions, hepatitis B immunization and BMI.

For the allele DRB1*08:01 the correlation coefficient at the *p*-value <0.05 dropped after controlling for: mobile cell-phone subscriptions and hepatitis B immunization; and increased after controlling for BMI in 3% (p = 0.001).

6.1.6 Discussion

Thanks to the information available in public databases, we identified genetic markers that were predictors of the variation in the geographical incidence of T1D.

T1D is a polygenetic disorder where the susceptibility for T1D follows a recessive pattern and incomplete penetrance in which the MHC plays a crucial role in pathogenesis (182). A previous study, in which only (HLA)-DQ loci were explored, suggest that the variation of the T1D risk for European populations is explained by variations in the distribution of DQ genotypes, that confer a high susceptibility of T1D in the general population (269).

We aimed to describe the relationship between certain HLA haplotypes and T1D incidence by geographical regions; however, the limited available global information did not allow us to reach this goal. Only a description of the currently available information for the respective susceptible and protective HLA haplotypes mentioned above is possible.

For the susceptible haplotype DRB1*03:01-DQA1*05:01-DQB1*02:01 (OR 3.64), we retrieved n = 49 populations reporting the frequency of this haplotype. The highest frequency (in %) of this haplotype was found in the population of *Italy Sardinia Sorgono* (25.3%), one of the highest incidences reported in the world whereas the lowest value is in the population of *Russia Siberia Irkutsk Tofalar* (1.2%). Surprisingly, countries whose low incidence rates of T1D are known, such as China or Slovenia, also present high frequencies of this susceptible haplotype: 13.1% in the population of *China Urumqi Kazak* and 22% in the population called *Slovenia population 2*. Similar heterogeneity across populations was observed for the five other susceptible haplotypes studied: DRB1*04:05-DQA1*03:01-DQB1*03:02 (OR 11.37), n = 14 retrieved populations, DRB1*04:01-DQA1*03:01-DQB1*03:02 (OR 8.39), n = 7 retrieved populations, DRB1*04:02-DQA1*03:01-DQB1*03:02 (OR 3.63), n = 14 retrieved populations, DRB1*04:04-DQA1*03:01-DQB1*03:02 (OR 1.59), n = 11 retrieved populations, and for DRB1*08:01-DQA1*04:01-DQB1*04:02 (OR 1.25), n = 21 retrieved populations.

Similar heterogeneity across populations was also observed for the three protective haplotypes studied. For example, for the haplotype DRB1*15:01-DQA1*01:02-DQB1*06:02 (OR 0.03), across n = 38 retrieved populations, the highest frequency was retrieved in the population of *Russia Tuva Todja* (20.5%) and as expected, the lowest value was reported in the populations of *Italy Sardinia Carbonia* and *Italy Sardinia Sassari* (1.1%); nevertheless also the *Ethiopia Amhara* region with low incidence of T1D reported, presented one of the

lowest frequencies for this protective haplotype (1.5%). For haplotype DRB1*14:01-DQA1*01:01-DQB1*05:03 (OR 0.02), we retrieved *n* = 22 populations and for haplotype DRB1*07:01-DQA1*02:01-DQB1*03:03 (OR 0.02), *n* = 24 populations. The complete list of the frequency of susceptible and protective HLA haplotypes against T1D and the populations where the T1D incidence is available is presented in **SI Table 23**. The entire list of all retrieved populations reporting susceptible and protective HLA haplotypes is available in the **Appendix A: Database V**.

Nonetheless, the limited data retrieved, revealed that some susceptible and protective haplotypes in one population could confer susceptibility or may constitute a certain protection in other populations, a phenomenon also described in a study that assessed the effect of Asian-specific HLA haplotypes (162). The second finding was that among all the alleles studied, DRB1*04:01 and DRB1*08:01 were significant predictors of the incidence of T1D in the ensemble of the 56 countries for which we could establish a correlation with the information of the frequency of the HLA allele. This finding suggests that these alleles are determinants of T1D risk, as was suggested by the *Type 1 Diabetes Genetics Consortium Families* who showed that the risk of T1D is conferred predominantly by DRB1 alleles (89).

6.1.7 Supporting Information

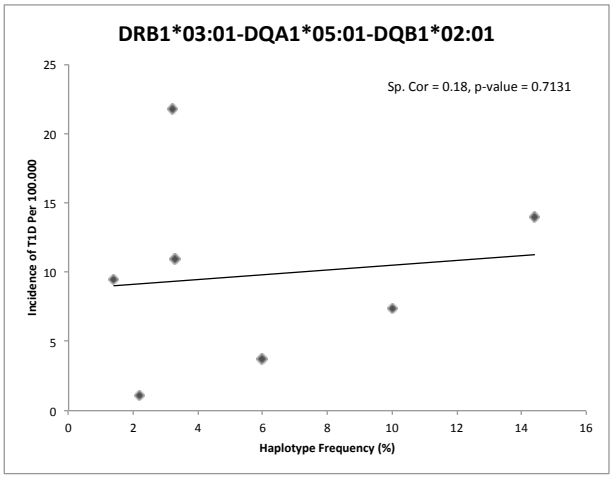
SI Table 23: Susceptible and protective HLA haplotypes against T1D vs incidence of T1D

Haplotype	Haplotype detail	Population	Country	Haplotype frequency (%)[a]	Incidence of T1D [b]
Susc_1	DRB1*03:01-DQA1*05:01/05:03/05:05-DQB1*02:01/02:02	Russia Siberia Ulchi	Russian Federation	1.4	9.5
Susc_1	DRB1*03:01-DQA1*05:01-DQB1*02:01	Canada British Columbia Athabaskan	Canada	3.2	21.7
Susc_1	DRB1*03:01-DQA1*05:01-DQB1*02:01	India Northeast Vaish	India	3.3	11
Susc_1	DRB1*03:01-DQA1*05:01-DQB1*02:01	South Korea pop 1	Dem. People's Republic of Korea	2.2	1.1
Susc_1	DRB1*03:01-DQA1*05:01-DQB1*02:01	Tunisia	Tunisia	10	7.4
Susc_1	DRB1*03:01-DQA1*05:01-DQB1*02:01	USA San Francisco Caucasian	United States of America	14.4	14
Susc_1	DRB1*03:01-DQA1*05:01-DQB1*02:01/06:01	Iran Azeri	Iran (Islamic Republic of)	6	3.7
Susc_2	DRB1*04:05-DQA1*03:01/03:02-DQB1*03:02	Ethiopia Amhara	Ethiopia	2	0.3
Susc_2	DRB1*04:05-DQA1*03:01-DQB1*03:02	Japan pop 2	Japan	2.1	2.4
Susc_3	DRB1*04:01-DQA1*03:01-DQB1*03:02	USA San Francisco Caucasian	United States of America	3.9	14
Susc_4	DRB1*04:02-DQA1*03:01-DQB1*03:02	USA San Francisco Caucasian	United States of America	1.4	14
Susc_5	DRB1*04:04-DQA1*03:01/03:02-DQB1*03:02	Ethiopia Amhara	Ethiopia	1	0.3
Susc_5	DRB1*04:04-DQA1*03:01-DQB1*03:02	USA San Francisco Caucasian	United States of America	14.0	2.7
Susc_6	DRB1*08:01-DQA1*04:01-DQB1*04:02	USA San Francisco Caucasian	United States of America	2.3	14
Prot_1	DRB1*15:01-DQA1*01:02-DQB1*06:02	Ethiopia Amhara	Ethiopia	1.5	0.3
Prot_1	DRB1*15:01-DQA1*01:02-DQB1*06:02	Japan pop 2	Japan	5.6	2.4
Prot_1	DRB1*15:01-DQA1*01:02-DQB1*06:02	South Korea pop 1	Dem. People's Republic of Korea	6.8	1.1
Prot_1	DRB1*15:01-DQA1*01:02-DQB1*06:02	Tunisia	Tunisia	2	7.4
Prot_1	DRB1*15:01-DQA1*01:02-DQB1*06:02	USA San Francisco Caucasian	United States of America	15.8	14
Prot_1	DRB1*15:01-DQA1*01:02-DQB1*06:02/06:11	Russia Siberia Ulchi	Russian Federation	4.8	9.5
Prot_2	DRB1*14:01-DQA1*01:01/01:02-DQB1*05:03	Iran Azeri	Iran (Islamic Republic of)	3.5	3.7
Prot_2	DRB1*14:01-DQA1*01:01/01:04/01:05-DQB1*05:03	Russia Siberia Ulchi	Russian Federation	4.8	9.5
Prot_2	DRB1*14:01-DQA1*01:01/01:04-DQB1*05:03	Ethiopia Amhara	Ethiopia	1	0.3
Prot_2	DRB1*14:01-DQA1*01:01-DQB1*05:03	Japan pop 2	Japan	2.6	2.4
Prot_2	DRB1*14:01-DQA1*01:01-DQB1*05:03	USA San Francisco Caucasian	United States of America	2.5	14
Prot_2	DRB1*14:01-DQA1*01:01-DQB1*05:03:01	Canada British Columbia Athabaskan	Canada	16.9	21.7
Prot_3	DRB1*07:01-DQA1*02:01-DQB1*03:03	Ethiopia Amhara	Ethiopia	0.3	1
Prot_3	DRB1*07:01-DQA1*02:01-DQB1*03:03	India Northeast Vaish	India	11	6.3
Prot_3	DRB1*07:01-DQA1*02:01-DQB1*03:03	Tunisia	Tunisia	7.4	2
Prot_3	DRB1*07:01-DQA1*02:01-DQB1*03:03	USA San Francisco Caucasian	United States of America	14	1.8

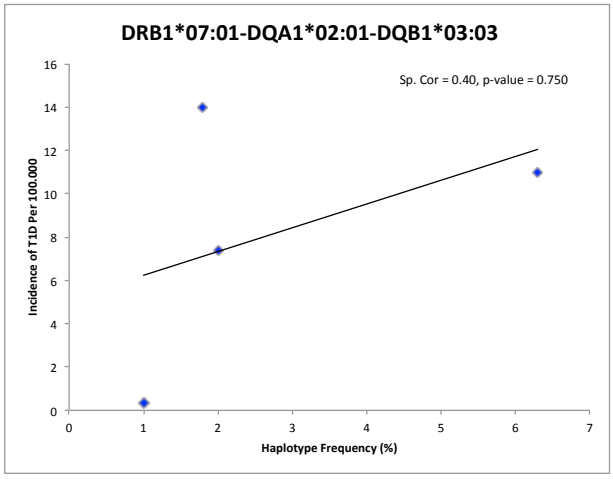
(b) Haplotype Frequencies: Total number of copies of the haplotype in the population sample (Haplotypes / 2n) shown in percentages (%). (a) Incidence of T1D per 100.000 persons per year among 0-14 years of age. Haplotypes source: **Allele frequency net:** a database and online repository for immune gene frequencies in worldwide populations. Gonzalez-Galarza FF, Christmas S, Middleton D and Jones AR Nucleic Acid Research 2011, 39, D913-D919. Liverpool, U.K. At: http://www.allelefrequencies.net/.

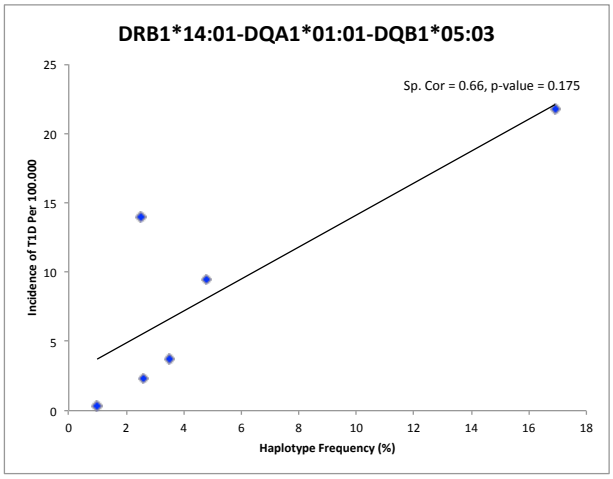
6.1.7.1 Susceptible/protective HLA haplotypes related with T1D

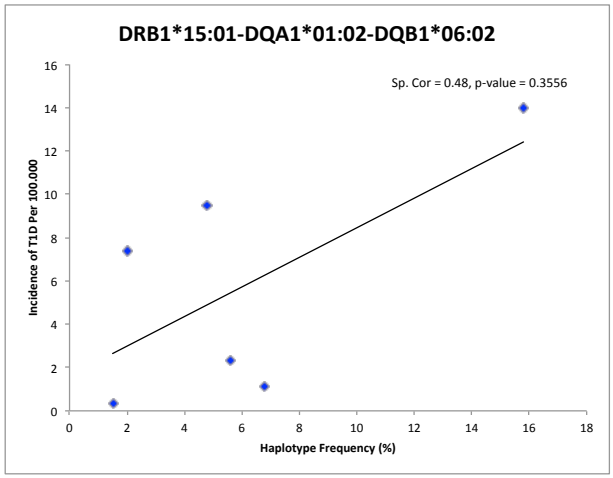
SI Figure 42: Susceptible HLA haplotypes against T1D



SI Figure 43: Protective HLA haplotypes against T1D

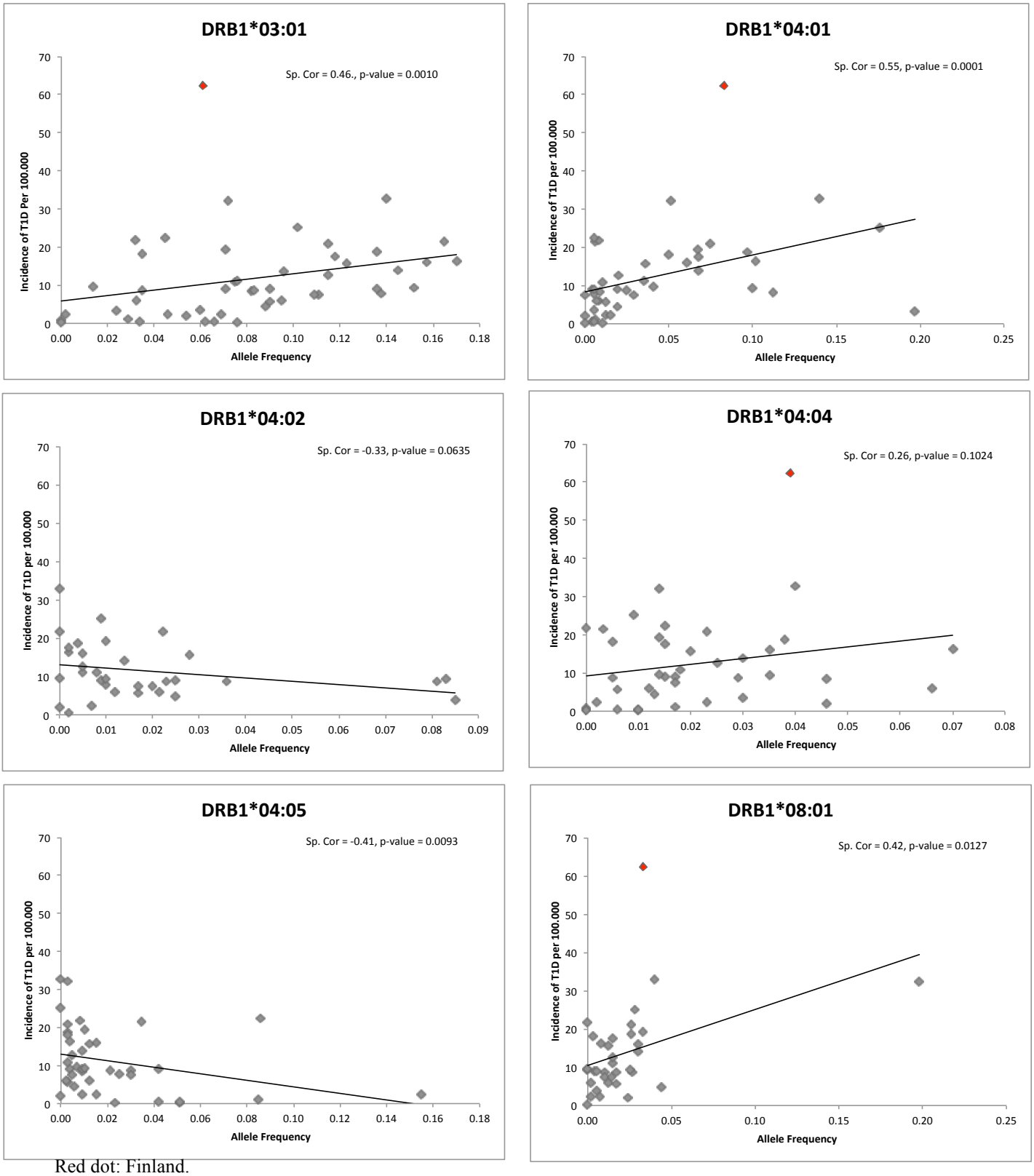






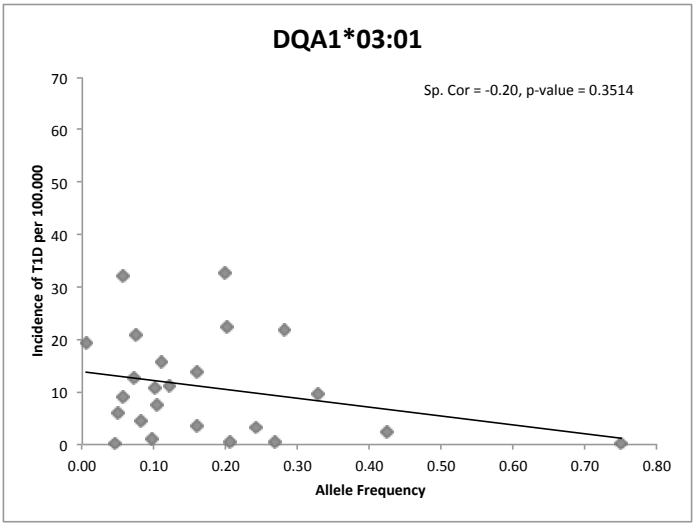
6.1.7.2 Susceptible/protective HLA alleles related with T1D

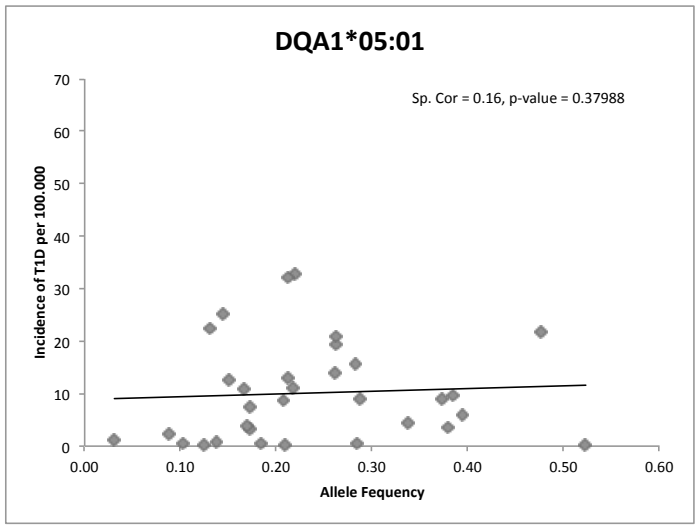
SI Figure 44: Major genetic determinants alleles at HLA-DR for susceptibility of T1D

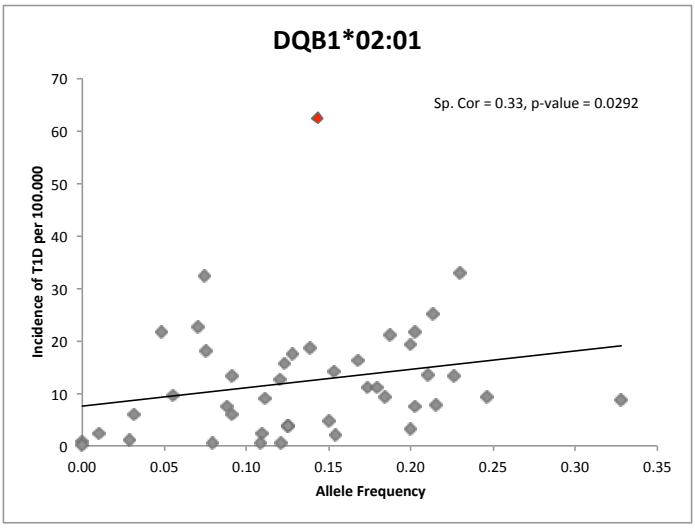


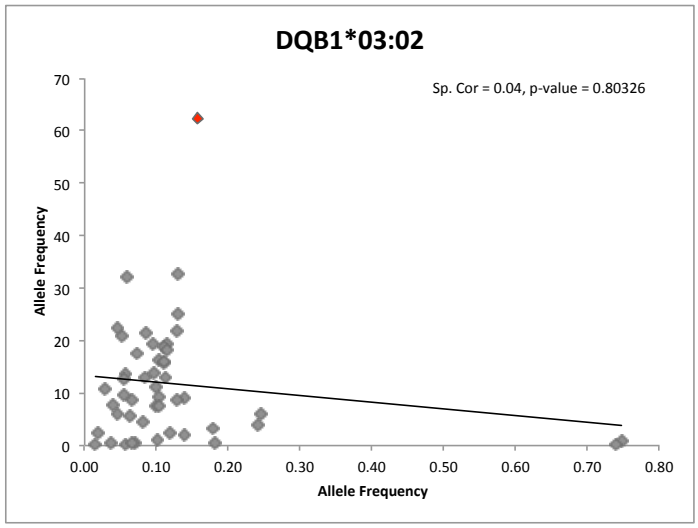
Red dot: Finland.

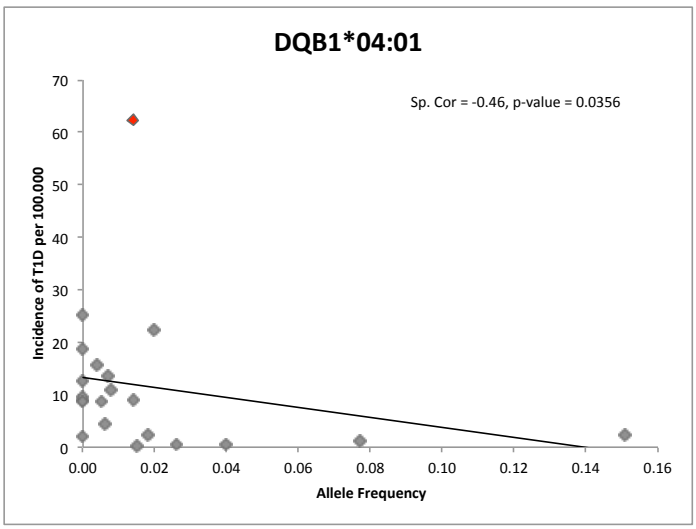
SI Figure 45: Major genetic determinants alleles at HLA-DQ for susceptibility of T1D

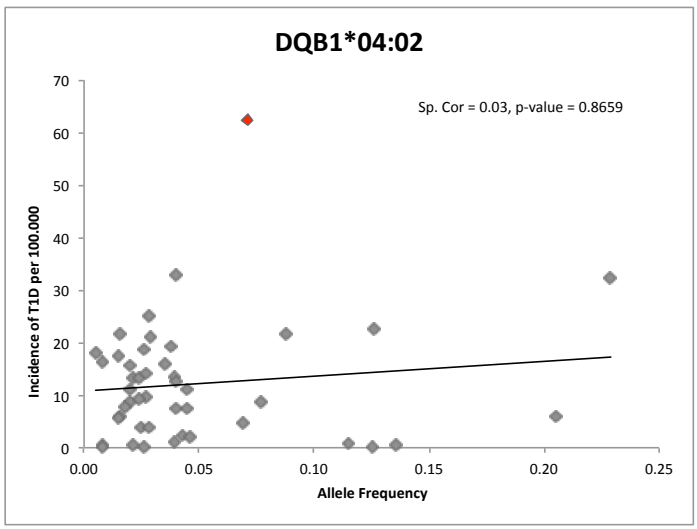






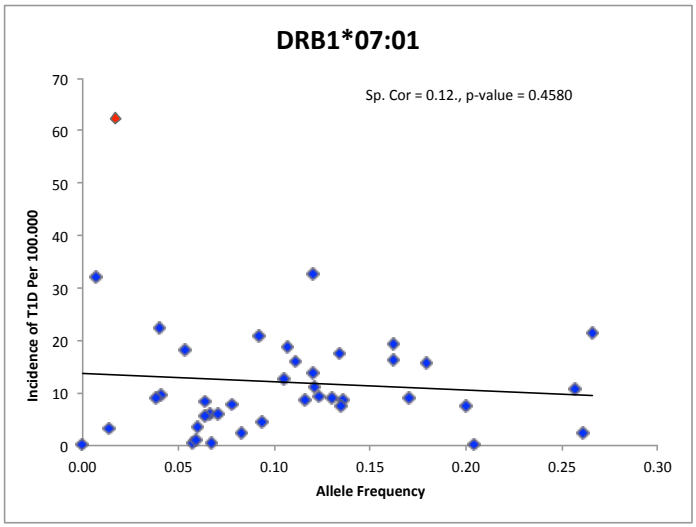


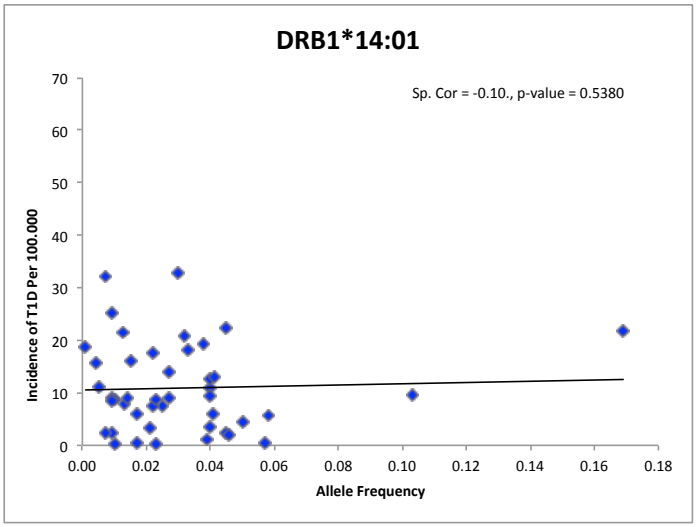


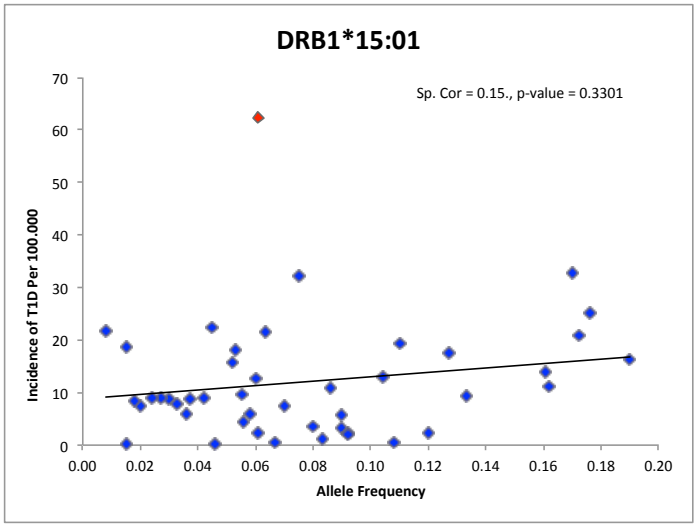


Red dot: Finland.

SI Figure 46: Major genetic determinants alleles at HLA-DR protective against T1D

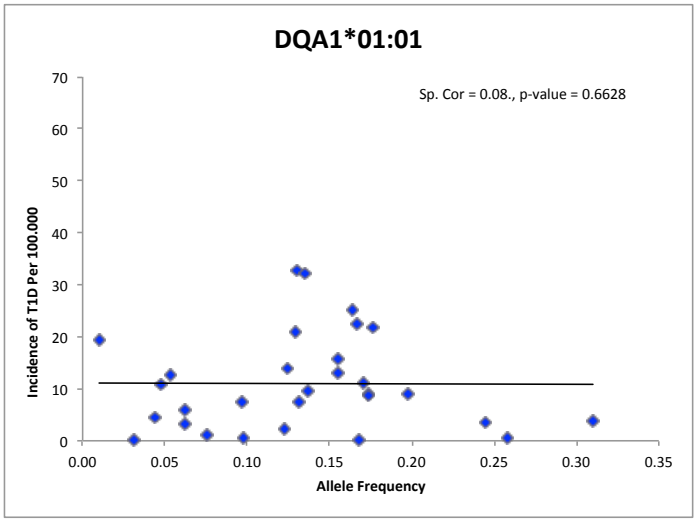


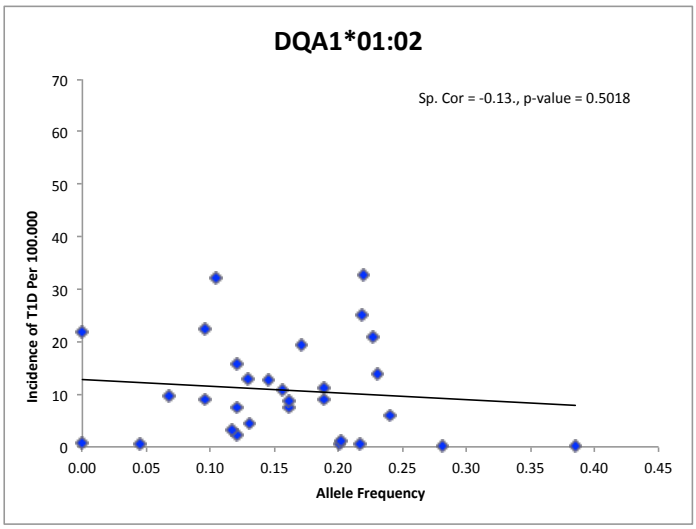


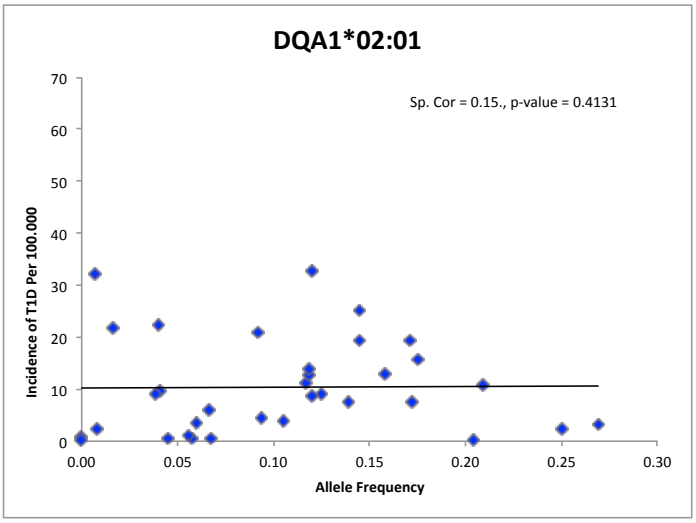


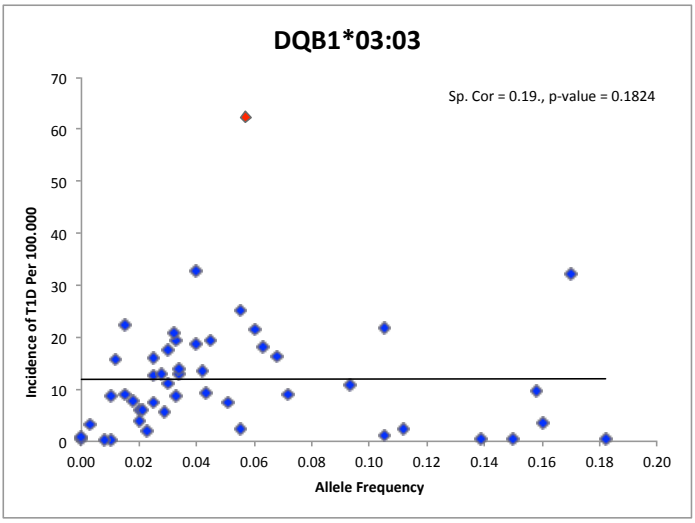
Red dot: Finland.

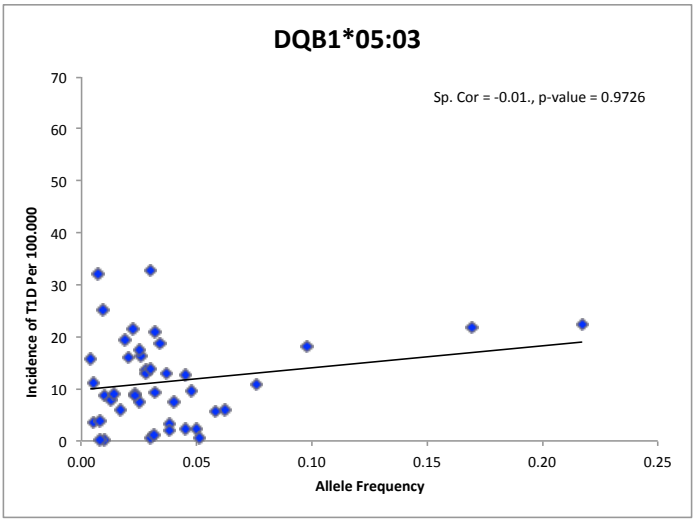
SI Figure 47: Major genetic determinants alleles at HLA-DQ protective against T1D

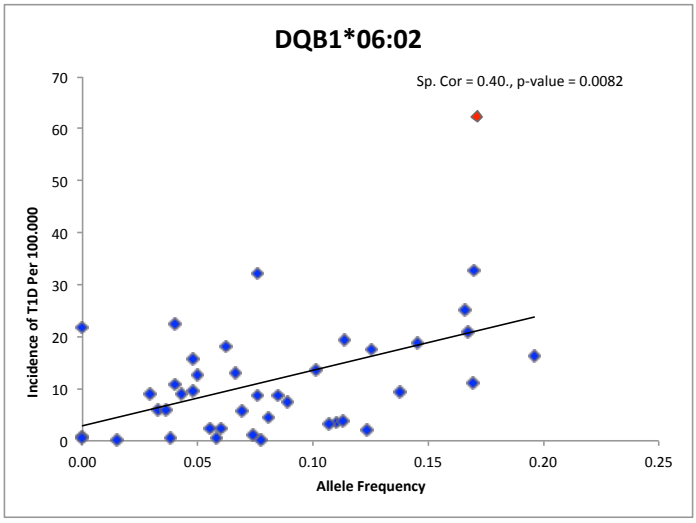












Red dot: Finland.

6.1.7.3 Details of the final Stepwise MLR model

SI Table 24: Final Stepwise MLR model

Model	Coefficients	Estimate	CI 2.5%	CI 97.5%	Std. Error	t-valeu	Pr(>|t|)
Res. standard error: 5.272 on 25 DF; **Adjusted R2: 0.6108**; F-statistic: 12.38 on 4 and 25 DF, p-value: 1.097e-05	(Intercept)	6.810	1.700	11.921	2.481	2.745	0.0110
	DRB1*03:01	-8.900	-60.334	42.529	24.972	-0.356	0.7245
	DRB1*04:01	115.620	62.493	168.739	25.794	4.482	0.0001
	DRB1*04:05	-36.550	-113.053	39.962	37.148	-0.984	0.3346
	DRB1*08:01	92.620	34.104	151.137	28.412	3.260	0.0032

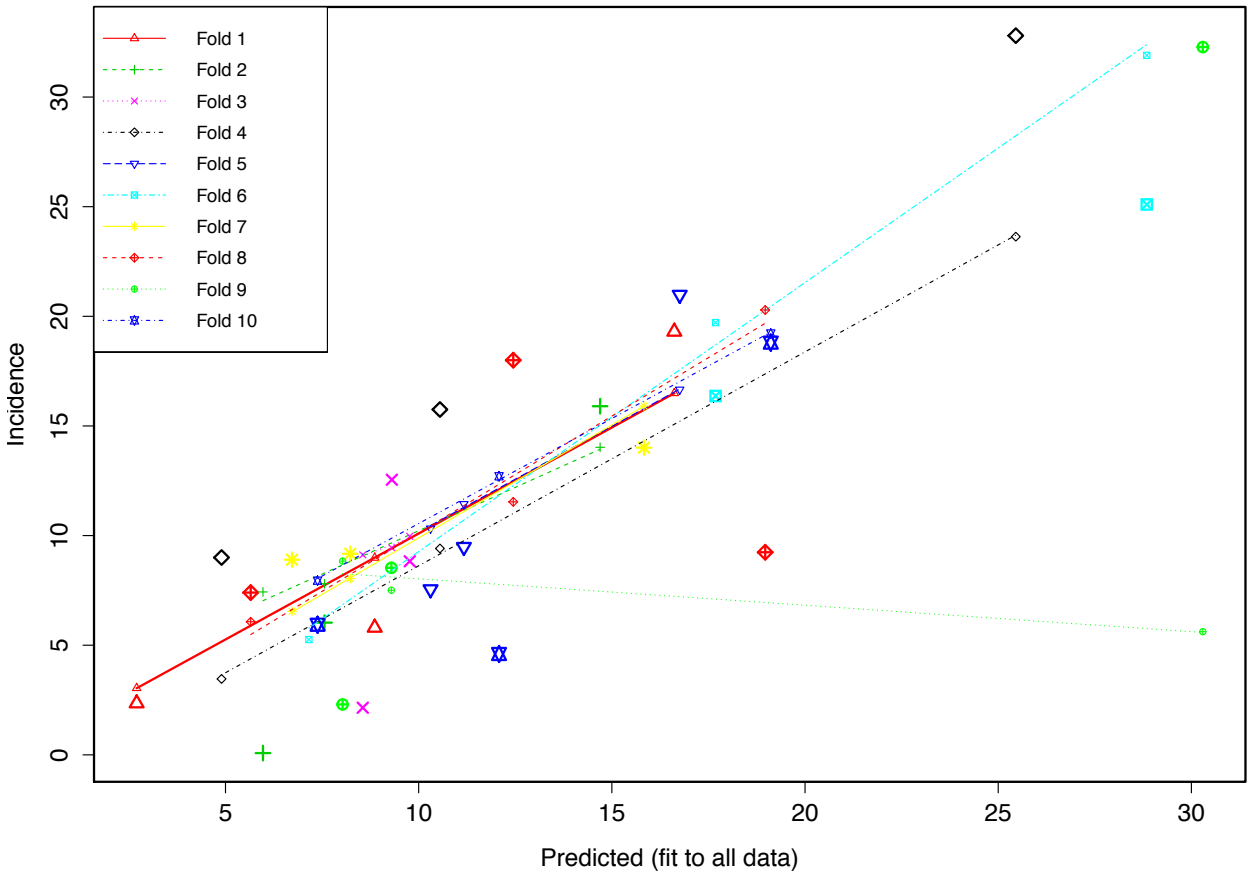
SI Table 25: Analysis of variance (Anova)

Coefficients	Df	Sum Sq	Mean Sq	F-value	Pr(>F)
DRB1*03:01	1	235.110	235.110	8.460	0.0075
DRB1*04:01	1	790.830	790.830	28.456	1.57×10^{-4}
DRB1*04:05	1	54.650	54.650	1.967	0.1731
DRB1*08:01	1	295.330	295.330	10.627	0.0032
Residuals	25	694.770	27.790		

SI Table 26: Residuals

Min	1Q	Median	3Q	Max
-9.729	-2.523	-0.557	2.558	14.572

6.1.7.4 Visualisation of 10-Fold Cross-Validation of the final model



Small symbols show cross-validated predicted values of T1D incidence vs. HLA alleles. Raw R^2 = 0.664, 10-Fold cross-validated R^2 =0.299.

SI Figure 48: 10-Fold Cross-Validation 10 fold-Cross validation of the final model

6.1.7.5 Partial correlations between incidence of T1D and HLA alleles controlling for environmental factors

SI Table 27: Partial correlation for DRB1*03.01

		Partial correlations for DRB1.03.01	Sp. cor	r^2	t	*p*
	XY	**Incidence * DRB1.03.01**	**0.459**	**0.211**		**0.001**
Z_1	XZ_1	Incidence * UV radiation	-0.709	0.503		
	YZ_1	DRB1.03.01 * UV radiation	-0.301	0.091		
	$XY.Z_1$	**Incidence * DRB1.03.01 * UV radiation**	**0.365**	**0.133**	**2.86**	**0.006**
Z_2	XZ_2	Incidence * Mobile cellular subscriptions	0.409	0.167		
	YZ_2	DRB1.03.01 * Mobile cellular subscriptions	0.245	0.060		
	$XY.Z_2$	**Incidence * DRB1.03.01 * Mobile cellular subscriptions**	**0.406**	**0.164**	**3.23**	**0.002**
Z_3	XZ_3	Incidence * Health expenditure per capita	0.765	0.585		
	YZ_3	DRB1.03.01 * Health expenditure per capita	0.391	0.153		
	$XY.Z_3$	**Incidence * DRB1.03.01 * Health expenditure per capita**	**0.270**	**0.073**	**2.04**	**0.046**
Z_4	XZ_4	Incidence * Hepatitis B immunization	-0.184	0.034		
	YZ_4	DRB1.03.01 * Hepatitis B immunization	0.024	0.001		
	$XY.Z_4$	**Incidence * DRB1.03.01 * Hepatitis B immunization**	**0.472**	**0.222**	**3.89**	**0.0003**
Z_5	XZ_5	Incidence * Mean BMI Male	0.587	0.345		
	YZ_5	DRB1.03.01 * Mean BMI Male	0.297	0.880		
	$XY.Z_5$	**Incidence * DRB1.03.01 * Mean BMI Male**	**0.368**	**0.136**	**2.88**	**0.006**

SI Table 28: Partial correlation for DRB1*04.01

		Partial correlations for DRB1.04.01	Sp. cor	r^2	t	*p*
	XY	**Incidence * DRB1.04.01**	**0.549**	**0.301**		**0.0001**
Z_1	XZ_1	Incidence * UV radiation	-0.709	0.503		
	YZ_1	DRB1.04.01 * UV radiation	-0.668	0.446		
	$XY.Z_1$	**Incidence * DRB1.04.01 * UV radiation**	**0.144**	**0.224**	**1.06**	**0.294**
Z_2	XZ_2	Incidence * Mobile cellular subscriptions	0.409	0.167		
	YZ_2	DRB1.04.01 * Mobile cellular subscriptions	0.355	0.126		
	$XY.Z_2$	**Incidence * DRB1.04.01 * Mobile cellular subscriptions**	**0.473**	**0.224**	**3.91**	**0.0003**
Z_3	XZ_3	Incidence * Health expenditure per capita	0.765	0.585		
	YZ_3	DRB1.04.01 * Health expenditure per capita	0.578	0.334		
	$XY.Z_3$	**Incidence * DRB1.04.01 * Health expenditure per capita**	**0.203**	**0.042**	**1.51**	**0.137**
Z_4	XZ_4	Incidence * Hepatitis B immunization	-0.184	0.034		
	YZ_4	DRB1.04.01 * Hepatitis B immunization	-0.351	0.123		
	$XY.Z_4$	**Incidence * DRB1.04.01 * Hepatitis B immunization**	**0.526**	**0.277**	**4.51**	**<0.0001**
Z_5	XZ_5	Incidence * Mean BMI Male	0.587	0.345		
	YZ_5	DRB1.04.01 * Mean BMI Male	0.392	0.154		
	$XY.Z_5$	**Incidence * DRB1.04.01 * Mean BMI Male**	**0.428**	**0.183**	**3.45**	**0.001**

SI Table 29: Partial correlation for DRB1*04.05

		Partial correlations for DRB1.04.05	Sp. cor	r^2	t	*p*
	XY	**Incidence * DRB1.04.05**	**-0.406**	**0.165**		**0.0093**
Z_1	XZ_1	Incidence * UV radiation	-0.709	0.503		
	YZ_1	DRB1.04.05 * UV radiation	0.386	0.149		
	XY.Z₁	**Incidence * DRB1.04.05 * UV radiation**	**-0.203**	**0.041**	**-1.51**	**0.137**
Z_2	XZ_2	Incidence * Mobile cellular subscriptions	0.409	0.167		
	YZ_2	DRB1.04.05 * Mobile cellular subscriptions	-0.140	0.020		
	XY.Z₂	**Incidence * DRB1.04.05 * Mobile cellular subscriptions**	**-0.386**	**0.149**	**-3.05**	**0.004**
Z_3	XZ_3	Incidence * Health expenditure per capita	0.765	0.585		
	YZ_3	DRB1.04.05 * Health expenditure per capita	-0.399	0.159		
	XY.Z₃	**Incidence * DRB1.04.05 * Health expenditure per capita**	**-0.171**	**0.029**	**-1.26**	**0.213**
Z_4	XZ_4	Incidence * Hepatitis B immunization	-0.184	0.034		
	YZ_4	DRB1.04.05 * Hepatitis B immunization	0.320	0.102		
	XY.Z₄	**Incidence * DRB1.04.05 * Hepatitis B immunization**	**-0.373**	**0.139**	**-2.92**	**0.005**
Z_5	XZ_5	Incidence * Mean BMI Male	0.587	0.345		
	YZ_5	DRB1.04.05 * Mean BMI Male	-0.330	0.109		
	XY.Z₅	**Incidence * DRB1.04.05 * Mean BMI Male**	**-0.278**	**0.077**	**-2.11**	**0.040**

SI Table 30: Partial correlation for DRB1*08.01

		Partial correlations for DRB1.08.01	Sp. cor	r^2	t	*p*
	XY	**Incidence * DRB1.08.01**	**0.417**	**0.174**		**0.0127**
Z_1	XZ_1	Incidence * UV radiation	-0.709	0.503		
	YZ_1	DRB1.08.01 * UV radiation	-0.501	0.251		
	XY.Z₁	**Incidence * DRB1.08.01 * UV radiation**	**0.101**	**0.010**	**0.74**	**0.463**
Z_2	XZ_2	Incidence * Mobile cellular subscriptions	0.409	0.167		
	YZ_2	DRB1.08.01 * Mobile cellular subscriptions	0.264	0.070		
	XY.Z₂	**Incidence * DRB1.08.01 * Mobile cellular subscriptions**	**0.351**	**0.123**	**2.73**	**0.009**
Z_3	XZ_3	Incidence * Health expenditure per capita	0.765	0.585		
	YZ_3	DRB1.08.01 * Health expenditure per capita	0.367	0.135		
	XY.Z₃	**Incidence * DRB1.08.01 * Health expenditure per capita**	**0.227**	**0.052**	**1.70**	**0.095**
Z_4	XZ_4	Incidence * Hepatitis B immunization	-0.184	0.034		
	YZ_4	DRB1.08.01 * Hepatitis B immunization	-0.300	0.090		
	XY.Z₄	**Incidence * DRB1.08.01 * Hepatitis B immunization**	**0.386**	**0.149**	**3.04**	**0.004**
Z_5	XZ_5	Incidence * Mean BMI Male	0.587	0.345		
	YZ_5	DRB1.08.01 * Mean BMI Male	0.088	0.008		
	XY.Z₅	**Incidence * DRB1.08.01 * Mean BMI Male**	**0.453**	**0.205**	**3.70**	**0.001**

Conclusions and Perspectives

"In laboratory science, technological advances typically have meant new instruments or techniques. However, in diabetes epidemiology, the population is our laboratory. Can there be a revolution in diabetes epidemiology based on new techniques to facilitate measurement? Can this directly lead to a revolution in how we view and quantitate health? We believe so".

LaPorte, et al. Diabetes Care, 1993 (179)

T1D is a chronic pathological condition that affects millions of children and young people around the world, with devastating consequences on patients, parents, and society. The well-known genetic component of T1D cannot explain the increase in the incidence and the decreased age at onset that has been observed worldwide. The geographic variability and the changes in temporal trends of incidence of T1D are influenced by still unknown environmental factors affecting the natural course of childhood diabetes. Understanding these environmental effects as they interact with the genetic component in T1D would be critical to identify potential modifiable factors of this disease.

In **chapter 2** of this thesis, we show that countries with information on T1D incidence present lower temperatures and UV radiation and are more "urbanized", characterized by reduced rural population, higher obesity rates and overweight, higher CO_2 emissions per inhabitant, as well as stronger economies (higher Gross National Income (GNI), improved sanitary facilities, and more expenses in health resources).

Then, observing in depth the countries with high T1D incidence for which we could collect information, three main related categories of environmental determinants were identified. First, higher incidences were present in wealthy countries with a large national income and a "western" life style, defined here as countries with high concentrations of urban population and more CO_2 emissions, in addition to higher rates of obesity and overweight; such factors may be implicated (or may cooperate) in accelerated beta-cell destruction, as proposed in the *accelerator hypothesis* (361) and the *overload hypothesis* (71)-. Second, high incidences were observed in countries in northern latitudes, in countries with traditionally low temperatures and with low UV exposition, factors that could be associated, for example, with a vitamin D deficiency, currently described in autoimmunity and alterations in the regulation of gene expression (367). Third, higher incidences were also found in countries with better health care, large education expenditure, and a more aged population, factors that could mirror better health care registers.

Paradoxically, countries with low incidence or without available information could be the result of an under-diagnosis and lack of notifications rather than real absence of incident cases. Nevertheless, it is also possible that both situations are present in the epidemiology of T1D: lower incidence countries presenting higher rates of under-diagnosis or miss-notifications of T1D incidence levels.

This enormous geographic variability in the incidence of T1D, and the changes in the incidence trends shown here in **chapters 1** and **5**, remains a challenge for the scientific community. The variety of climatic, environmental, economic, and health factors that seem correlated with T1D incidence presented in **chapter 3** of this thesis deserve deeper exploration. The strong geographical correlation of the incidence in adults and children as observed in **chapter 4** may be explained by the fact that adults with T1D could share the same genetic alleles known to be associated to juvenile T1D, for example the alleles DRB1*04:01 and DRB1*08:01 that we found here to be significant predictors of the incidence of T1D in children described in **chapter 6**, but also because they share some predisposing environmental causes (81).

The string birth cohort effect presented in **chapter 5** allow us to suggest that research focused on pregnancy, and the neonatal period is required to recognize the factors implicated in T1D reflecting the birth cohort effect. In addition, epidemics due to infection diseases, environmental expositions or quick changes, such as weight gain during early childhood (91) or adolescence, could be risk factors of T1D and a manifestation of a calendar period effect also observed. If the downward tendency observed when we observe the model with out the effect of Finland is real, it means that variations of environmental factors could induce changes in the incidence of T1D in relatively short periods. Revealing all the factors associated with T1D incidence is not a feasible task for the moment, since most of them are unknown and/or information is unavailable. However, this thesis showed that some environmental and genetic factors available publicly, could be associated at the level of the global epidemiology of T1D. We are confident that in the near future high quality information on the incidence of T1D will be accessible, as well as genetic and environmental indicators that will allow deepening the approach used here, and will unravel new clues on the gene-environment causality of T1D and potential target factors for preventive measures.

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8 Appendices

8.1 Appendix A: List of Databases

The databases mentioned here will be placed for public examination and access, in the author's Github website at: https://github.com/PaulaDiaz, once the press embargo of the manuscripts expires**.**

- **Database I:** 6824 lines x 59 columns tidy database. It contains raw data extracted from articles and introduced manually into a standard data collection grid.
- **Database II:** 529 lines x 67 columns tidy database. It contains the detailed list and breakdown by place and time of the mean incidence, retrieved in 265 references reporting incidence of T1D among children aged 0-14 years retrieved during the entire SR (234 primary research papers from PubMed and Google Scholar. 28 additional papers, abstracts and updated information were from the IDF Atlas (300)).
- **Database III:** 85 lines x 80 columns tidy database. It contains the T1D incidence retrieved in 80 countries and the list of 77 environmental indicators used in the correlations of environmental factors and T1D incidence among children.
- **Database IV:** 1974 lines x 26 columns tidy database. It contains the selected information of incidence of T1D among children by age class, period, and country used in the APC analyses.
- **Database V:** 204 lines x 7 columns tidy database. It contains the HLA haplotypes used in the analyses of **chapter 6.**
- **Database VI:** 82 lines x 25 columns tidy database. It contains the HLA alleles frequency database used in the analyses of **chapter 6**.
- **Database VII:** 58 lines x 13 columns tidy database. It contains information of HLA alleles frequency and environmental variables used in the partial correlation analyses presented in **chapter 6.**

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8.2 Appendix B: First search query of the literature (Query # 0)

Two independent searches performed during December 2011, which allow the identification of the initial 92 references. The first in the database MedLine access through PubMed and the second in Thompson Reuters through Web of Science. **AP Figure 49**. Definition of used terms at the end of this appendix.

8.2.1 PubMed

Advanced search was used, for published articles in the literature between 1 January 1990 and November 2011.

The equations for the query in the search history section were:

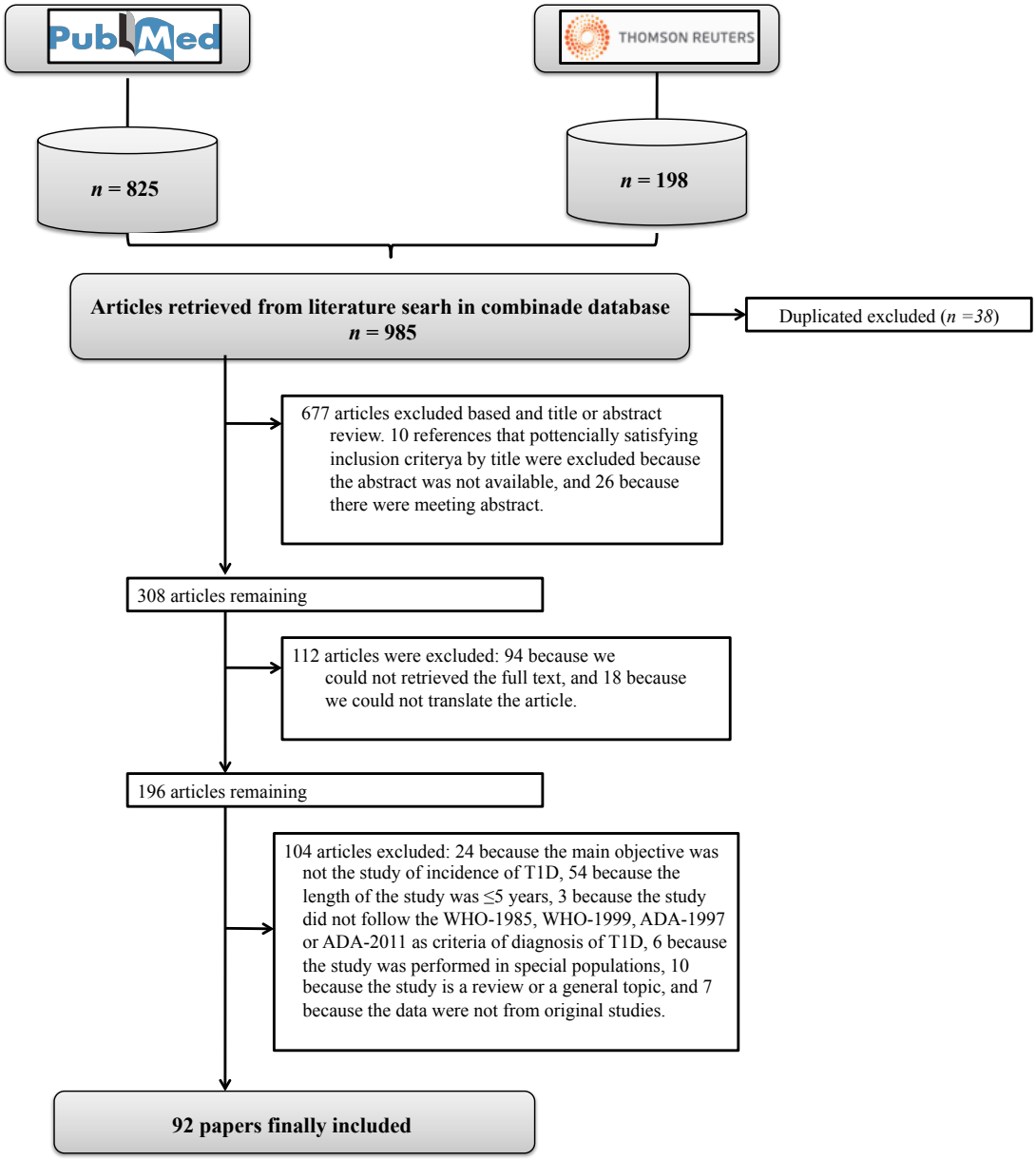
- *Search #1* ("diabetes mellitus, type 1/epidemiology" [Mesh Terms]) AND ("incidence" [MeSH Terms] OR "models, statistical"[MeSH Terms] OR cohort studies [MH])
- *Search #2* ((trend [TI] AND incidence [TI]) OR (trends [TI] AND incidence [TI]) OR (onset [TI] AND Incidence [TI]) OR "birth cohort"[TIAB] OR "age period cohort"[TIAB] OR age-period-cohort [TIAB]) OR "incidence" [TIAB])
- *Search #3* Journal Article [PT] NOT (Letter [PT] OR comment [PT] OR editorial [PT] OR news [PT]) AND ("1990/1/1" [PDAT]: "2011/11/28" [PDAT]). Limits: Humans.
- At the end the equation was search ((*#1*) AND *#2*) AND *#3)*. We will call this query #0.

8.2.2 Web of Science

Search articles published during the period 1 January 1990 and November 2011 using the following search equation:

- *Topic* = (cohort studies OR (trend* OR incidence* OR tendency*) OR epidemiology*) AND
- *Title* = ("type 1 diabetes" OR "IDDM" OR "childhood diabetes" OR "juvenile diabetes" OR "diabetes") AND

- *Title* = ((trend AND incidence) OR (trends AND incidence) OR (onset AND Incidence) OR "birth cohort" OR "age period cohort" OR age-period-cohort).
- The search was refined excluding: document type = (proceedings paper OR editorial material OR letter OR correction OR note). Databases=SCI-EXPANDED. Lemmatization=Off.



AP Figure 49: Initial search query of the literature

8.2.3 Glossary for searching:

8.2.3.1 PubMed:

- **MeSH Major Topic [MAJR]:** a MeSH term that is one of the main topics discussed in the article denoted by an asterisk on the MeSH term or MeSH/Subheading combination, e.g., Cytokines/physiology*. See MeSH Terms [MH] below.
- **MeSH Subheadings [SH]:** MeSH Subheadings are used with MeSH terms to help describe more completely a particular aspect of a subject. For example, the drug therapy of asthma is displayed as asthma/drug therapy, see MeSH/Subheading Combinations in MeSH Terms [MH] below.
- **MeSH Terms [MH]:** the NLM Medical Subject Headings controlled vocabulary of biomedical terms that is used to describe the subject of each journal article in MEDLINE. MeSH terms are arranged hierarchically by subject categories with more specific terms arranged beneath broader terms. MeSH terms in PubMed automatically include the more specific MeSH terms in a search.
- **Publication Type [PT]:** describes the type of material the article represents (e.g., Review, Clinical Trial, Retracted Publication, Letter); see the PubMed Publication Types, e.g., review[pt].
- **Title/Abstract [TIAB]:** words and numbers included in the title, abstract, and other abstract of a citation. English language abstracts are taken directly from the published article. If an article does not have a published abstract, NLM does not create one.
- **Publication Date [DP]:** the date that the article was published.
- Source and details in: http://www.ncbi.nlm.nih.gov.gate2.inist.fr/books/NBK3827/

8.2.3.2 Web of Science:

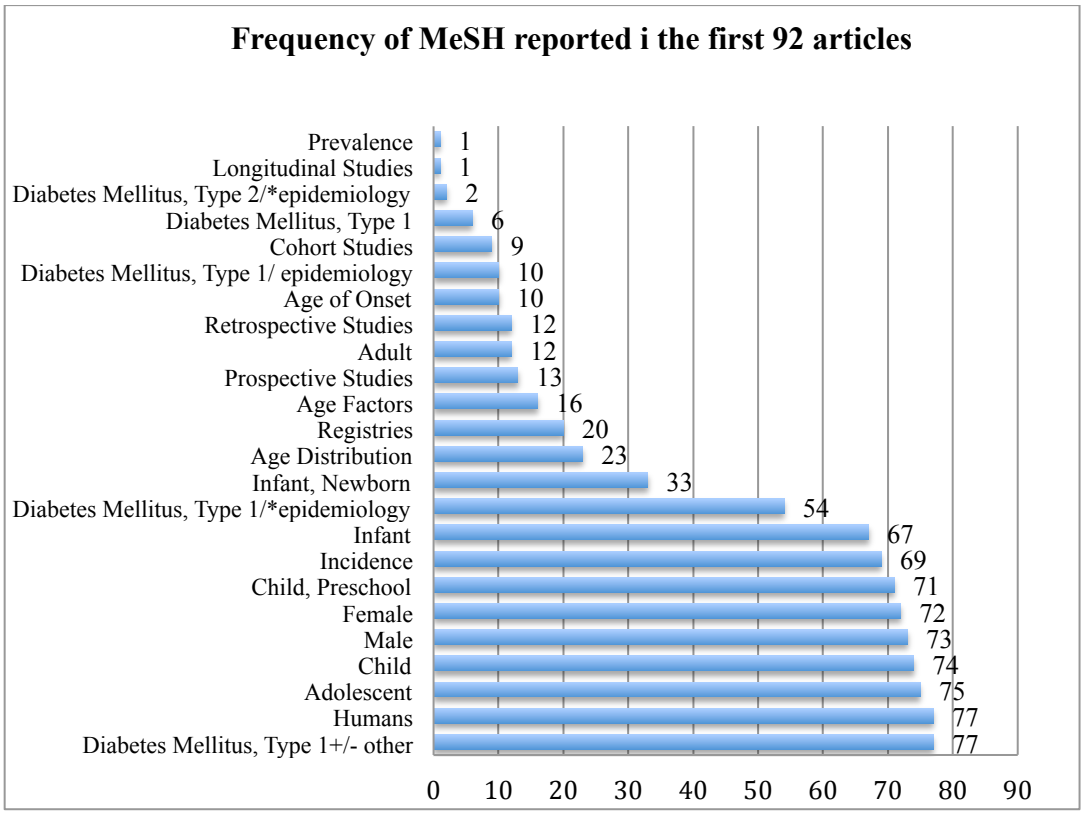
- **SCI-EXPANDED:** Science Citation Index Expanded (--1975-present)
- **SSCI:** Social Sciences Citation Index (--1975-present)
- **A&HCI:** Arts & Humanities Citation Index (--1975-present)
- **CPCI-S:** Conference Proceedings Citation Index- Science (--1990-present)

- **CPCI-SSH:** Conference Proceedings Citation Index- Social Science & Humanities (--1990-present)
- **Searching the Topic Field:** enter Topic terms to search the following fields within a record: title, abstract, author keywords, Keywords Plus®. The product returns every record containing all your search terms.
- **Searching the Title Field:** enter Title terms to limit your search to article titles.
- **Lemmatization:** it finds (On) or not (Off) alternative forms of the search term, for example, tooth and teeth.
- Source and details in: http://images.webofknowledge.com.gate2.inist.fr/WOKRS55B6/help/WOS/contents.html

8.3 Appendix C: Seven steps used to obtain the final query equation

8.3.1 Step 1. MeSH term reported in the articles retrieved from query# 0

All MeSH term included in the 92 database references were listed and ordered using Excel. Nine hundred and ninety-one (991) MeSH terms were found using relevant MeSH terms (for example Diabetes Mellitus, Type 1) reported in each article. One hundred and fourteen (114) irrelevant terms as Kuwait/epidemiology or Hospitalizations/statistics or numerical data were discarded. **AP Figure 50** presents the distribution of the main MeSH terms reported in the first 92 articles.



AP Figure 50: Frequency of MeSH terms included in selected articles

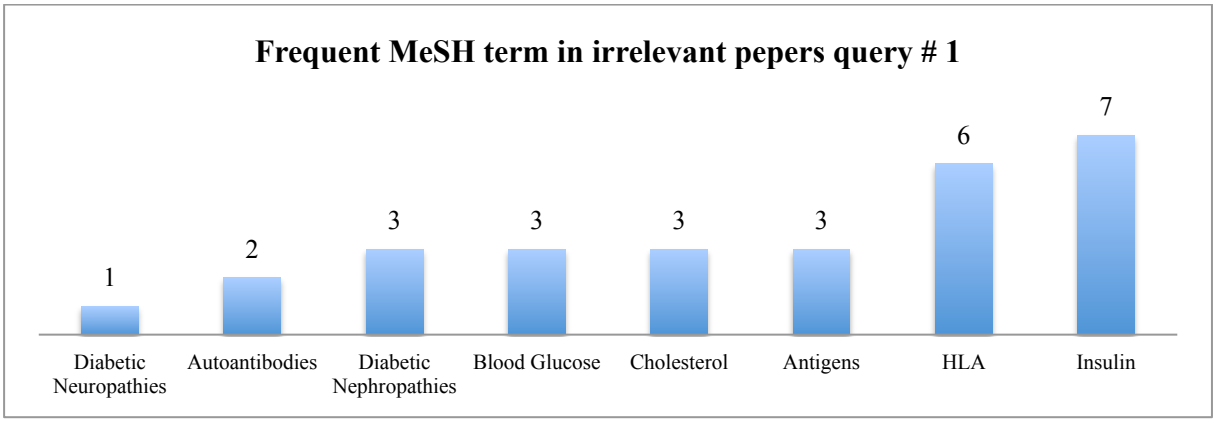
8.3.2 Step 2. Query # 1 using the main MeSH terms retrieved from selected articles

Query #1	No. Ref. retrieved	Observations
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] OR "age	9817	Query #1 included the main MeSH terms retrieved in the step 1.

groups"[MeSH Terms][6] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT]))		

8.3.3 Step 3. Frequent MeSH term retrieved from irrelevant papers

The query # 1 showed 9817 references arranged in 491 pages into PubMed Website. I examined all MeSH terms reported in the first irrelevant reference each 50 pages, starting on the first page (for example: reference 1 in page 1, reference 981 in page 50, reference 1981 in page 100, … reference 8889 in page 450). Using Excel software, 167 MeSH terms were listed and arranged. Following criteria of relevance and frequency, 8 MeSH terms were selected as irrelevant. See **AP Figure 51**.



AP Figure 51: Frequency of irrelevant MeSH terms included in query #1

8.3.4 Step 4. New query including selected MeSH terms retrieved from irrelevant papers

Query #2	No. Ref. retrieved	Observations
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] OR "age groups"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR	4230	Query #2 is equal to query #1, except for the inclusion of the terms: ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms]

[6] "age groups"[MeSH Terms] included: Adolescent, Adult, Aged +, Middle Aged, Young Adult, Child, Child, Preschool, Infant, Infant, Newborn +.

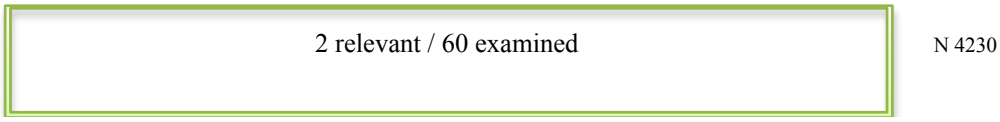
"insulin"[MeSH Terms])		OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms])

8.3.5 Step 5. Analysis of references linked in different queries:

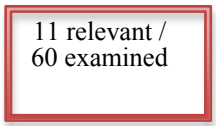
i) Query #2 vs. query #3

Query #3	No. Ref. retrieved	Observations
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms])	956	Query #3 is equal to query #2, except for the exclusion of the term: "age groups"[MeSH Terms]

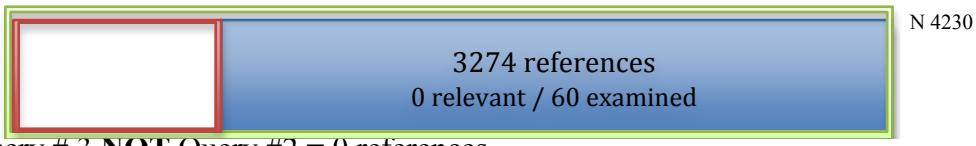
Query # 2 = **4230** references



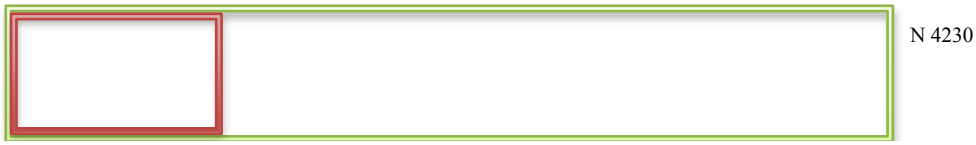
Query # 3 = **956** references



Query # 2 **NOT** Query # 3 = 3274 references



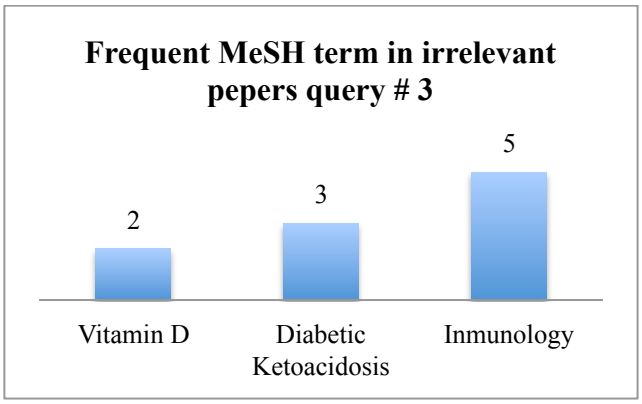
Query # 3 **NOT** Query #2 = 0 references



Note: according to step 4, the query selected to continue the process is the # 3.

Repeating step 3 for frequent MeSH term in irrelevant papers of query # 3.

The query # 3 showed 956 references arranged in 48 pages into PubMed Website. I examined all MeSH terms reported in the first irrelevant reference each 5 pages, starting on the first page. Using Excel software, 150 MeSH terms were listed and arranged. Following criteria of relevance and frequency, 3 MeSH terms were selected as irrelevant[7]. See **AP Figure 52.**



AP Figure 52: Frequency of irrelevant MeSH terms included in query #3

ii) Query #3 vs. query #4

Query #4	No. Ref. retrieved	Observations
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "immunology" [Subheading])	866	Query #4 is equal to query #3, except for the inclusion of the terms: "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Inmunology"[MeSH Terms])

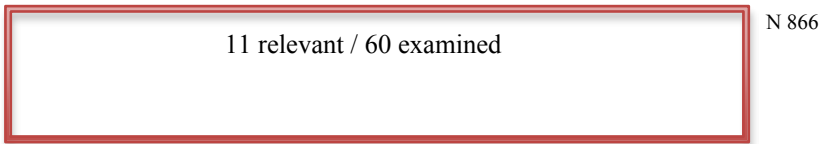
Query # 3 = **956** references

N 956

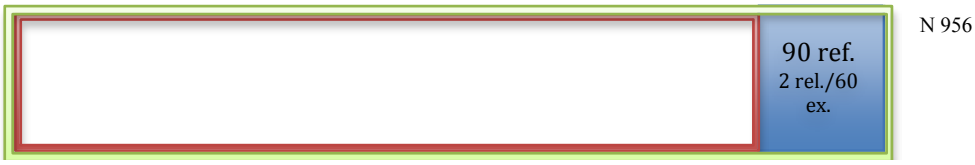
11 relevant / 60 examined

[7] Inmunology as Subheanding.

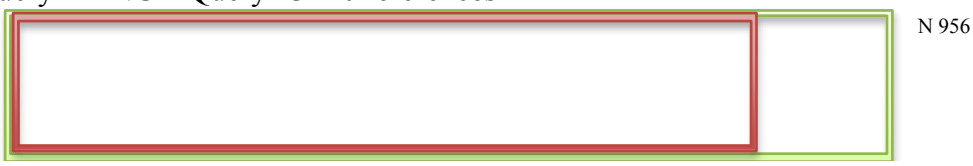
Query # 4 = **866** references



Query # 3 **NOT** Query # 4 = 90 references



Query # 4 **NOT** Query #3 = 0 references

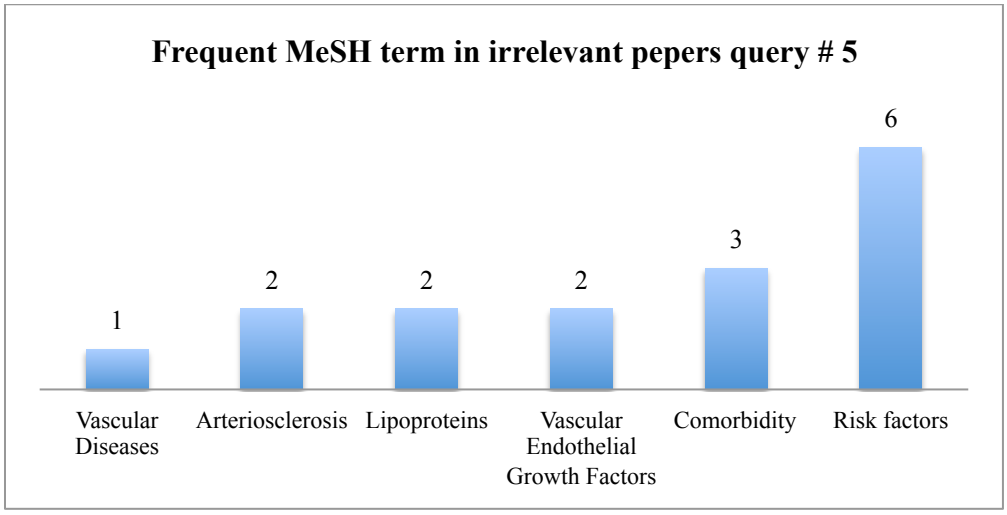


Note: In the Query # 3 NOT Query # 4 = 90, were found 2 relevant references in the first 60 examined. The common MeSH term of these references was *immunology*. In consequence, a new query to keep the Subheading *immunology* was necessary.

Query #5	**No. Ref. retrieved**	**Observations**
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms])	915	Query #5 is equal to query #4, except for the exclusion of the term: "immunology" [Subheading]

Repeating step 3 for frequent MeSH term in irrelevant papers of query # 5.

The query # 5 showed 915 references arranged in 46 pages into PubMed Website. I examined all MeSH terms reported in the first irrelevant reference each 5 pages, starting on the first page. Using Excel software, 188 MeSH terms were listed and arranged. Following criteria of relevance and frequency, 6 MeSH terms were selected as irrelevant. See **AP Figure 53.**

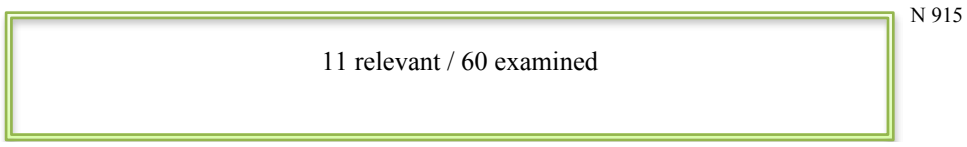


AP Figure 53: Frequency of irrelevant MeSH terms included in query #5

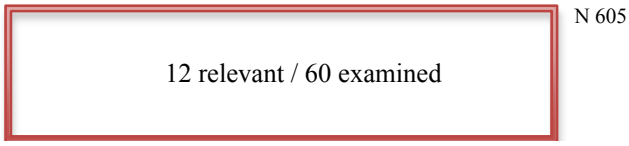
iii) Query #5 vs. query #6

Query #6	No. Ref. retrieved	Observations
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Vascular Diseases" [MeSH Terms] OR "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms] OR "Risk Factors" [MeSH Terms])	605	Query #6 is equal to query #5, except for the inclusion of the terms: "Vascular Diseases" [MeSH Terms] "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms] OR "Risk Factors" [MeSH Terms]

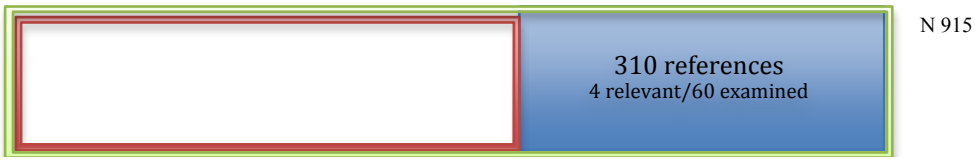
Query # 5 = **915** references



Query # 6 = **605** references



Query # 5 **NOT** Query # 6 = 310 references



Query # 6 **NOT** Query # 5 = 0 references

Note: In the Query # 5 NOT Query # 6 = 310, were found 4 relevant references in the first 60 examined. The common MeSH term of these references was risk factors. In consequence, a new query to keep the MeSH term *Risk Factors* was necessary.

Query #7	**No. Ref. retrieved**	**Observations**
("diabetes mellitus, type 1/epidemiology"[MAJR] OR "type 1 diabetes"[TIAB]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Vascular	776	Query #7 is equal to query #6, except for the exclusion of the term: "Risk Factors" [MeSH Terms]

Diseases" [MeSH Terms] OR "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms])		

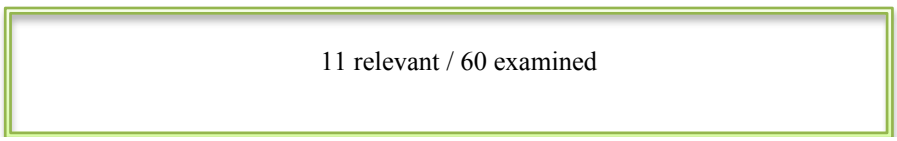
Repeating step 3 for frequent MeSH term in irrelevant papers of query # 7.

The query # 7 showed 776 references arranged in 39 pages into PubMed Website. We examined all MeSH terms reported in the first irrelevant reference each 5 pages, starting on the first page. Using Excel software, 115 MeSH terms were listed and arranged. Following criteria of relevance and frequency, 0 MeSH terms were selected as irrelevant. As consequence, we decided to exclude only the term "type 1 diabetes"[TIAB] of the equation in order to analyze if was possible obtain a query more specific but keeping sensitivity.

iv) Query #7 vs. query #8

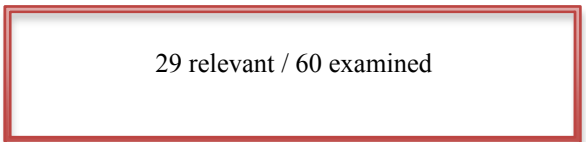
Query #8	**No. Ref. retrieved**	**Observations**
("diabetes mellitus, type 1/epidemiology"[MAJR]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Blood Glucose"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Vascular Diseases" [MeSH Terms] OR "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms])	459	Query #8 is equal to query #7, except for the exclusion of the term: OR "type 1 diabetes"[TIAB]

Query # 7 = **776** references



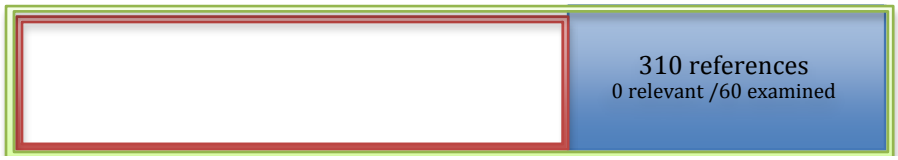
N 776

Query # 8 = **459** references

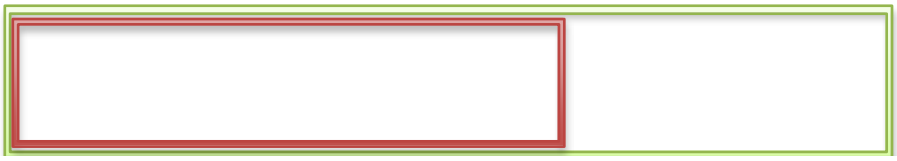


N 459

Query # 7 **NOT** Query # 8 = 317 references



Query # 8 **NOT** Query # 7 = 0 references



Note: according to step 5, the query selected to continue the process is the # 8.

8.3.6 Step 6. The results of selected query are compared with the 92 references found in query #0

We compared each one of the references retrieved from the query # 0 (92 references) with each reference retrieved from the query #8 (423 references). The following 8 references were missed:

1. Bruno G, Merletti F, De Salvia A, Lezo A, Arcari R, Pagano G. Comparison of incidence of insulin-dependent diabetes mellitus in children and young adults in the Province of Turin, Italy, 1984-91. Piedmont Study Group for Diabetes Epidemiology. Diabet Med. 1997 Nov;14(11):964-9.
2. Cardwell C, Carson D, Patterson C. Secular trends, disease maps and ecological analyses of the incidence of childhood onset Type 1 diabetes in Northern Ireland, 1989-2003. Diabetic Med. 2007;24:289-95.
3. Carrasco E, Angel B, Codner E, Garcia D, Ugarte F, Bruzzone ME, et al. [Type 1 diabetes mellitus incidence in Santiago, Chile. Analysis by counties in the period 2000-2004]. Rev Med Chil. 2006 Oct;134(10):1258-64. ESPANOL
4. Pishdad GR. Low incidence of type 1 diabetes in Iran. Diabetes Care. 2005 Apr;28(4):927-8.
5. Rytkönen M, Ranta J, Tuomilehto J, Karvonen M. Bayesian analysis of geographical variation in the incidence of Type I diabetes in Finland. SPAT Study Group The Finnish Childhood Diabetes Registry Group. Diabetologia. 2001;44(Suppl 3):B37-44.
6. Skordis N, Theodorou S, Apsiotou T, Stavrou S, Herakleous E, Savva SC. The incidence of type 1 diabetes mellitus in Greek-Cypriot children and adolescents in 1990-2000. Pediatr Diabetes. 2002 Dec;3(4):200-4. NO MESH
7. Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith G, Bloch C, et al. Increasing Incidence of Type 1 Diabetes in 0- to 17-Year-Old Colorado Youth. Diabetes Care. 2007;30(3):503-9.

8. Vlajinac HD, Bojovic BM, Sipetic SB, Adanja BJ, Jarebinski MS, Radmanovic SZ, et al. Insulin dependent diabetes mellitus: incidence in childhood in Belgrade 1982-92. J Epidemiol Community Health. 1995 Feb;49(1):107-8.

All MeSH terms reported in these 8 references were listed and arranged using Excel software, 100 in total. The MeSH term *"Blood Glucose"* introduced in the query #2 was found in the article No.1 (Bruno, 1997). Also, the report of groups of age (adolescent, child, etc.) was a predominant condition of the MeSH terms in the lost references.

Two articles of this list have particular conditions: the article No.3 (Carrasco E, 2006) was published in Spanish, and the article No. 6 (Skordis, 2002) did not report any MeSH term.

As consequence of this analyses, the decision was to modify the query #8, excluding the term: "Blood Glucose"[MeSH Terms] of the equation and including the term: "age groups"[MeSH Terms].

8.3.7 Step 7. Repetition of steps 2 to 7 until the majority of 92 articles are included.

Repeating step 2: Query # 9 using the main MeSH terms retrieved from articles retrieved in step 6.

Query #9	No. Ref. retrieved	Observations
("diabetes mellitus, type 1/epidemiology"[MAJR]) AND (("incidence"[MeSH Major Topic] OR incidence[Title/Abstract]) AND (age[Title/Abstract] OR "age distribution"[MeSH Terms] OR "age factors"[MeSH Terms] OR "age groups"[MeSH Terms]) AND "humans"[MeSH Terms]) AND (Journal Article[ptyp] AND English[lang] AND ("1990/1/1"[PDAT] : "2011/11/28"[PDAT])) NOT ("Diabetic Neuropathies"[MeSH Terms] OR "Diabetic Nephropathies"[MeSH Terms] OR "Autoantibodies"[MeSH Terms] OR "Cholesterol"[MeSH Terms] OR "Antigens"[MeSH Terms] OR "histocompatibility antigens class ii"[MeSH Terms] OR "insulin"[MeSH Terms] OR "Vitamin D"[MeSH Terms] OR "Diabetic ketoacidosis"[MeSH Terms] OR "Vascular Diseases" [MeSH Terms] OR "Arteriosclerosis" [MeSH Terms] OR "Lipoproteins" [MeSH Terms] OR "Vascular Endothelial Growth Factors" [MeSH Terms] OR "Comorbidity" [MeSH Terms])	423	Query #9 is equal to query #8, except for the exclusion of the term: OR "Blood Glucose"[MeSH Terms], and the inclusion of the term: OR "age groups"[MeSH Terms]

With the query # 9 we lost 2 of 92 database references: the article No.3 (Carrasco E, 2006) because it was published in Spanish, and the article No. 6 (Skordis, 2002) because it did not report any MeSH term.

We retrieved 57 additional papers expanding the search for all published articles before 1990/01/01. After 2011/11/28, there were not new indexed references by February 2012. Updated searches were performed on November 2014 and January 2015.

With the methodology proposed in this document, the best query equation for conduct a literature review of the study of incidence of T1D considering the age at onset worldwide is the query # 9.

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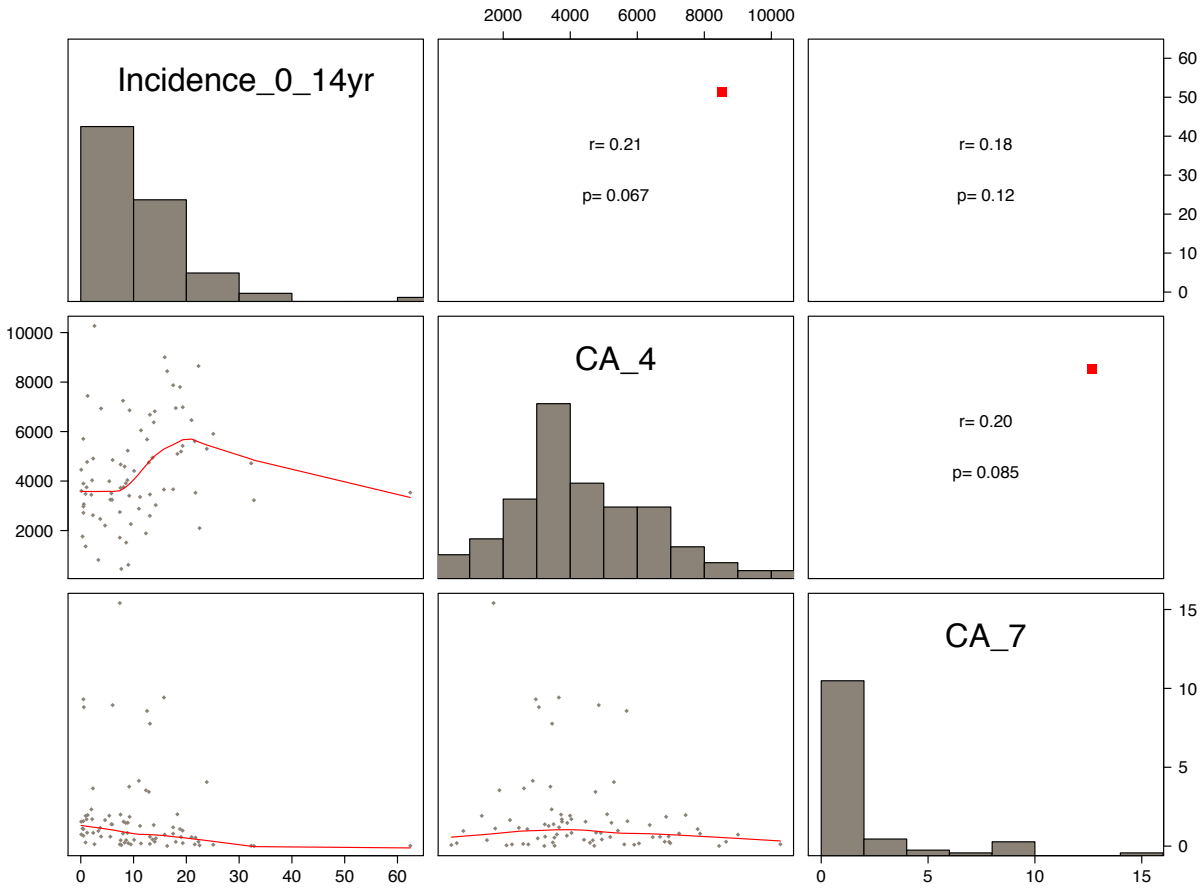
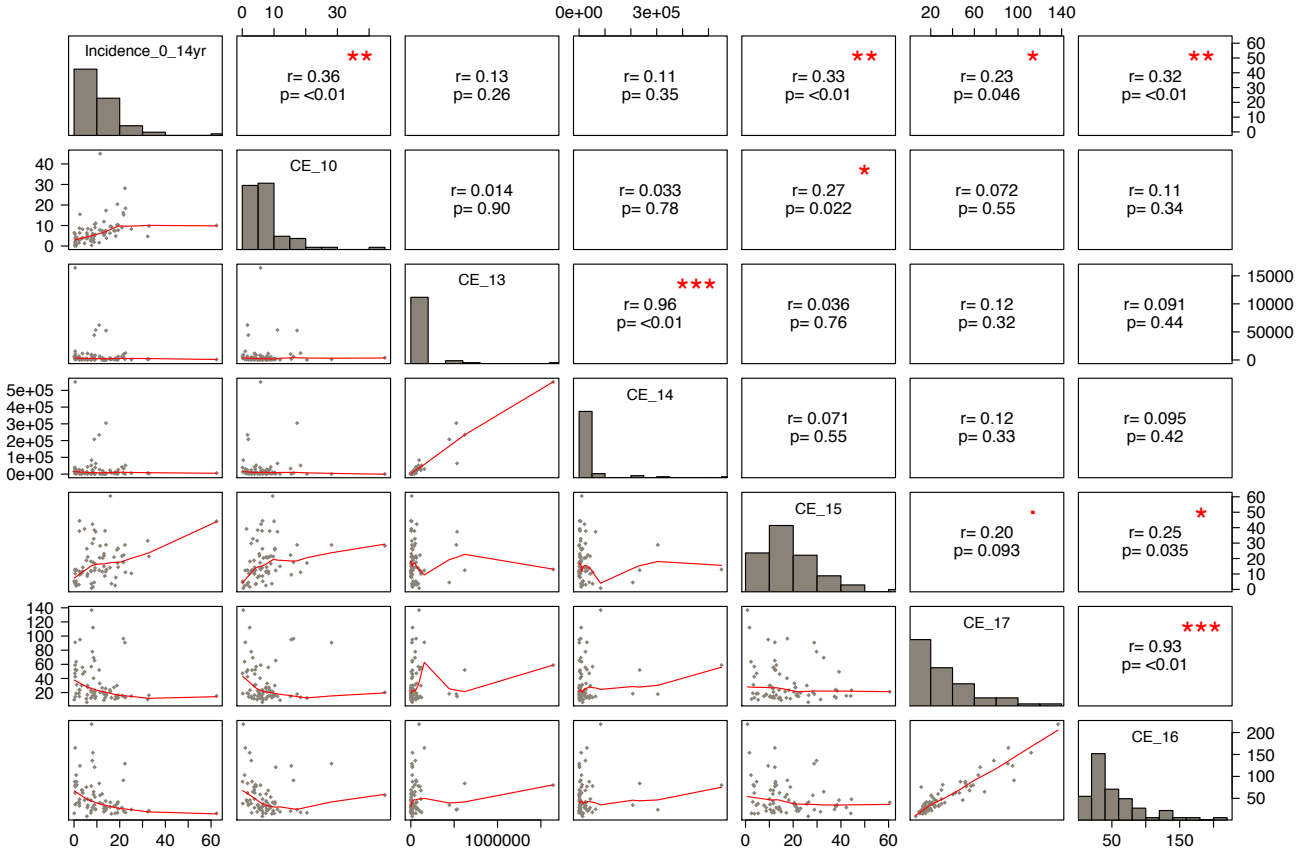
8.4 Appendix D: Correlation matrix between incidence of T1D and independent variables by domains presented in chapter 3

8.4.1 Correlation matrix incidence of T1D and climate and environment domain

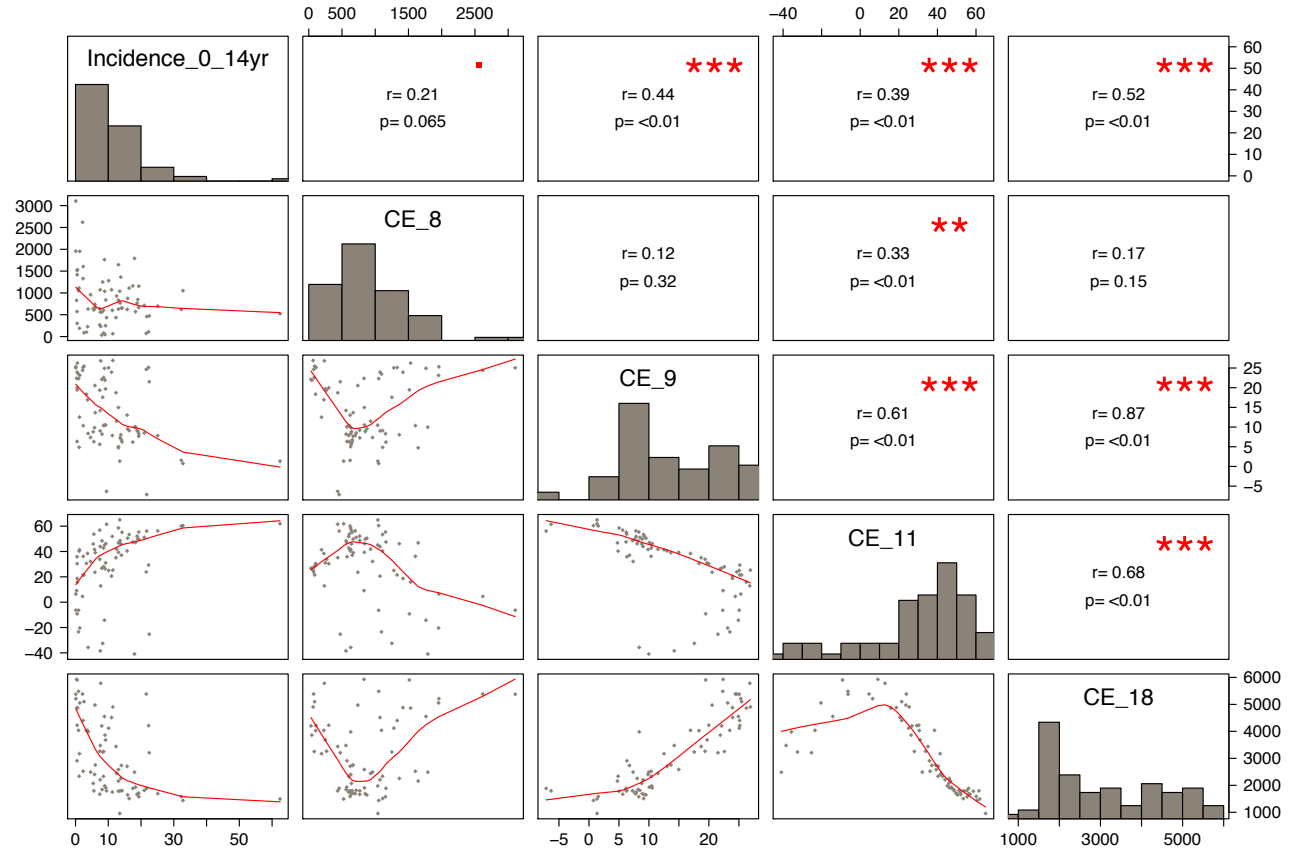
Selected variables: CA_1 + CE_10 + CE_15 + CE_16 + CE_8 + CE_11 + CE_18. See **Table 12** for name of codes.



AP Figure 54: Correlation matrix: environment domain (Agriculture)



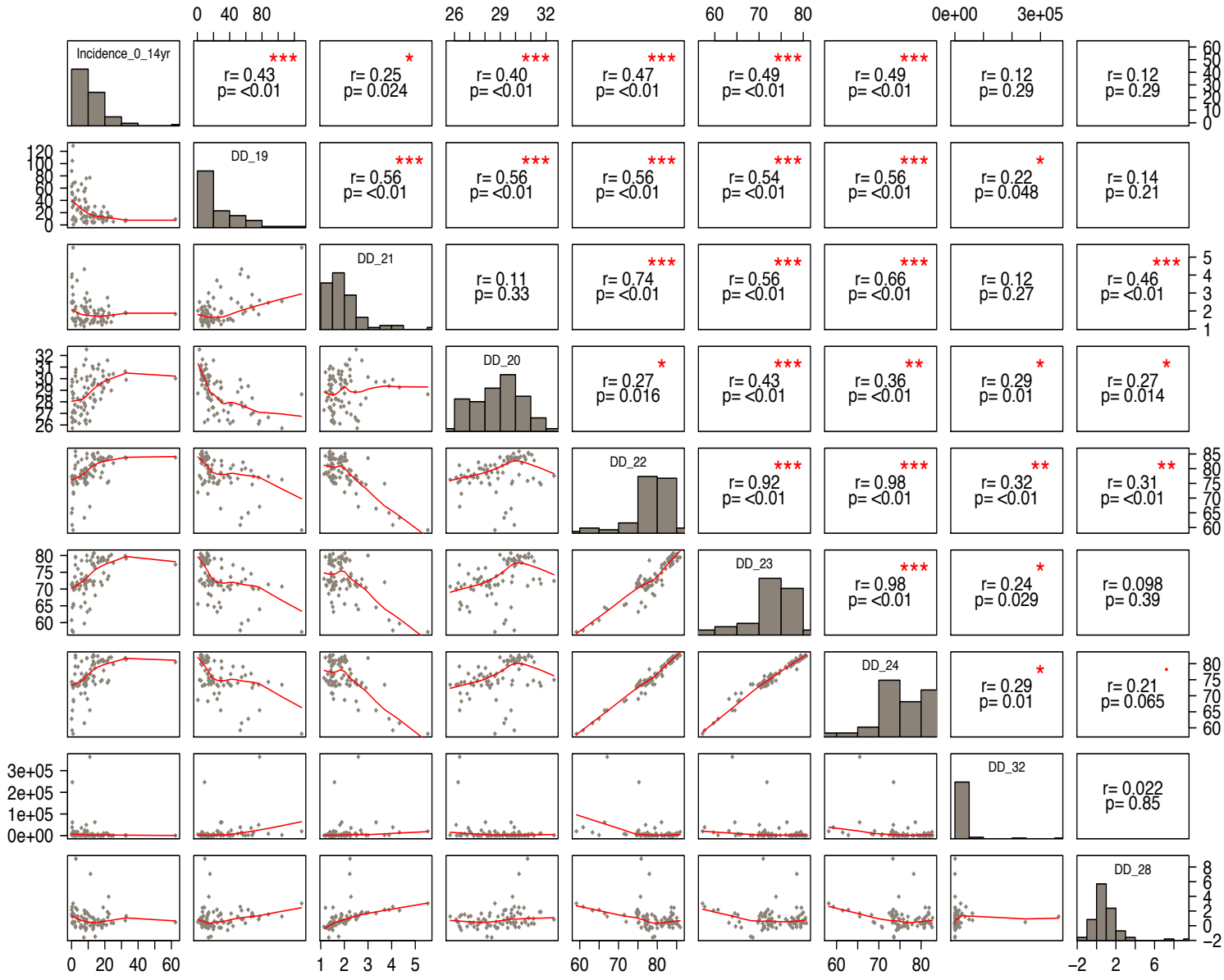
AP Figure 55: Correlation matrix: climate and environment domain (Environment 1 of 2)



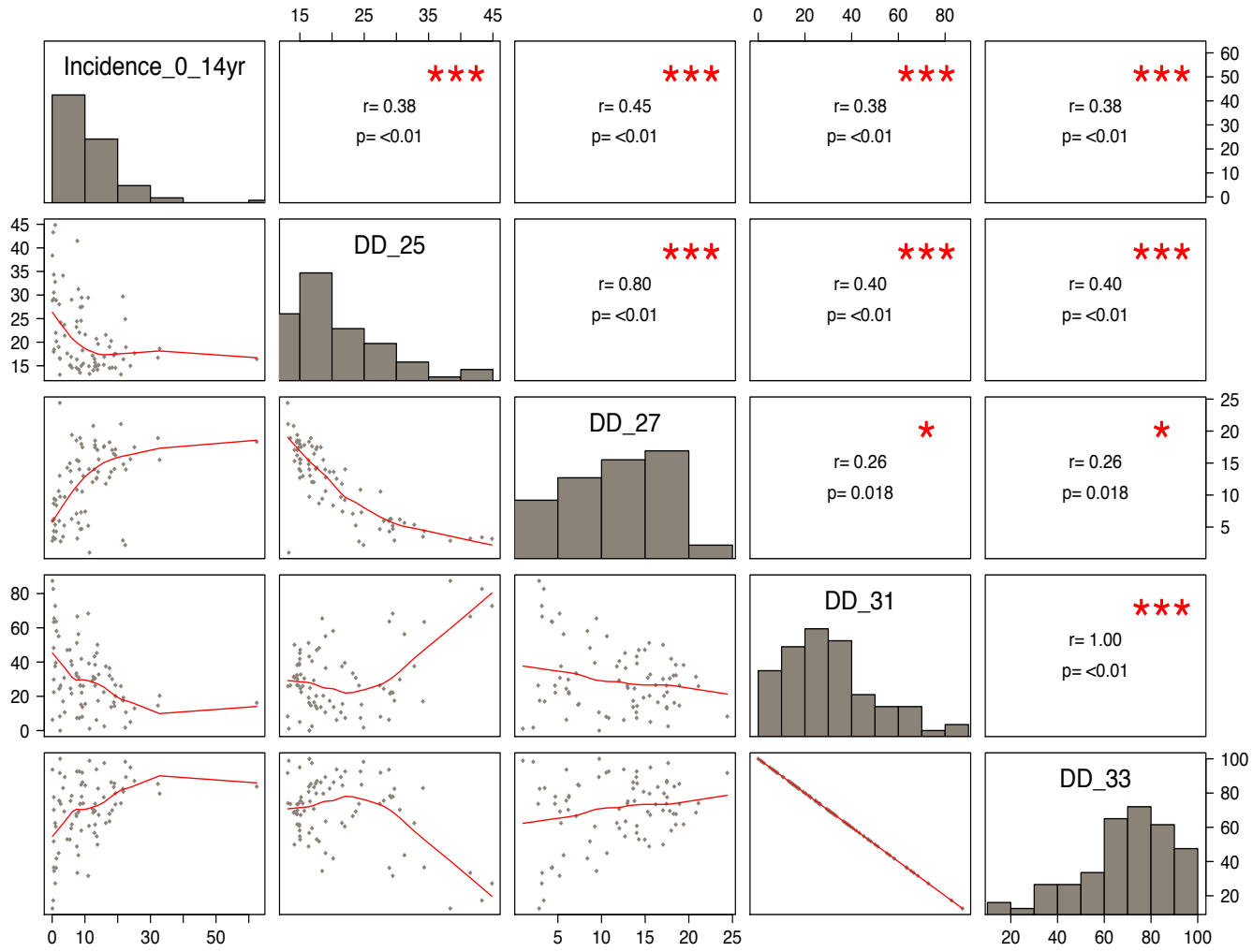
AP Figure 56: Correlation matrix: climate and environment domain (Environment 2 of 2)

8.4.2 Correlation matrix incidence of T1D and demography domain

Selected variables: DD_19 + DD_21 + DD_20 + DD_24 + DD_27 + DD_33. See **SM Table 11** for name of codes.



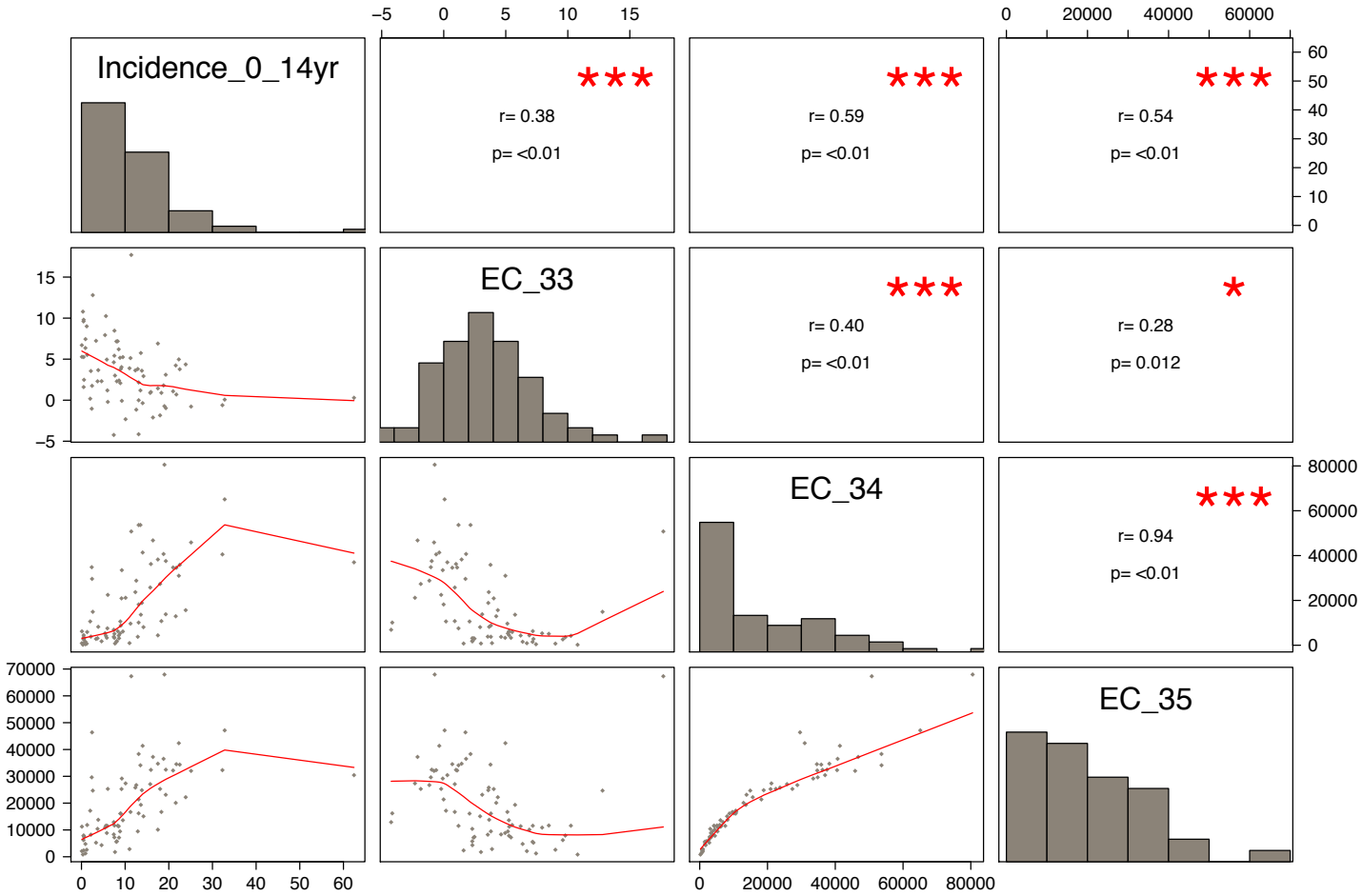
AP Figure 57: Correlation matrix: demography domain (Demography 1 of 2)



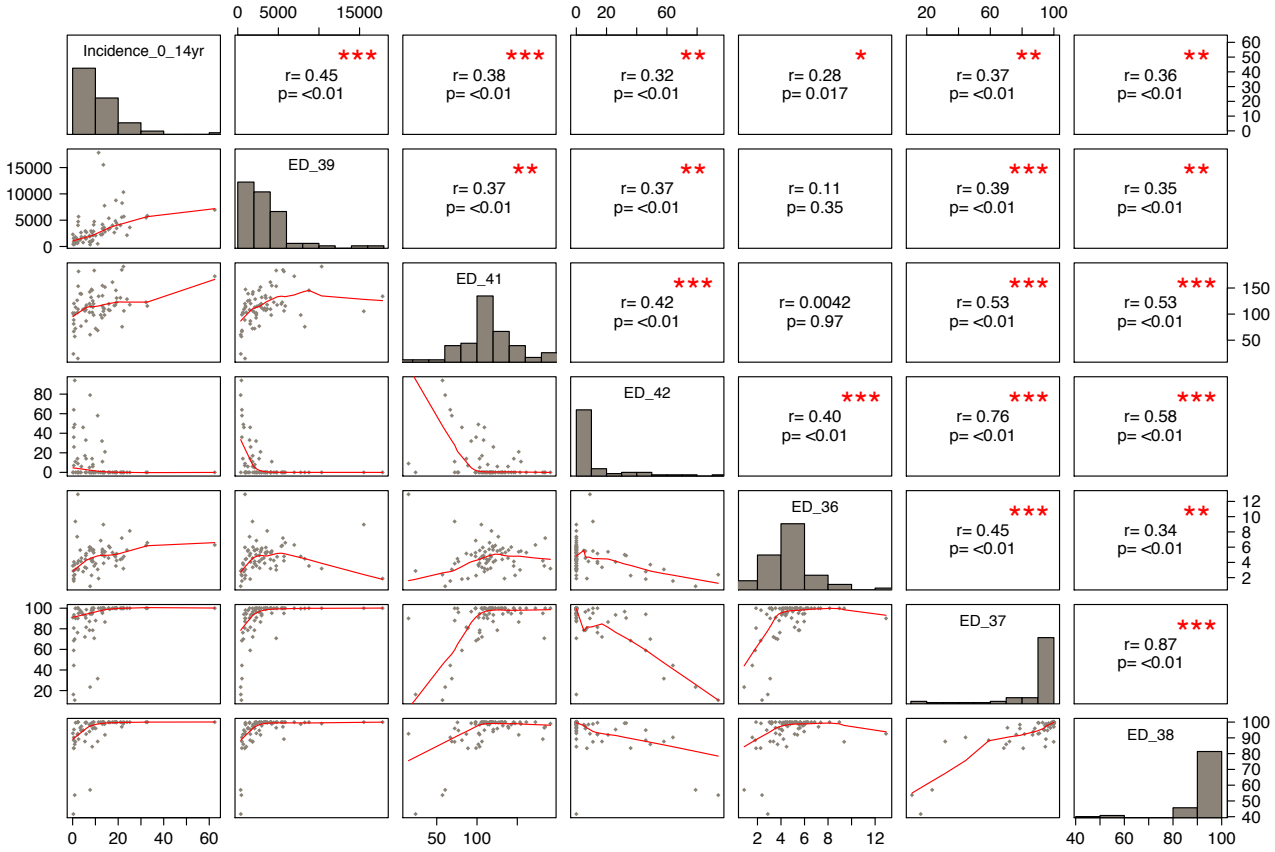
AP Figure 58: Correlation matrix: demography domain (Demography 2 of 2)

8.4.3 Correlation matrix incidence of T1D and economic factors domain

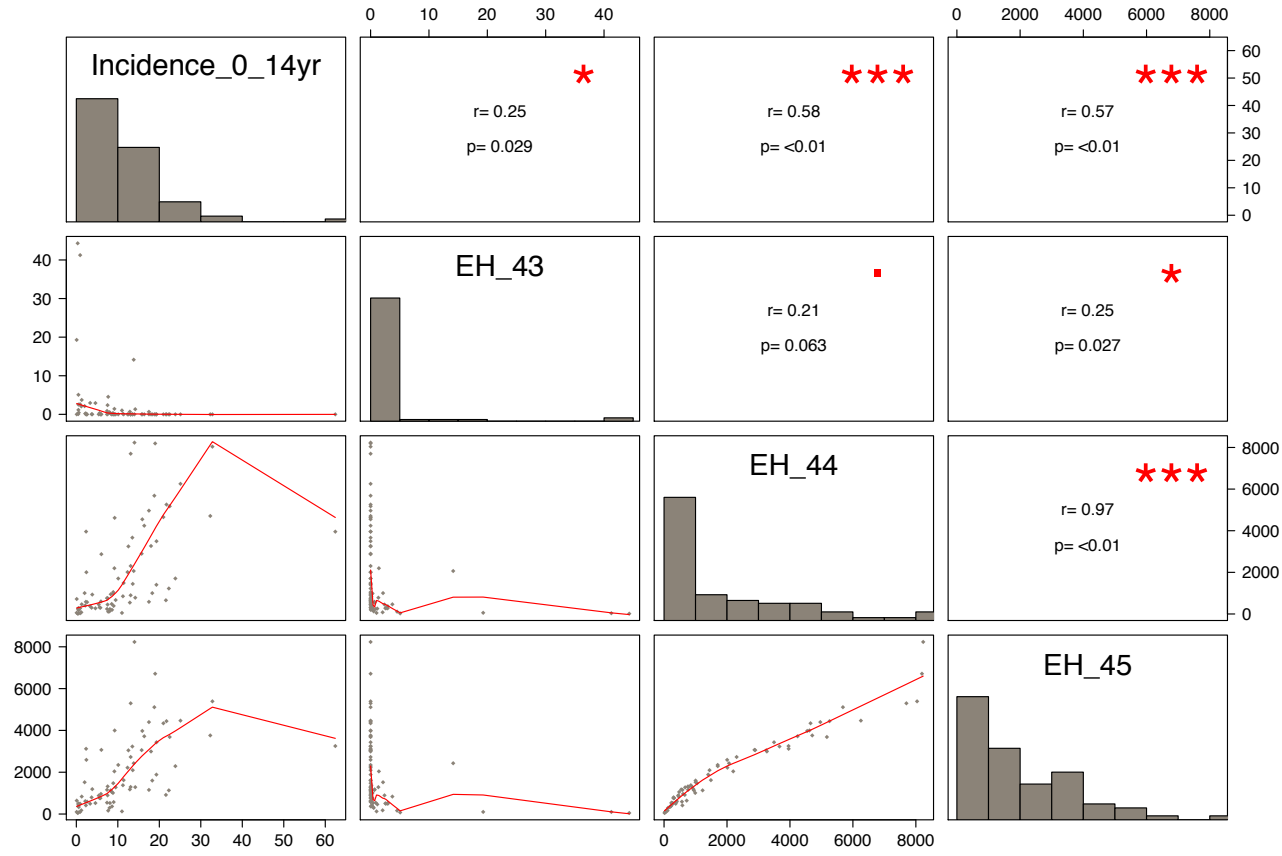
Selected variables: ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33 + EC_34. See **Table 12** for name of codes.



AP Figure 59: Correlation matrix: economic factors domain (Country economy)



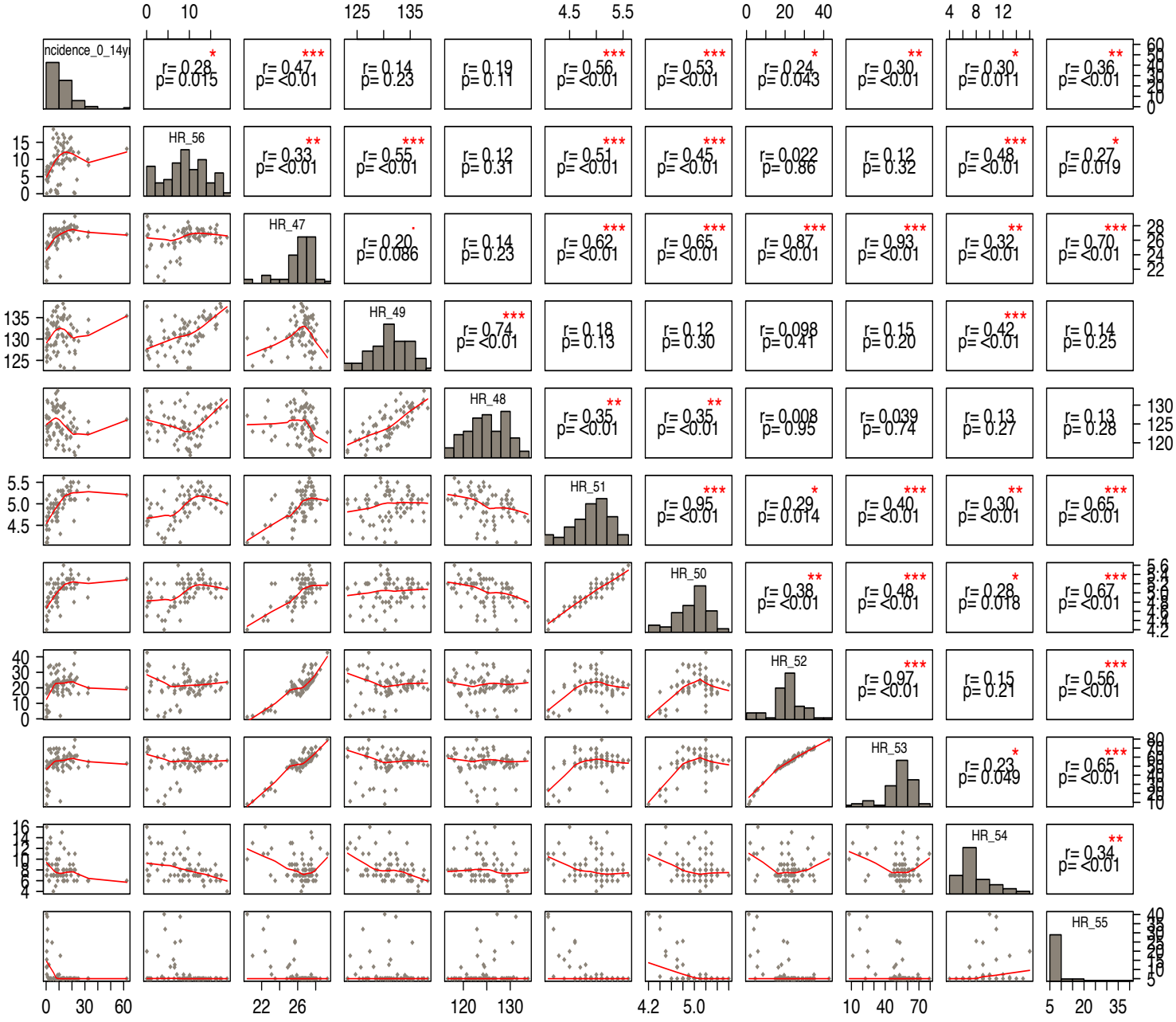
AP Figure 60: Correlation matrix: economic factors domain (Development)



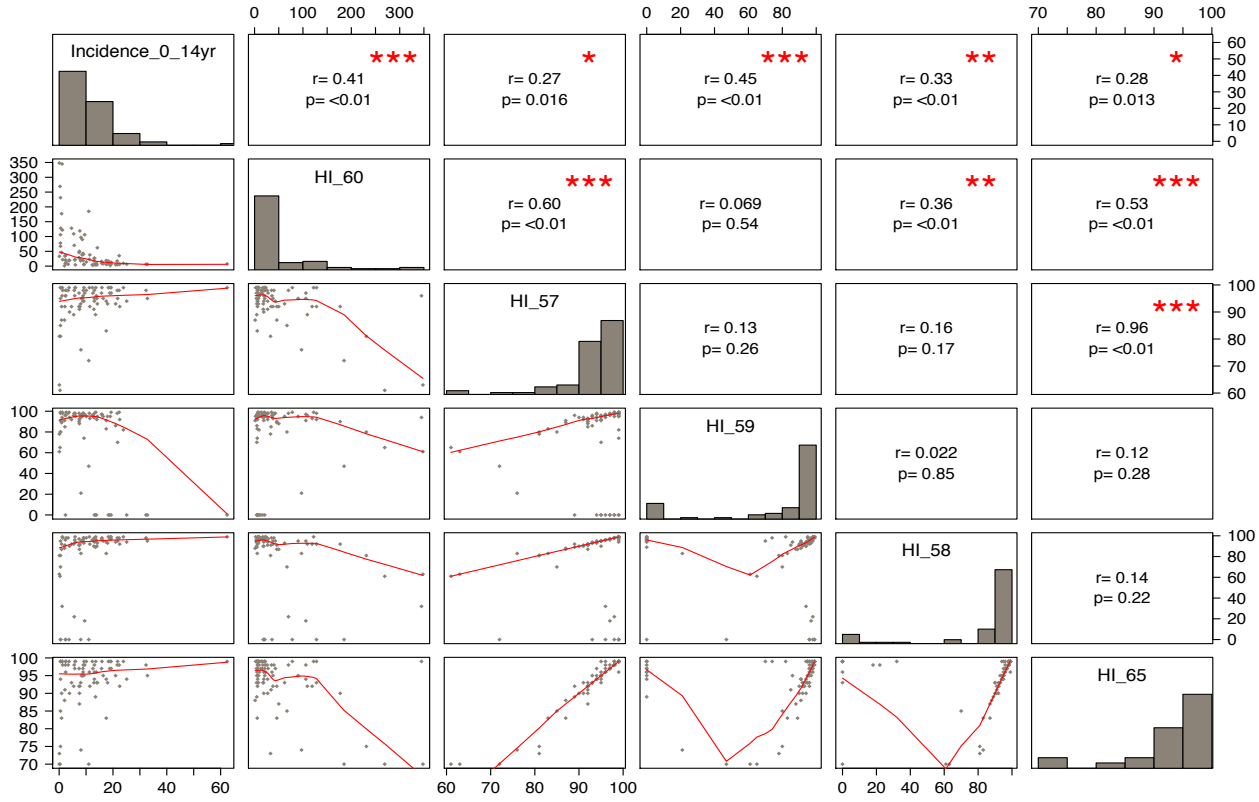
AP Figure 61: Correlation matrix: economic factors domain (Health economy)

8.4.4 Correlation matrix incidence of T1D and health conditions domain

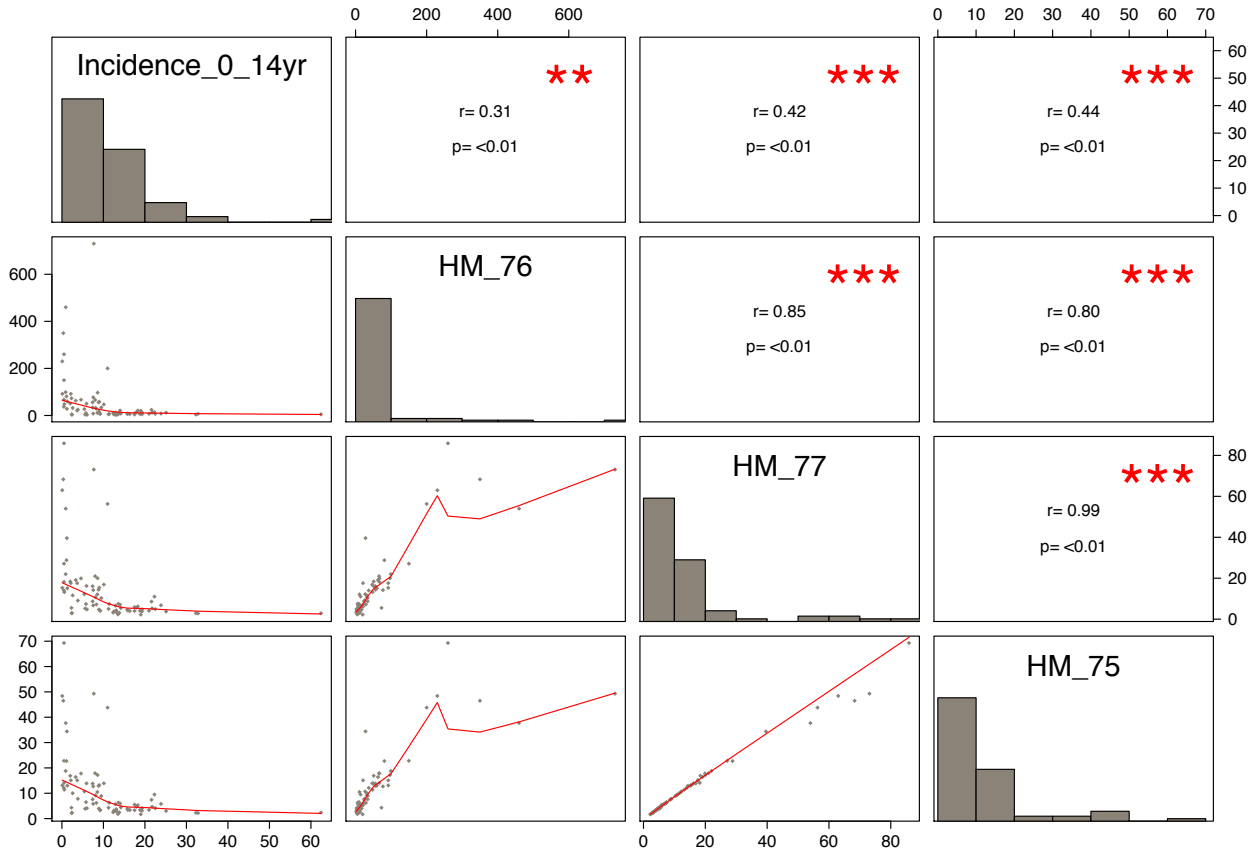
Selected variables: HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55. See **Table 12** for name of codes.



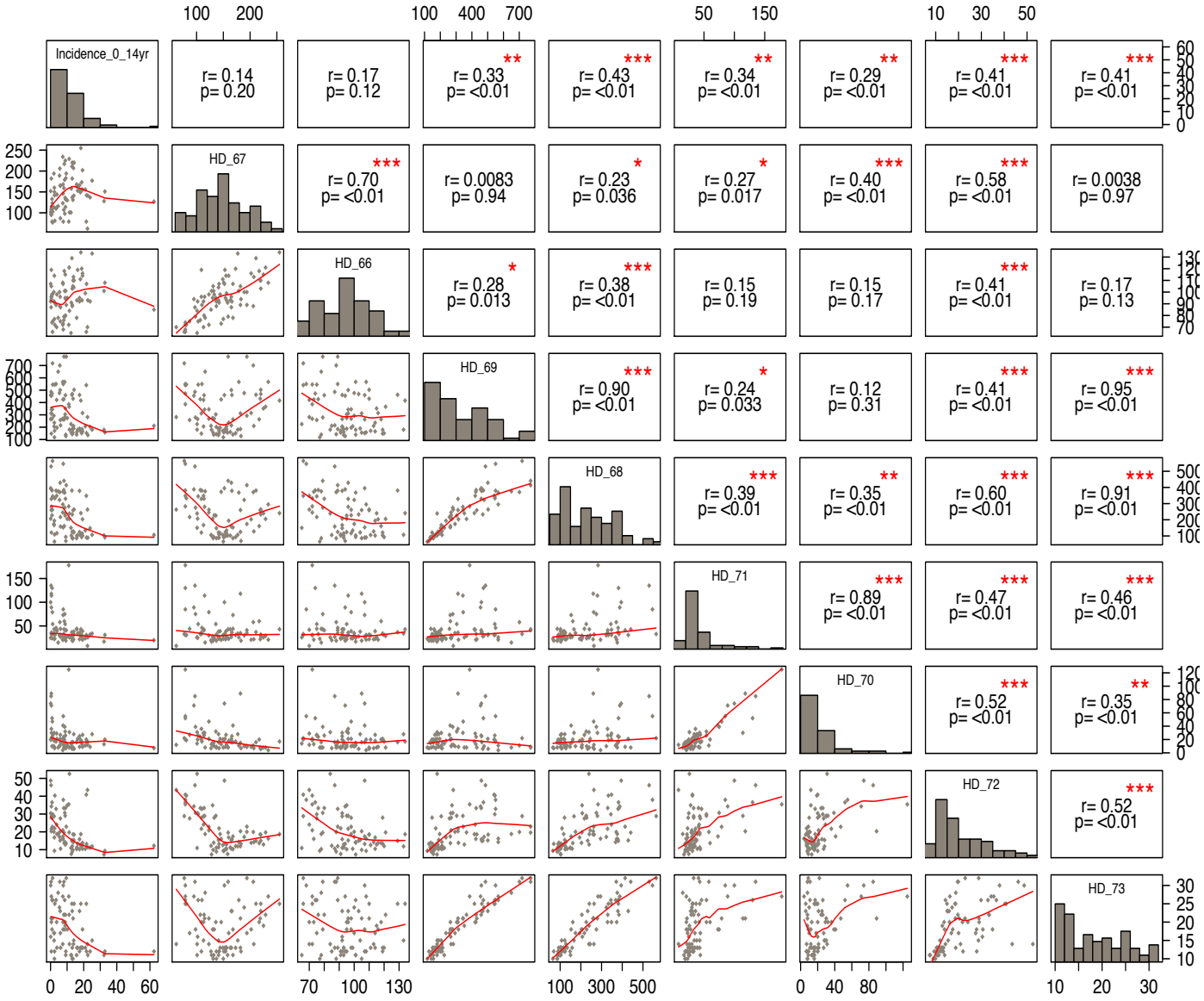
AP Figure 62: Correlation matrix: health conditions domain (Risk factors for non-communicable diseases)



AP Figure 63: Correlation matrix: health conditions domain (Deaths from non-communicable diseases)



AP Figure 64: Correlation matrix: health conditions domain (Infant and maternal mortality rates)



AP Figure 65: Correlation matrix: health conditions domain (Infectious diseases and immunization)

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8.5 Appendix E: Selection of variables by domain and graphic validation of the models presented in chapter 3

8.5.1.1 Stepwise selection climate and environment domain

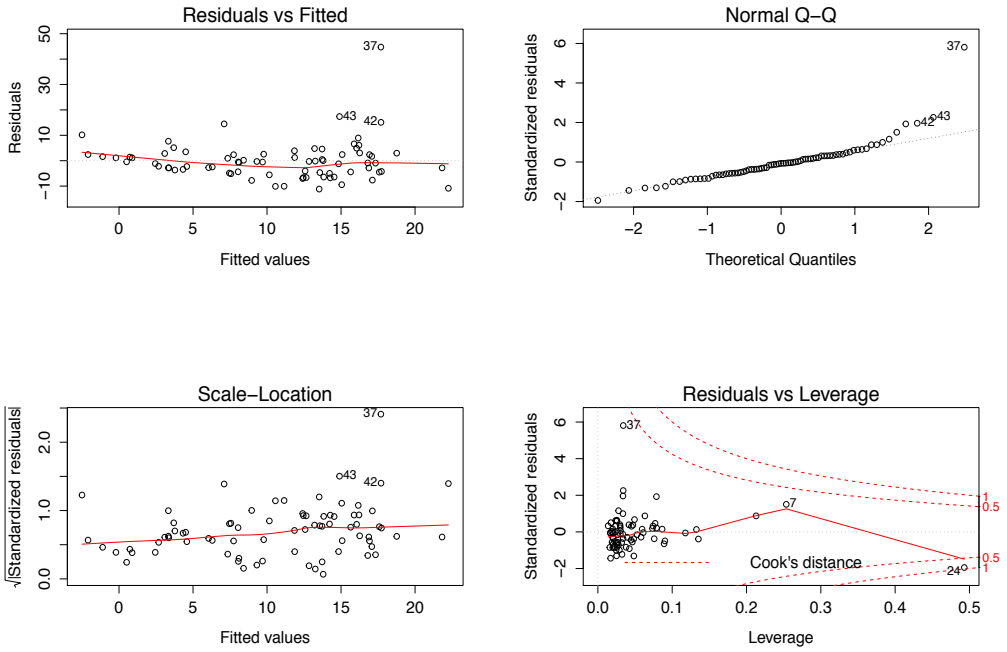
AP Table 31: Manual backward selection of the variables of climate and environment domain

Backwards elimination - adjusted R2

Domain: climate and environment

Step	Variables included	Removed	Adjusted R2	
Full	Inc T1D ~ CA_1 + CE_10 + CE_15 + CE_16 + CE_8 + CE_11 + CE_18		0.2886	
Step 1	Inc T1D ~ CE_10 + CE_15 + CE_16 + CE_8 + CE_11 + CE_18	[- CA_1]	0.3000	
	Inc T1D ~ CA_1 + CE_15 + CE_16 + CE_8 + CE_11 + CE_18	[- CE_10]	0.2476	
	Inc T1D ~ CA_1 + CE_10 + CE_16 + CE_8 + CE_11 + CE_18	**[- CE_15]**	**0.3166**	*
	Inc T1D ~ CA_1 + CE_10 + CE_15 + CE_8 + CE_11 + CE_18	[- CE_16]	0.2977	
	Inc T1D ~ CA_1 + CE_10 + CE_15 + CE_16 + CE_11 + CE_18	[- CE_8]	0.2983	
	Inc T1D ~ CA_1 + CE_10 + CE_15 + CE_16 + CE_8 + CE_18	[- CE_11]	0.2993	
	Inc T1D ~ CA_1 + CE_10 + CE_15 + CE_16 + CE_8 + CE_11	[- CE_18]	0.2258	
Step 2	Inc T1D ~ CE_10 + CE_16 + CE_8 + CE_11 + CE_18	[- CA_1]	0.3254	
	Inc T1D ~ CA_1 + CE_16 + CE_8 + CE_11 + CE_18	[- CE_10]	0.2703	
	Inc T1D ~ CA_1 + CE_10 + CE_8 + CE_11 + CE_18	[- CE_16]	0.3240	
	Inc T1D ~ CA_1 + CE_10 + CE_16 + CE_11 + CE_18	**[- CE_8]**	**0.3325**	*
	Inc T1D ~ CA_1 + CE_10 + CE_16 + CE_8 + CE_18	[- CE_11]	0.3266	
	Inc T1D ~ CA_1 + CE_10 + CE_16 + CE_8 + CE_11	[- CE_18]	0.2459	
Step 3	Inc T1D ~ CE_10 + CE_16 + CE_11 + CE_18	**[- CA_1]**	**0.3433**	*
	Inc T1D ~ CA_1 + CE_16 + CE_11 + CE_18	[- CE_10]	0.2551	
	Inc T1D ~ CA_1 + CE_10 + CE_11 + CE_18	[- CE_16]	0.3314	
	Inc T1D ~ CA_1 + CE_10 + CE_16 + CE_18	[- CE_11]	0.3419	
	Inc T1D ~ CA_1 + CE_10 + CE_16 + CE_11	[- CE_18]	0.2445	
Step 4	Inc T1D ~ CE_16 + CE_11 + CE_18	[- CE_10]	0.2559	
	Inc T1D ~ CE_10 + CE_11 + CE_18	[- CE_16]	0.3417	
	Inc T1D ~ CE_10 + CE_16 + CE_18	**[- CE_11]**	**0.3519**	**
	Inc T1D ~ CE_10 + CE_16 + CE_11	[- CE_18]	0.2541	
Step 5	Inc T1D ~ CE_16 + CE_18	[- CE_10]	0.2612	
	Inc T1D ~ CE_10 + CE_18	[- CE_16]	0.3499	
	Inc T1D ~ CE_10 + CE_16	[- CE_18]	0.1891	

(*) Model with higher adjusted R2, (**) Best model



AP Figure 66: Graphic validation of the best model for the climate and environment domain

8.5.1.2 Stepwise selection demography domain

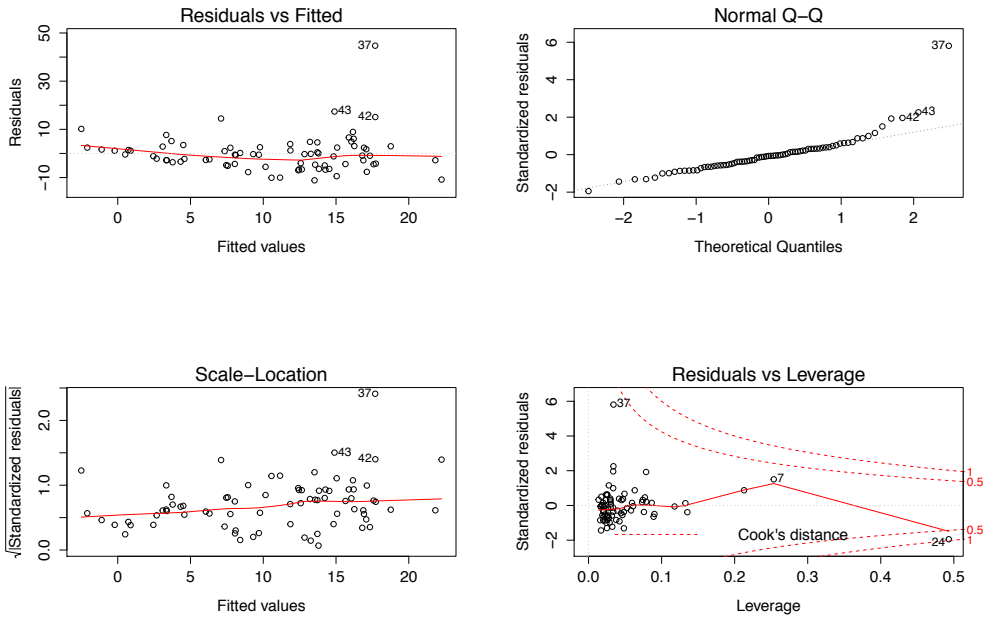
AP Table 32: Manual backward selection of the variables of demography domain

Backwards elimination - adjusted R2

Domain: demography

Step	Variables included	Removed	Adjusted R2	
Full	Inc T1D ~ DD_19 + DD_21 + DD_20 + DD_24 + DD_27 + DD_33		0.3236	
Step 1	Inc T1D ~ DD_21 + DD_20 + DD_24 + DD_27 + DD_33	[- DD_19]	0.3235	
	Inc T1D ~ DD_19 + DD_20 + DD_24 + DD_27 + DD_33	[- DD_21]	0.3210	
	Inc T1D ~ DD_19 + DD_21 + DD_24 + DD_27 + DD_33	**[- DD_20]**	**0.3266**	**
	Inc T1D ~ DD_19 + DD_21 + DD_20 + DD_27 + DD_33	[- DD_24]	0.3304	
	Inc T1D ~ DD_19 + DD_21 + DD_20 + DD_24 + DD_33	[- DD_27]	0.2632	
	Inc T1D ~ DD_19 + DD_21 + DD_20 + DD_24 + DD_27	[- DD_33]	0.3121	
Step 2	Inc T1D ~ DD_21 + DD_24 + DD_27 + DD_33	[- DD_19]	0.2829	
	Inc T1D ~ DD_19 + DD_24 + DD_27 + DD_33	[- DD_21]	0.2780	
	Inc T1D ~ DD_19 + DD_21 + DD_27 + DD_33	[- DD_24]	0.3274	
	Inc T1D ~ DD_19 + DD_21 + DD_24 + DD_33	[- DD_27]	0.2674	
	Inc T1D ~ DD_19 + DD_21 + DD_24 + DD_27	[- DD_33]	0.3148	

(**) Best model



AP Figure 67: Graphic validation of the best model for the demography domain

8.5.1.3 Stepwise selection economic factors domain

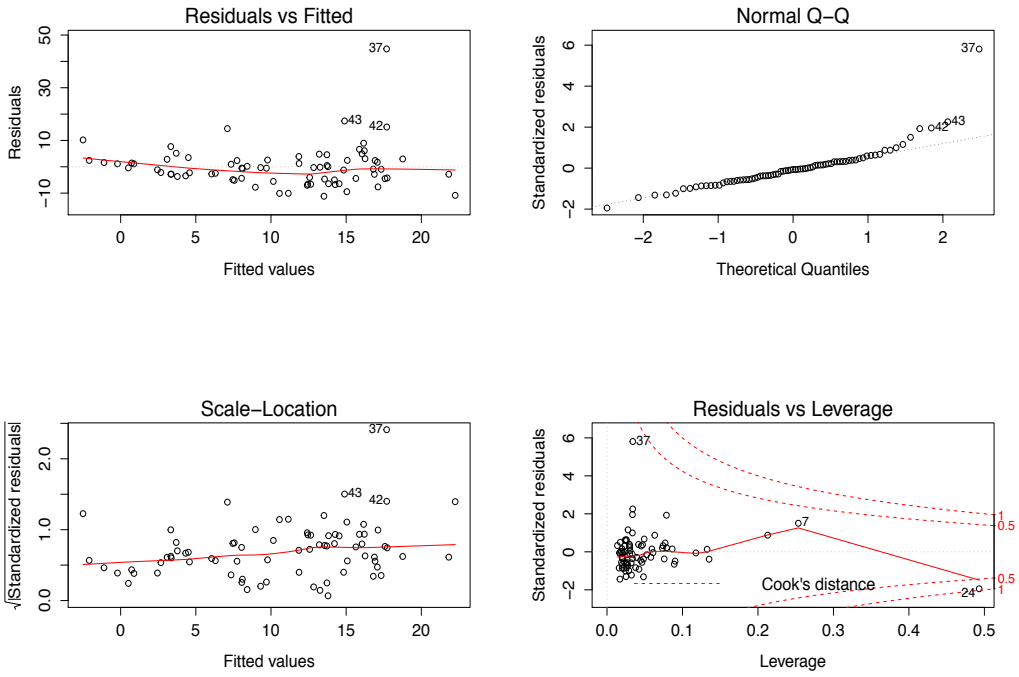
AP Table 33: Manual backward selection of the variables of economic factors domain

Backwards elimination - adjusted R2

Domain: economic factors

Step	Variables included	Removed	Adjusted R2	
Full	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33 + EC_34		0.4240	
Step 1	Inc T1D ~ ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33 + EC_34	[- ED_39]	0.4187	
	Inc T1D ~ ED_39 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33 + EC_34	[- ED_41]	0.3479	
	Inc T1D ~ ED_39 + ED_41 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33 + EC_34	[- ED_42]	0.4327	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_37 + EH_43 + EH_45 + EC_33 + EC_34	[- ED_36]	0.3959	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + EH_43 + EH_45 + EC_33 + EC_34	[- ED_37]	0.4274	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_45 + EC_33 + EC_34	[- EH_43]	0.4329	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EC_33 + EC_34	[- EH_45]	0.4150	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_34	[- EC_33]	0.4094	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33	**[- EC_34]**	**0.4330**	*
Step 2	Inc T1D ~ ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33	[- ED_39]	0.4153	
	Inc T1D ~ ED_39 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33	[- ED_41]	0.3577	
	Inc T1D ~ ED_39 + ED_41 + ED_36 + ED_37 + EH_43 + EH_45 + EC_33	[- ED_42]	0.4414	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_37 + EH_43 + EH_45 + EC_33	[- ED_36]	0.4045	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + EH_43 + EH_45 + EC_33	[- ED_37]	0.4358	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_45 + EC_33	**[- EH_43]**	**0.4416**	*
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EC_33	[- EH_45]	0.3680	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_43 + EH_45	[- EC_33]	0.4184	
Step 3	Inc T1D ~ ED_41 + ED_42 + ED_36 + ED_37 + EH_45 + EC_33	[- ED_39]	0.4241	
	Inc T1D ~ ED_39 + ED_42 + ED_36 + ED_37 + EH_45 + EC_33	[- ED_41]	0.3671	
	Inc T1D ~ ED_39 + ED_41 + ED_36 + ED_37 + EH_45 + EC_33	**[- ED_42]**	**0.4499**	**
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_37 + EH_45 + EC_33	[- ED_36]	0.4118	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + EH_45 + EC_33	[- ED_37]	0.4399	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EC_33	[- EH_45]	0.3753	
	Inc T1D ~ ED_39 + ED_41 + ED_42 + ED_36 + ED_37 + EH_45	[- EC_33]	0.4270	
Step 4	Inc T1D ~ ED_41 + ED_36 + ED_37 + EH_45 + EC_33	[- ED_39]	0.4326	
	Inc T1D ~ ED_39 + ED_36 + ED_37 + EH_45 + EC_33	[- ED_41]	0.3766	
	Inc T1D ~ ED_39 + ED_41 + ED_37 + EH_45 + EC_33	[- ED_36]	0.4199	
	Inc T1D ~ ED_39 + ED_41 + ED_36 + EH_45 + EC_33	[- ED_37]	0.4400	
	Inc T1D ~ ED_39 + ED_41 + ED_36 + ED_37 + EC_33	[- EH_45]	0.3842	
	Inc T1D ~ ED_39 + ED_41 + ED_36 + ED_37 + EH_45	[- EC_33]	0.4343	

(*) Model with higher adjusted R2, (**) Best model



AP Figure 68: Graphic validation of the best model for the economic factors domain

8.5.1.4 Stepwise selection health conditions domain

AP Table 34: Manual backward selection of the variables of health conditions domain

Backwards elimination - adjusted R2

Domain: health conditions

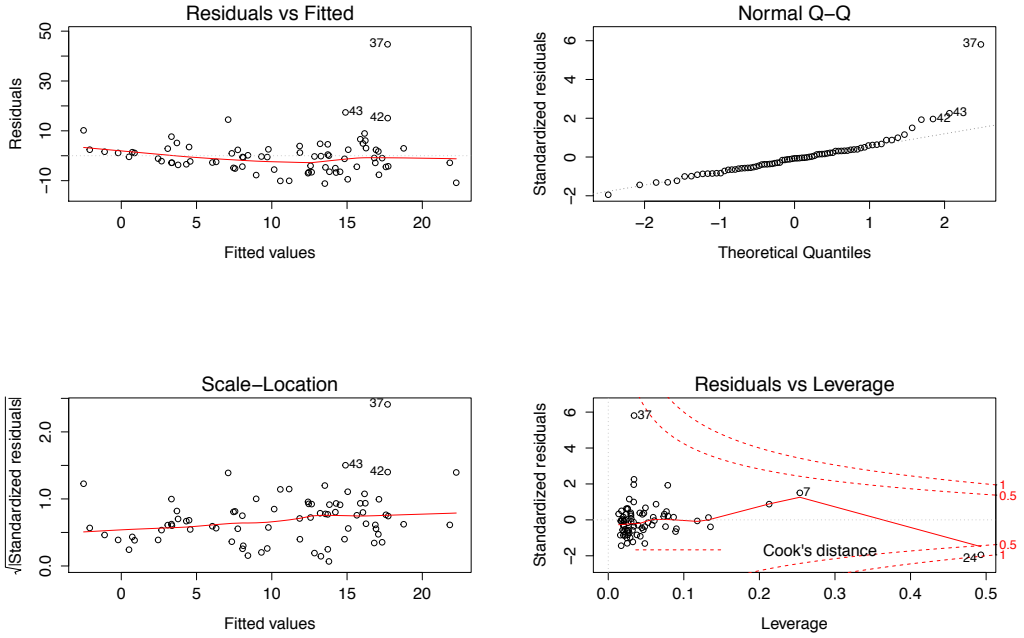
Step	Variables included	Removed	Adjusted R2	
Full	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55		0.4293	
Step 1	Inc T1D ~ HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_68]	0.4365	
	Inc T1D ~ HD_68 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4142	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_72]	0.4385	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_60]	0.4263	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_57]	0.4369	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.2861	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_58]	0.4321	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	**[- HM_75]**	**0.4387**	*
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75+ HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4240	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3600	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4210	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4159	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4353	
Step 2	Inc T1D ~ HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_68]	0.4455	
	Inc T1D ~ HD_68 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4236	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	**[- HD_72]**	**0.4477**	*
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_60]	0.4353	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_57]	0.4457	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.2977	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_58]	0.4412	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4333	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3673	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4301	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4246	
	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4438	
Step 3	Inc T1D ~ HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_68]	0.4527	
	Inc T1D ~ HD_68 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4318	
	Inc T1D ~ HD_68 + HD_71 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_60]	0.4443	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	**[- HI_57]**	**0.4544**	*
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.3075	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_58]	0.4500	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4423	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3755	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4387	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4333	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_57 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4480	
Step 4	Inc T1D ~ HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	**[- HD_68]**	**0.4584**	*
	Inc T1D ~ HD_68 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4403	
	Inc T1D ~ HD_68 + HD_71 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_60]	0.4508	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.3169	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_58]	0.4573	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HI_58 + HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4478	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3807	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4448	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4362	
	Inc T1D ~ HD_68 + HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4383	
Step 5	Inc T1D ~ HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4428	
	Inc T1D ~ HD_71 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_60]	0.4580	
	Inc T1D ~ HD_71 + HI_60 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.3174	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	**[- HI_58]**	**0.4595**	*
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HI_58 + HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4520	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3898	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4251	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4429	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HI_58 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4433	
Step 6	Inc T1D ~ HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4433	
	Inc T1D ~ HD_71 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	**[- HI_60]**	**0.4604**	**
	Inc T1D ~ HD_71 + HI_60 +HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.3158	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4538	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3627	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4288	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4450	
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4399	
Step 7	Inc T1D ~ HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HD_71]	0.4399	

Backwards elimination - adjusted R2

Domain: health conditions

Step	Variables included	Removed	Adjusted R2
Full	Inc T1D ~ HD_68 + HD_71 + HD_72 + HI_60 + HI_57 + HI_59 + HI_58 + HM_75 + HR_56 + HR_47 + HR_51 + HR_54 + HR_55		0.4293
	Inc T1D ~ HD_71 + HI_60 +HR_56 + HR_47 + HR_51 + HR_54 + HR_55	[- HI_59]	0.3238
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_47 + HR_51 + HR_54 + HR_55	[- HR_56]	0.4580
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_51 + HR_54 + HR_55	[- HR_47]	0.3699
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_54 + HR_55	[- HR_51]	0.4362
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_55	[- HR_54]	0.4510
	Inc T1D ~ HD_71 + HI_60 + HI_59 + HR_56 + HR_47 + HR_51 + HR_54	[- HR_55]	0.4477

(*) Model with higher adjusted R2, (**) Best model



AP Figure 69: Graphic validation of the best model for the health conditions domain

8.5.1.5 Stepwise selection all significant variables

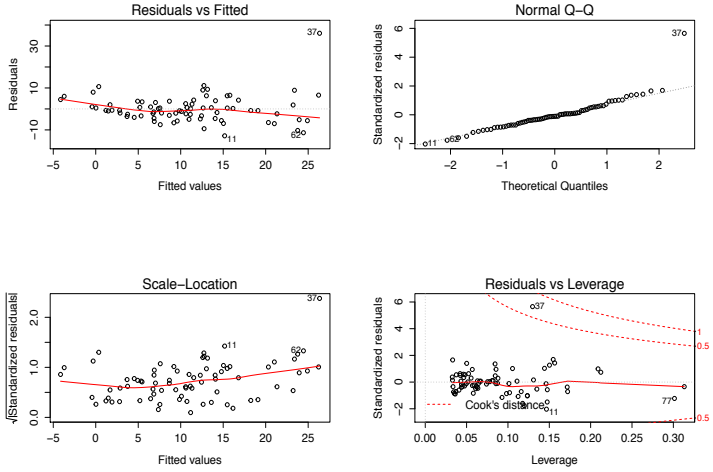
AP Table 35: Manual backward selection of all significant variables

Backwards elimination - adjusted R2

All significant variables at p-value ≤0.05 after applied MLM by each domain

Step	Variables included	Removed	Adjusted R2	
Full	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47		0.4915	
Step 1	Inc T1D ~ CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_10]	0.4872	
	Inc T1D ~ CE_10 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_18]	0.4873	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	**[- DD_19]**	**0.4984**	*
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_21]	0.4747	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_27]	0.4977	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_33]	0.4978	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_36 + EH_45 + HI_59 + HR_47	[- ED_41]	0.4688	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + EH_45 + HI_59 + HR_47	[- ED_36]	0.4970	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + HI_59 + HR_47	[- EH_45]	0.4827	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HR_47	[- HI_59]	0.4351	
	Inc T1D ~ CE_10 + CE_18 + DD_19 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59	[- HR_47]	0.4891	
Step 2	Inc T1D ~ CE_18 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_10]	0.4891	
	Inc T1D ~ CE_10 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_18]	0.4883	
	Inc T1D ~ CE_10 + CE_18 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_21]	0.4828	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	**[- DD_27]**	**0.5046**	*
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_33]	0.5040	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + DD_33 + ED_36 + EH_45 + HI_59 + HR_47	[- ED_41]	0.4725	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + DD_33 + ED_41 + EH_45 + HI_59 + HR_47	[- ED_36]	0.5009	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + HI_59 + HR_47	[- EH_45]	0.4879	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HR_47	[- HI_59]	0.4437	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_27 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59	[- HR_47]	0.4969	
Step 3	Inc T1D ~ CE_18 + DD_21 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_10]	0.4968	
	Inc T1D ~ CE_10 + DD_21 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_18]	0.4809	
	Inc T1D ~ CE_10 + CE_18 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_21]	0.4891	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	**[- DD_33]**	**0.5101**	*
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_33 + ED_36 + EH_45 + HI_59 + HR_47	[- ED_41]	0.4777	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_33 + ED_41 + EH_45 + HI_59 + HR_47	[- ED_36]	0.5073	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_33 + ED_41 + ED_36 + HI_59 + HR_47	[- EH_45]	0.4855	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_33 + ED_41 + ED_36 + EH_45 + HR_47	[- HI_59]	0.4469	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + DD_33 + ED_41 + ED_36 + EH_45 + HI_59	[- HR_47]	0.5033	
Step 4	Inc T1D ~ CE_18 + DD_21 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_10]	0.5034	
	Inc T1D ~ CE_10 + DD_21 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- CE_18]	0.4814	
	Inc T1D ~ CE_10 + CE_18 + ED_41 + ED_36 + EH_45 + HI_59 + HR_47	[- DD_21]	0.4929	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_36 + EH_45 + HI_59 + HR_47	[- ED_41]	0.4855	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + EH_45 + HI_59 + HR_47	**[- ED_36]**	**0.5138**	**
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + ED_36 + HI_59 + HR_47	[- EH_45]	0.4930	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + ED_36 + EH_45 + HR_47	[- HI_59]	0.4552	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + ED_36 + EH_45 + HI_59	[- HR_47]	0.5106	
Step 5	Inc T1D ~ CE_18 + DD_21 + ED_41 + EH_45 + HI_59 + HR_47	**[- CE_10]**	**0.5114**	*
	Inc T1D ~ CE_10 + DD_21 + ED_41 + EH_45 + HI_59 + HR_47	[- CE_18]	0.4849	
	Inc T1D ~ CE_10 + CE_18 + ED_41 + EH_45 + HI_59 + HR_47	[- DD_21]	0.5017	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + EH_45 + HI_59 + HR_47	[- ED_41]	0.4919	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + HI_59 + HR_47	[- EH_45]	0.5026	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + EH_45 + HR_47	[- HI_59]	0.4470	
	Inc T1D ~ CE_10 + CE_18 + DD_21 + ED_41 + EH_45 + HI_59	[- HR_47]	0.5024	

(*) Model with higher adjusted R2, (**) Best model



AP Figure 70: Graphic validation of the final summary model with all significant variables

8.6 Appendix F: Validation of the model presented in chapter 6

8.6.1 Selection of HLA alleles related with T1D incidence and graphic validation of the model

For details see **Table 23** and **SI Table 24-26**.

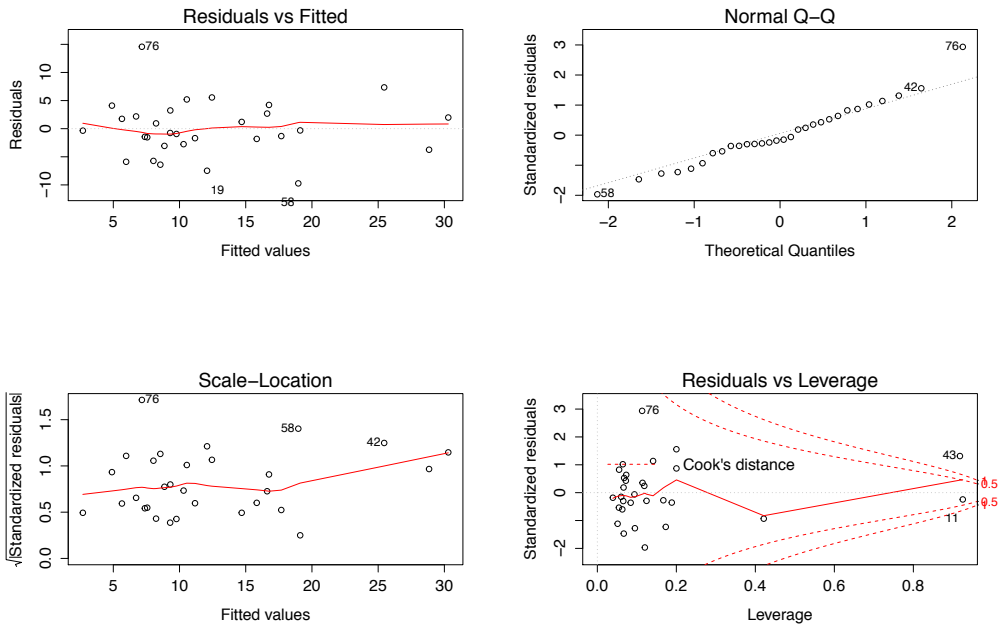
AP Table 36: Manual backward selection of the HLA alleles against T1D

Backwards elimination - adjusted R2

Significant HLA alleles correlated with incidence of T1D at *p*-value ≤0.05

Step	Variables included	Removed	Adjusted R2	
Full	Inc T1D ~ DRB1.03.01+ DRB1.04.01+DRB1.04.05+ DRB1.08.01+ DQB1.02.01+DQB1.04.01+ DQB1.06.02		0.9432	
Step 1	Inc T1D ~ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.02.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.03.01]	0.6531	
	Inc T1D ~ DRB1.04.05+ DRB1.03.01+ DRB1.08.01+ DQB1.02.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.04.05]	0.5219	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.08.01+ DQB1.02.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.04.05]	-0.1261	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DQB1.02.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.08.01]	0.8368	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.04.01+ DQB1.06.02	[-DQB1.02.01]	0.9606	*
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.02.01+ DQB1.06.02	[-DQB1.04.01]	0.5877	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.02.01+ DQB1.04.01	[-DQB1.06.02]	0.9544	
Step 2	Inc T1D ~ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.03.01]	0.6685	
	Inc T1D ~ DRB1.03.01+ DRB1.04.05+ DRB1.08.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.04.01]	0.5795	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.08.01+ DQB1.04.01+ DQB1.06.02	[-DRB1.04.05]	0.0971	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DQB1.04.01+ DQB1.06.02	[-DRB1.08.01]	0.8218	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.06.02	[-DQB1.04.01]	0.6288	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.04.01	[-DQB1.06.02]	0.9640	* *
Step 3	Inc T1D ~ DRB1.04.01+ DRB1.04.05+ DRB1.08.01+ DQB1.04.01	[-DRB1.03.01]	0.7008	
	Inc T1D ~ DRB1.03.01+ DRB1.04.05+ DRB1.08.01+ DQB1.04.01	[-DRB1.04.01]	0.2945	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.08.01+ DQB1.04.01	[-DRB1.04.05]	0.0968	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DQB1.04.01	[-DRB1.08.01]	0.6874	
	Inc T1D ~ DRB1.03.01+ DRB1.04.01+ DRB1.04.05+ DRB1.08.01	[-DQB1.04.01]	0.6108	***

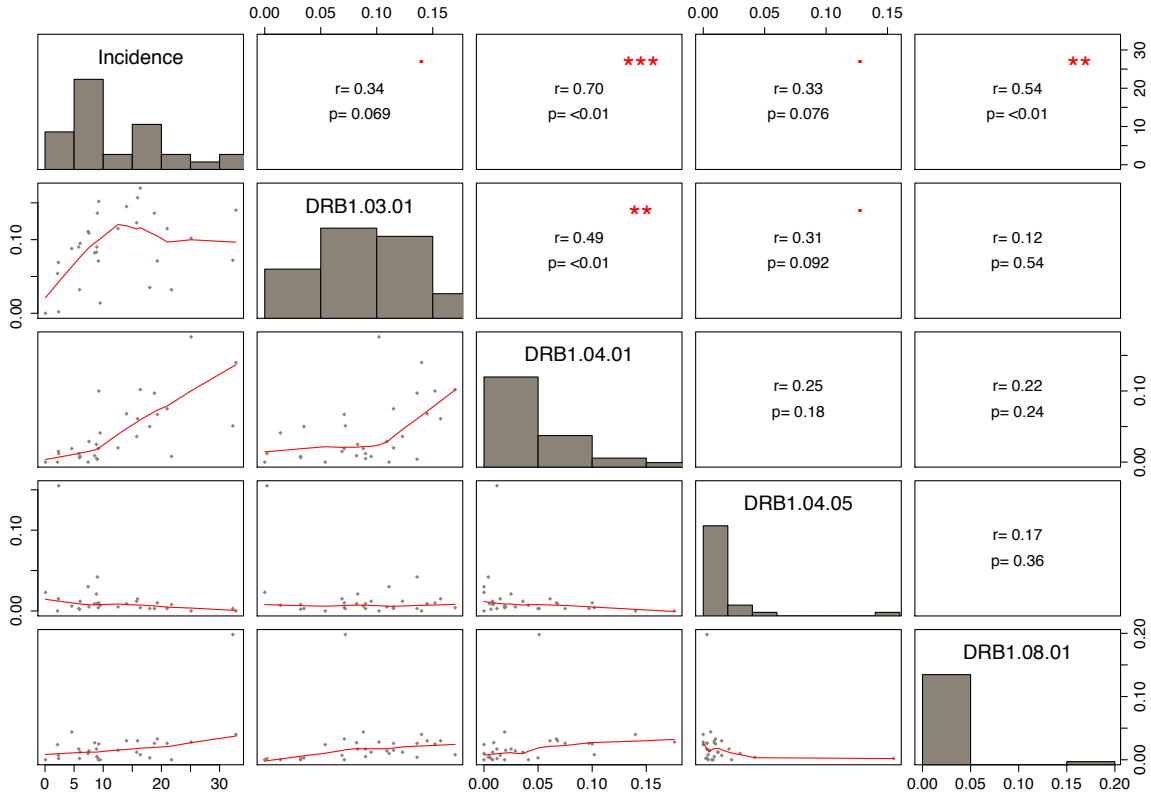
(*) Model with higher adjusted R2, (**) Best model by higher adjusted R^2 but colinearity problem. (***) Best model. Included variables in the full model were significant at *p*-value ≤ 0.05.



AP Figure 71: Graphic validation of the final model

8.6.2 Correlation matrix of HLA alleles against T1D included in the final model

For details see **Table 22** and **SI Table 24-26**.



AP Figure 72: Correlation matrix of HLA alleles against T1D included in the final model

List of Figures

List of Tables

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Épidémiologie de diabète du type 1: incidence mondiale et ses déterminants

Résumé :

Introduction : Le diabète de type 1 (DT1) est une des maladies métaboliques les plus répandues chez les enfants (298). L'augmentation de l'incidence mondiale du DT1 a été calculée à 3,0% par année en moyenne et il a été prédit qu'elle serait de 40% en 2010 (231) chez les enfants âgés de 0 à 14 ans. Les causes de cette augmentation ne sont pas encore déterminées; cette thèse met à jour les connaissances actuelles sur l'incidence mondiale du DT1, en profitant de la disponibilité croissante des bases de données publiques et en examinant la corrélation entre l'incidence et les caractéristiques des pays.

Méthodes : Une recherche exhaustive et systématique des articles publiés sur l'incidence du DT1 dans le monde a été effectuée pour étudier les variations globales de cette incidence dans les divers pays. Nous avons suivi les recommandations de PRISMA[8] (213). L'objectif initial de cette thèse était d'étudier la corrélation entre les variables environnementales disponibles dans les bases de données publiques, et l'incidence du DT1 selon les pays. Nous avons également réalisé une analyse similaire à celle décrite ci-dessus concernant les variables environnementales, pour les composantes génétiques du DT1. La fréquence des haplotypes de HLA (Human Leukocyte Antigens) qui confèrent la susceptibilité à, ou la protection contre le DT1, a été exploré (89). Les principales méthodes statistiques utilisées étaient des corrélations et des modèles de régression linéaire. Enfin, afin de mieux comprendre les tendances dynamiques du DT1 avec toutes les informations récupérées sur l'incidence du DT1, nous avons utilisé l'Âge-Période-Cohorte (APC). Pour les analyses statistiques et graphiques le logiciel R (version 3.0.1) a été utilisé (255), et pour la visualisation des données le logiciel Tableau (262).

Principaux résultats : Grâce à la revue de la littérature publiée entre 1975 et 2014, 265 références ont été sélectionnées, qui contenaient les données épidémiologiques sur les cas incidents de DT1 chez les individus âgés de 0-14 ans portant sur 90 pays. Chez les personnes de plus de 15 ans, 70 références ont été sélectionnées portant sur 35 pays. L'incidence du DT1 est très variable selon les pays et régions du monde pour les enfants et les adultes. Contrairement à ce qui est connu chez les enfants, chez les adultes l'incidence était généralement plus élevée chez les hommes que chez les femmes. Indépendamment de l'incidence initiale, on a trouvé une tendance à l'augmentation de l'incidence dans tous les continents entre 1960 et 2010. Finalement, nous avons extrait des données à analyser (223 articles sélectionnés) en utilisant des modèles Age-Période-Cohorte, des informations équivalentes à 2,327,604,529 années-personnes à risque de 192,741 cas de DT1. Avec le modèle APC un fort effet de cohorte a été observé; le modèle indique également un effet période probable qui diminue après 1987. Comme prévu, l'incidence du DT1 augmente avec l'âge. Ces variations s'expliquent en partie par l'interaction entre les facteurs environnementaux et les composants génétiques des populations. Pour la composante environnementale, en utilisant des modèles de régressions linéaires multiples (MLR) *Stepwise*, les facteurs prédictifs environnementaux les plus importants de la variation de l'incidence du DT1 d'un pays à l'autre étaient: les rayons UV, le nombre d'abonnements aux téléphones mobiles dans le pays, les dépenses de santé par habitant, la vaccination contre l'hépatite B et l'IMC (indice de masse corporelle) moyen. Pour les composants génétiques, en utilisant des modèles de MLR *Stepwise*, les variables significatives étaient les allèles sensibles: DRB1*04:01 ($p = 0,0001$) et DRB1*08:01 ($p = 0,003$). Aussi, une grande hétérogénéité des haplotypes susceptibles ou protecteurs face au DT1 au sein des populations a été trouvée.

Conclusions et implications : Au cours de cette thèse, nous avons quantifié la variation pays par pays de l'incidence du DT1 dans le monde chez les enfants et les adultes, montrons qu'une grande partie de cette incidence pourrait s'expliquer par la variabilité de facteurs environnementaux d'un pays à l'autre. Cette thèse a également profité de la disponibilité croissante de données publiques sur la variation des facteurs environnementaux et génétiques de pays à pays, qui peuvent être impliqués dans le fort effet de cohorte de naissance qui a été observé ; il est conseillé d'approfondir la recherche sur la grossesse et la période néonatale et son implication dans DT1. Nous avons pu quantifier que l'augmentation de l'incidence du DT1 était encore plus grande que ce qui avait été prédit dans une étude antérieure (231).

Mots clés : Le diabète de type 1, l'incidence, corrélations, modèles de régression linéaire, modèles de Âge-Période-Cohorte, Revue systématique.

[8] Le numéro d'inscription à PROSPERO est : CRD42012002369.

Disponible sur http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369

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Epidemiology of Type 1 Diabetes: Global incidence and determinants

Abstract:

Background: Type 1 Diabetes (T1D) is one of the most common metabolic diseases in childhood (298). The increase of worldwide incidence of T1D was calculated to be on average 3.0% per year and it was predicted that it would be 40% higher in 2010 (231) in children aged 0-14 years. The causes of this increase are still under study; this thesis updates our current knowledge on the global incidence of T1D, and taking advantage of the increasing availability of public databases examines the correlation between incidence and country characteristics.

Methods: A comprehensive systematic literature search of published articles on the incidence of T1D worldwide was conducted to study global variations of the incidence within countries. We followed the PRISMA[9]group recommendations (213). The initial goal of this thesis was to study the correlation between environmental variables available in public databases with the country incidence of T1D. We also achieved a similar analysis of the genetic component of T1D. The frequency of major HLA susceptible and protective haplotypes reported elsewhere (89) was explored. The principal statistical methods used were correlations and multiple linear regressions (MLR). Finally, we used the Age-Period-Cohort (APC) approaches. For statistical and graphical analyses the R software (255), and for data visualization the Tableau software (262) were used.

Key findings: Through the literature review, 265 selected references that contained epidemiological data about incidence cases of T1D among individuals aged 0-14 years, and 70 references of T1D incidence in those aged over 15 years, published between 1975 and 2014, were collected. Information was available on 90 countries and in 35 countries for those over 15 years of age. The incidence of T1D is highly variable among countries and regions worldwide in both children and adults. T1D incidence in adults paralleled those reported in children. Also, as opposed to what is known in children, we found that the incidence was in most studies larger in males than in females.
Independently of the initial level of incidence, an increase in incidence was observed in all continents from 1960 to 2010. Finally, using the Age-Period-Cohort model we analyzed information from 2,327,604,529 person-years at risk from 192,741 cases. A strong effect cohort was observed; in addition the model shows an apparent effect period that decreases after 1987. Also as expected, the incidence of T1D increases with age. These variations are in part explained by the interaction between the environmental factors and the genetic components of the populations.
For the environmental component, using Stepwise MLR models the most significant environmental predictors of the country-to-country variation of T1D incidence were UV radiation, number of mobile cellular subscriptions in the country, health expenditure per capita, hepatitis B immunization and mean BMI. For the genetic component, using Stepwise MLR models, significant variables were the susceptible alleles: DRB1*04:01 and DRB1*08:01. High heterogeneity of susceptible and protector haplotypes for T1D within populations was found.

Conclusions and implications: During this thesis, we quantified the country-to-country variation in T1D incidence worldwide in children and adults, and show that a large part of this incidence could be accounted for by the variability of environmental factors within the countries taking advantage of the increasing availability of public databases. Environmental factors may be involved in the strong cohort effect we found; it is advisable to deepen the research on pregnancy and neonatal period and its implications on T1D. Here we could quantify that the increase of T1D was even larger than had been predicted in an earlier study (231).

Keywords : Type 1 Diabetes, incidence, correlation, multiple linear regressions, Age-Period-Cohort model, systematic literature review.

[9] PROSPERO registration number: CRD42012002369.

Available on: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002369

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