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Meta-analysis

The association between GAD65 antibody levels and incident Type 2 Diabetes Mellitus in an adult population: A meta-analysis

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ABSTRACT

Context: Antibodies to the 65 kD isoform of glutamic acid decarboxylase (GAD65) have been associated with incident Type 2 Diabetes Mellitus, however results are inconsistent.
Objective: To assess the association between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus in a non-diabetic adult (≥18 years) population, in a systematic review and meta-analysis.
Data Sources: A systematic literature search was conducted in Pubmed (MEDLINE) and Embase until January 14th, 2019.
Study Selection: Included studies were 1) prospective studies on the association between GAD65 antibodies and incident Type 2 Diabetes Mellitus; 2) in a non-diabetic adult (≥18 years) population. To strengthen the review, unpublished data from 1302 Hoorn Study participants were included.
Data Extraction: Data extraction and quality assessment were performed independently by two observers. Ten studies were rated for methodological quality and seven were pooled using a random-effects meta-analysis, of which 2 strong, 2 moderate and 3 of low methodological quality.
Data Synthesis: The pooled risk estimate of incident Type 2 Diabetes Mellitus for GAD65 antibody positivity, compared to GAD65 antibody negativity was 3.36 (95% CI: 1.9–5.9). This result was robust to sensitivity analyses. Heterogeneity between studies was significant with I^2 statistic of 79% ($p < 0.0001$). However, excluding one study showed a decrease of I^2 to 19% ($p < 0.0001$), explaining a large part of the heterogeneity.
Conclusion: GAD65 antibody positivity was associated with an increased risk of future Type 2 Diabetes Mellitus in adults.

Contents

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1. Introduction

GAD antibodies are autoantibodies against the enzyme glutamic acid decarboxylase (GAD), which is involved in the production of the neurotransmitter gamma-aminobutyric acid (GABA). The genes GAD1 and GAD2 produce two isoforms of GAD: GAD67 and GAD65. The former is needed throughout the development of normal cellular functioning in the brain, while the latter is involved in the regulation of beta-cells of the pancreas [1].

Autoimmunity for GAD65, as reflected by GAD65 antibody positivity, often defined as GAD65 antibody levels above the 99th or 97.5th percentile, is associated with rapid progression to insulin deficiency in Type 2 Diabetes Mellitus patients [2–6]. In addition, the presence of GAD65 antibodies is also strongly associated with the development of Type 1 Diabetes Mellitus and latent autoimmune diabetes in the adult (LADA) [7], usually combined with a family history of diabetes [8,9]. Up until now it is not clear whether GAD65 antibody positivity is also associated with future risk of Type 2 Diabetes Mellitus in an adult population without diabetes at baseline.

Several cross-sectional studies have described GAD65 positivity to be more prevalent in people with impaired glucose metabolism or Type 2 Diabetes Mellitus [3–5,10–12]. However, cross-sectional studies are inadequate to provide information about cause and effect. Prospective studies [8,13–17] on GAD65 antibody positivity and incident Type 2 Diabetes Mellitus showed inconsistent results ranging from no association [13,14,16] to a >7 times increased Type 2 Diabetes Mellitus risk [17].

We therefore performed a systematic review and meta-analysis, to assess the association between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus in the non-diabetic adult population. To strengthen the review, we included unpublished data from a prospective population-based cohort, the Hoorn Study.

2. Materials and Methods

2.1. Data Sources and Searches

A systematic literature search was conducted in Pubmed (MEDLINE) and Embase until January 14th, 2019. In short, the search strategy focused on a combination of these terms and their synonyms: (Type 2 diabetes OR diabetes) AND (Glutamic acid decarboxylase 65 OR GAD65 OR Glutamate Decarboxylase). Studies with Type 1 Diabetes Mellitus or LADA as only outcome were excluded, but by using a broad term for diabetes, studies with mixed types of diabetes or studies without a clear description of type of diabetes could still be included. The full search strategy is provided in Supplementary file 1. In addition, reference lists of included studies were searched manually for additional studies. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for observational studies [18]. The protocol of this review was registered in the PROSPERO database under number CRD42018089877.

2.2. Study Selection

Studies were included if 1) if adults (≥18 years) without diabetes at baseline were studied; 2) the association between GAD65 antibodies and incident Type 2 Diabetes Mellitus was studied; 3) the follow-up duration was ≥1 year; 4) the peer-reviewed article was available as full text; and 5) the article was written in English or Dutch. Studies with Type 1 Diabetes Mellitus or LADA as only outcome were excluded.

All studies identified in the literature search were screened for eligibility on title and abstract by two independent investigators (FR and AK/MG). The full text versions of potentially eligible studies were independently assessed for inclusion by AK and FR. Discrepancies were resolved in consensus meetings, consulting a third investigator, MG, if necessary.

2.3. Data Extraction

Data extraction was performed independently by AK and FR. A prepiloted form was used to extract data from the included studies. Data extraction included: study design, study population, period of analysis, country, number of participants (%male), age, follow-up duration, Type 2 Diabetes Mellitus incidence (%), diabetes method of measurement (e.g. self-report, oral glucose tolerance test (OGTT)), cut-off values for GAD65 antibody positivity and GAD65 antibody levels. If studies did not show risk measures for the association between GAD65 antibodies and incident Type 2 Diabetes Mellitus, authors were requested via email to provide the data [3,13,19]. Studies were only included in the meta-analysis when (data to calculate) a risk measure of incident Type 2 Diabetes Mellitus was reported in the study or could be provided by the authors afterwards. Discrepancies identified during the data extraction were resolved through consensus, consulting a third reviewer, MG, when necessary.

2.4. Methodological Quality Assessment

An adaptation of the Quality Assessment Tool for Quantitative Studies as developed by the Effective Public Health Practice Project (EPHPP) was used to rate the methodological quality of the included studies [20]. This nineteen-item tool was adapted by Mackenbach et al. and is suitable for assessing the methodological quality of studies of observational and experimental design [21]. It contains eight domains of methodological quality: 1) study design; 2) blinding; 3) representativeness with regard to selection bias; 4) representativeness with regard to withdrawals/dropouts; 5) confounders; 6) data-collection; 7) data-analysis; and 8) reporting.

The ratings of some domains are less straight forward and are therefore further explained. Confounding was scored as 'weak' when data were not corrected for confounders; a 'moderate' score was attributed to studies that corrected for at least age, sex, fasting plasma glucose and BMI; and 'strong' was attributed to studies additionally correcting for other parameters. Data-collection was scored as 'weak' when no information was provided in the study itself or in the design paper on how GAD65 antibody levels were assessed. Information on the method of GAD65 antibody analysis was scored 'moderate' and inclusion of intra/inter-assay coefficients or sensitivity/specificity resulted in a 'strong' rating for data-collection. Data-analysis was scored as 'weak' when data was not or inappropriately tested and 'strong' for multivariable analysis.

Studies can have between five to eight component ratings resulting in one overall rating, ranging from high methodological quality (low risk of bias) to low methodological quality (high risk of bias). For example, when seven component ratings were given: high methodological quality was attributed to those studies with no 'weak' ratings and at least four 'strong' ratings; moderate methodological quality was

attributed to those studies with one 'weak' rating or fewer than four 'strong' ratings; low methodological quality was attributed to those studies with two or more 'weak' ratings. All included studies were independently assessed for methodological quality by two raters (AK and FR). The ratings of each domain and the overall ratings were compared between the two raters to reach consensus.

2.5. Hoorn Study Data

We also included unpublished data from a prospective population-based cohort, the Hoorn Study, which is representative for the general Dutch population. Details on the study design have been described elsewhere [22]. From 2484 participants, those without follow-up (398 moved/died and 573 declined participation), without data on GAD65 antibodies at baseline ($n = 71$) or with diabetes at baseline ($n = 140$) were excluded, leaving 1302 participants for analysis. The participants gave written informed consent. The Ethics Committee of the VU University Medical Centre, Amsterdam, approved the Hoorn Study.

GAD65 antibody levels were obtained at baseline and measured in serum and stored at −70 °C, using a radioligand binding assay [23]. GAD65 antibody levels were measured in counts per minute (cpm) and expressed as index values. Index values were calculated as 1 + (cpm [unknown sample] − cpm [negative standard serum]) / (cpm [positive standard serum] − cpm [negative standard serum]). The mean value of three tests was used in the analysis. The interassay coefficient of variation was 7.5% [4]. Participants with GAD65 antibody indexes ≥the 99th percentile of the study population were arbitrarily considered GAD65 positive (First and Second International GAD Autoantibody Workshops) [24,25].

Type 2 Diabetes Mellitus was defined after a median follow-up of 6.5 years based on the WHO 2011 and ADA 2012 criteria [26–28]: fasting glucose levels ≥7.0 mmol/l, and/or 2 h post load plasma glucose ≥11.1 mmol/l and/or HbA1c levels ≥6.5% (48 mmol/mol) and/or use of glucose lowering treatment by diet or medication [26–28].

In accordance to most other studies included in the meta-analysis, the association between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus was assessed using Cox regression, adjusted for age, sex, BMI, fasting glucose and HbA1c levels at baseline.

2.6. Data Synthesis and Analysis

We used the inverse variance method to perform a random-effects meta-analysis for GAD65 antibody positivity and the risk for incident Type 2 Diabetes Mellitus in Review Manager 5.3 [Nordic Cochrane Center]. Analyses were stratified for type of risk measure: Hazard Ratio (HR), Relative Risk (RR) and Odds Ratio (OR). Data of the risk estimates were entered on a log scale, which were then pooled and inverse log transformed. Three out of the ten included studies could not be included in the meta-analysis.

Statistical heterogeneity was assessed with the I^2 statistic, reflecting the percentage of total variance that can be explained by heterogeneity, ranging from 0% (no heterogeneity) to 100% (differences can completely be explained by chance alone) [29]. A p-value <0.05 was considered statistically significant. A funnel plot was used to assess publication bias.

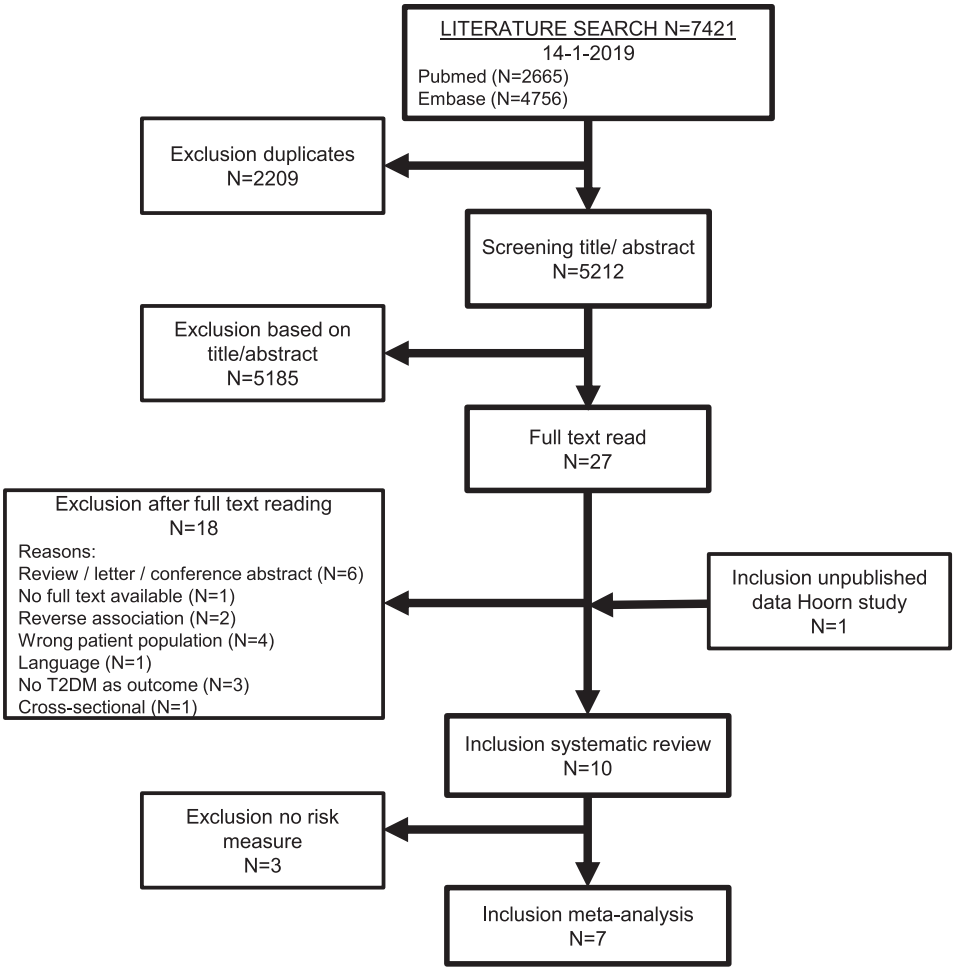

Fig. 1. Flow-chart of the search and selection process.

Table 1
Methodological quality rating per domain per study.

Author (year) [ref]	SD	BL	RSB	RWD	CF	DC	DA	RP	Overall
Bosi (1999) [13]	M	NR	S	M	W	S	W	M	Weak
Dabelea (2014) [14]	S	M	W	M	S	S	S	S	Moderate
Hampe (2007) [15]	M	NR	S	M	W	S	W	M	Weak
Hoorn Study data	M	NR	S	S	S	S	S	S	Strong
Lundgren (2010) [8]	M	NR	M	M	S	S	S	S	Strong
Niskanen (1995) [3]	M	NR	S	M	W	M	W	M	Weak
Rolandsson (2001) [19]	M	NR	M	S	M	S	S	W	Moderate
Sorgjerd (2015) [17]	M	NR	S	W	W	S	W	M	Weak
Vigo (2007) [16]	M	NR	S	M	S	S	S	W	Moderate
Zimmet (1994) [30]	M	NR	W	W	S	S	S	M	Weak

Abbreviations: SD = study design; BL = blinding; RSB = representativeness with regard to selection bias; RWD = representativeness with regard to withdrawals/dropouts; CF = confounding; DC = data-collection; DA = data-analysis; RP = reporting; W = weak; M = moderate; S = strong; NR = no rating.

For the meta-analysis (all random-effects), sensitivity analyses were performed to examine possible sources of heterogeneity and conducted by, 1) excluding studies with an OR as risk estimate, 2) excluding studies with an unadjusted risk estimate, 3) excluding studies with a population at risk for Type 2 Diabetes Mellitus, 4) by excluding low quality studies, 5) by excluding case-control studies, 6) by excluding studies that determined GAD65 antibody using assay methods other than radioligand binding assays, 7) by excluding one study at a time to determine the effect of a single study on the pooled estimate.

3. Results

3.1. Description of Included Studies

The systematic literature search identified 5212 articles. After screening the titles and abstracts, 27 potentially eligible articles were read full text. Nine studies met the inclusion criteria of this review and were therefore included in this systematic review [3,8,13–17,19,30] (see Fig. 1). In addition, we included unpublished data from the Hoorn Study. An overview of the 18 excluded studies and reason for exclusion is provided in Supplementary file 2.

An overview of the ten studies is shown in Supplementary Table 1. The sample sizes varied from 126 to 3050 participants. Most studies were conducted in Europe (7 studies) and three studies were conducted in the USA. Nine of the ten studies had observational designs (6 prospective, 3 case-control studies) and one was an experimental study [14]. The majority of studies were population-based (7 studies). In one study [8] the population included non-diabetic relatives and spouses of diabetic patients and in two other studies the population was considered to be at increased risk for development of Type 2 Diabetes Mellitus [14] or coronary heart disease (CHD) [30].

As shown in Supplementary Table 1, GAD65 antibody positivity was defined differently among the studies. Four studies defined it as levels >99th percentile, corresponding with different values of GAD65 antibodies; >3 units/ml, >33 DK, antibody index (ai) > 0.17 and ai >1.12. The other studies used absolute cut-off values that were defined differently per study, namely in U/ml, units or ai. The follow-up duration varied from three to 11 years.

3.2. Methodological Quality Rating

An overview of the methodological quality assessment of the studies is presented in Table 1. Methodological quality was considered to be strong (low risk of bias) in two of the studies, moderate (moderate risk of bias) in three studies and weak (high risk of bias) in five studies. The studies were considered to be of weak quality, because they received two weak ratings for confounding, data-analysis and/or representativeness.

3.3. GAD65 Antibody Positivity

Three out of the ten included studies could not be included in the meta-analysis, because they lacked description of a risk measure of incident Type 2 Diabetes Mellitus nor was it provided afterwards by the authors [3,10,17]. A random-effects meta-analysis of seven studies showed that people who were GAD65 antibody positive had a 3.36 times increased risk (95% CI 1.9; 5.9) for incident Type 2 Diabetes Mellitus, compared to people who were GAD65 antibody negative. Heterogeneity between studies was significant with I^2 statistic of 79% ($p < 0.0001$) (Fig. 2). As shown in Fig. 2, the stratified analyses for HR, RR and OR resulted in an incident Type 2 Diabetes Mellitus risk of respectively; 2.57 (95% CI 1.0; 6.8), 4.89 (95% CI 2.7; 8.9) and 3.56 (95% CI 0.7; 18.9).

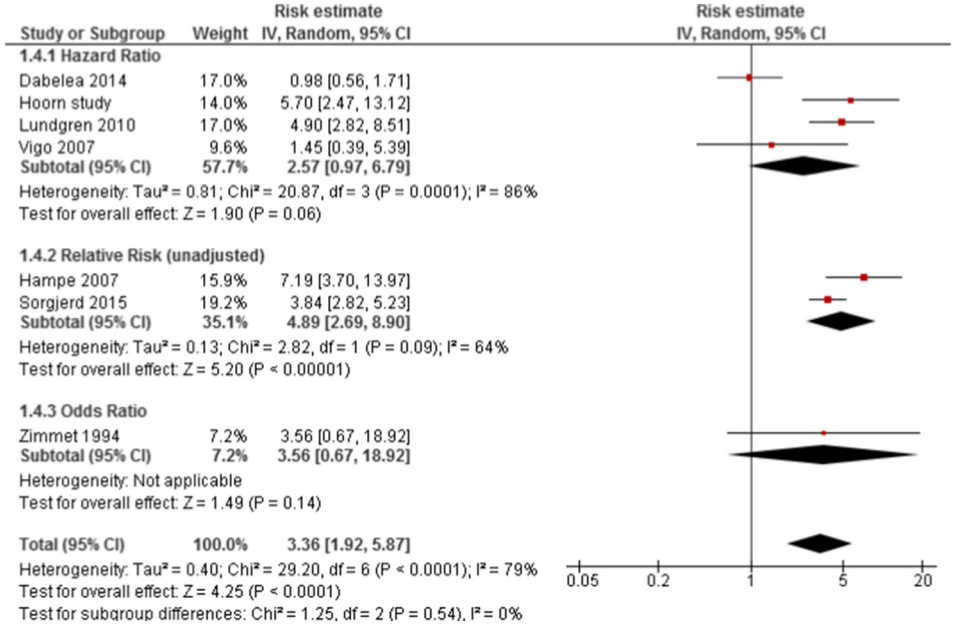

Fig. 2. Forest plot of the association between GAD65 antibody positivity and incident diabetes. Weight: inverse of the variance of each study, reflecting the weight of each study in the meta-analysis

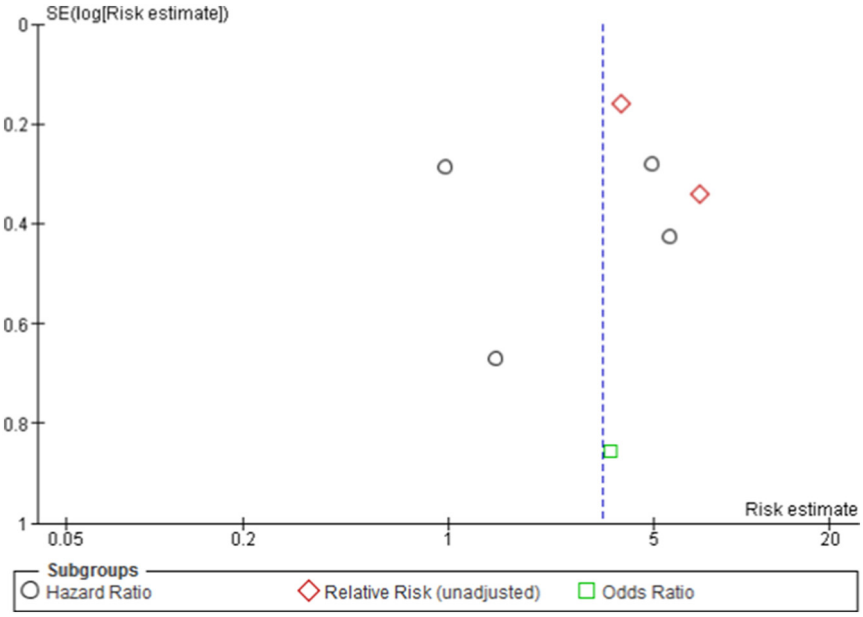

Fig. 3. Funnel plot of studies included in the meta-analysis.

Examination of the funnel plot did not raise suspicion of publication bias, however as this was based on only 7 studies, reporting HR, RR and OR no strong conclusions regarding publication bias can be drawn (Fig. 3).

Due to the heterogeneity between the studies, several sensitivity analyses were conducted (Table 2). All sensitivity analyses, except the one on quality, showed a significant association between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus. The sensitivity analyses excluding studies with OR as risk estimate and unadjusted risk estimates resulted in a less pronounced association. While the sensitivity analyses without populations at risk, with radioligand binding assay and without case-control studies, revealed a stronger association. The sensitivity analysis without populations at risk decreased the heterogeneity to 49%, explaining a large part of the heterogeneity. Finally, to try to account for the remaining heterogeneity, we excluded one study at a time to determine the effect of a single study on the pooled estimate. None of the studies affected the heterogeneity when excluded, nor did this

Table 2
Results of included studies in the random-effects meta-analysis ($n = 7$).

Author (year), reference	Conditional probabilities DM+ DM− GAD+ | GAD−	Risk estimate (95% CI) Confounders	Sensitivity analyses						
			1. Excl. OR	2. Excl. unadjusted	3. Study population	4. Quality	5. Assay method	6. Study design	7. Excl. one study
Dabelea (2014), [14]	Not reported	- HR: 0.98 (0.6; 1.7) - Age, sex, ethnicity, treatment, fpg, 2 h glucose, insulin, HbA1c, HOMA-IR, BMI	√	√		√	√	√	4.45 (3.3; 6.0)
Hampe (2007), [15]	7 | 18 86 | 2123	- RR: 7.19 (3.7; 14.0) - Unadjusted	√		√		√	√	2.91 (1.6; 5.4)
Hoorn study data	6 | 7 139| 1150	- HR: 5.70 (2.5; 13.1) - Age, sex, fpg, HbA1c, BMI	√	√	√	√	√	√	3.07 (1.6; 5.8)
Lundgren (2010), [8]	2 | 34 15 | 367	- HR: 4.90 (2.8; 8.5) - Age, sex, fpg, BMI, family history	√	√		√	√	√	3.10 (1.6; 6.1)
Sorgjerd (2015), [17]	32 | 76 370 | 4420	- RR: 3.84 (2.8; 5.2) - Unadjusted	√		√			√	3.23 (1.5; 7.0)
Vigo (2007), [16]	41 | 43 539 | 501	- HR: 1.45 (0.4; 5.4) - Age, sex, ethnicity, fpg, insulin, BMI, family history, WHR, hypertension, inflammation score	√	√	√	√			3.67 (2.0; 6.6)
Zimmet (1994), [30]	2 | 34 15 | 367	- OR: 3.56 (0.7; 18.9) - Age, ethnicity, fpg, 1 h glucose, insulin, BMI		√					3.34 (1.8; 6.1)
Pooled risk estimate (95% CI)			3.34 (1.8; 6.1)	2.68 (1.1; 6.4)	4.42 (2.8; 7.1)	2.57 (1.0; 6.8)	3.68 (1.4; 9.6)	3.67 (2.0; 7.0)	NA
I^2			83%	81%	49%	90%	89%	82%	NA

BMI = body mass index; CI = confidence interval; Excl. = exclusion; FPG = fasting plasma glucose; HOMA-IR: homeostatic model assessment of insulin resistance; HR = hazard ratio; NA = not applicable; OR = odds ratio; RR = relative risk; WHR = waist hip ratio; √ = studies included for the sensitivity analyses.
Sensitivity analyses:
1: Excluding studies with OR as risk estimate.
2: Excluding studies with an unadjusted risk estimate.
3: Excluding studies with high diabetes risk populations.
4: Excluding studies rated as low quality studies.
5: Excluding studies that determined GAD65 antibody using assay methods other than radioligand binding assays.
6: Excluding studies with case-control study design.
7: Excluding one study at the time: estimate when excluding the specific study is shown.

affect the overall conclusion (Table 2). However by excluding the study of Dabelea et al. [14] the I^2 decreased to 19% ($p < 0.001$) and the pooled risk estimate increased to 4.45 (95% CI 3.3; 6.0), suggesting this study accounted for a large part of the heterogeneity.

4. Discussion

In our systematic review and meta-analysis, a strong association was observed between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus in a non-diabetic adult population. In the meta-analysis, we observed a pooled risk estimate of 3.36 (95% CI 1.9; 5.9) for developing Type 2 Diabetes Mellitus in participants with GAD65 antibody positivity, compared to participants who were GAD65 antibody negative. In addition, due to the limited number of studies included, one estimate may have strong effects on our results. Nevertheless, several sensitivity analyses, including the exclusion of each study at the time, provided broadly consistent results and showed that the heterogeneity was mainly driven by the studies with high risk populations, of which one study [14] acted as an outlier. This suggest that overall, the presence of GAD65 antibodies increases the risk of developing Type 2 Diabetes Mellitus in the future.

The study of Dabelea et al. [14] was the only one to show no association between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus. This study included a selected population at baseline, namely those with prediabetes and high BMI as well as had shortest follow up duration, i.e. only 3 years versus on average 8 years. Furthermore, the relatively few subjects with elevated GAD65 antibodies may have caused the large instability of the risk estimate in the study of Zimmet et al. [30]. Excluding the study of Dabelea et al. [14], Zimmet et al. [30] as well as the study of Lundgren et al. [8] in a sensitivity analysis, all studies with high risk populations, decreased the heterogeneity between the studies to 49% and resulted in a risk estimate of 4.42 (95% CI 2.8;7.1). However, the study of Dabelea et al. [14] accounted for most of the heterogeneity. Excluding this study decreased the heterogeneity between the studies to a negligible 19%.

The results of our meta-analysis were in line with Niskanen et al. [3]. This study is one of the three studies that were identified in our systematic review, but were not included in the meta-analysis. These studies were not included in the meta-analysis, because they lacked a risk measure of incident Type 2 Diabetes Mellitus or could not provide one afterwards by the authors [3,13,19]. For example, in the study of Niskanen et al. [3], 33% of the non-diabetic participants (1 of 3) at baseline who were GAD65 antibody positive developed Type 2 Diabetes Mellitus 10 years later. In contrast to our results, in the Cremona Italy study [13] and the Swedish Västerbotten County Health study [19], none of the participants with normal glucose tolerance who were GAD65 antibody- and/or insulinoma-associated-2 autoantibody (IA-2A) positive developed Type 2 Diabetes Mellitus during 8 years of follow-up. In both studies, the low predictive value of GAD65 antibody positivity might be explained by the low number of GAD65 antibody positive subjects, 19 [13] and 23 [19] respectively, and thereby affecting the power of the study.

The presence of GAD65 antibodies is known to be strongly associated with the development of Type 1 Diabetes Mellitus and LADA [8,9]. In addition, in Type 2 Diabetes Mellitus patients, GAD65 positivity is associated with rapid progression to insulin deficiency, due to destruction of pancreatic beta-cells [2–6]. In people without Type 2 Diabetes Mellitus, GAD65 antibody positivity was associated with a decrease in maximal insulin secretory capacity, suggesting that the presence of GAD65 antibodies is a pancreatic marker of a subclinical autoimmune process that could lead to insulin deficiency and Type 2 Diabetes Mellitus [31]. In line with this finding, we showed in our meta-analysis a more than three times increased risk of developing Type 2 Diabetes Mellitus in participants with GAD65 antibody positivity, compared to participants who were GAD65 antibody negative.

Next to using GAD65 antibodies to discriminate between different types of Type 2 Diabetes Mellitus, our results suggest that GAD65 antibodies may be used to refine the identification of high risk subjects and the characterization of subjects who have a high risk to develop Type 2 Diabetes Mellitus. In addition, it is important to know how much beta-cell function is left in subjects who are GAD65 antibody positive. If GAD65 antibody positivity is present when people are near the critical level of beta-cell capacity, GAD65 antibodies may be used for primary prevention, instead of screening.

This is the first systematic review to quantify the association between GAD65 antibody positivity and incident Type 2 Diabetes Mellitus in a non-diabetic adult population. Strengths of this review include the systematic assessment of the methodological quality of each study and the sensitivity analyses that were conducted. However, some weaknesses must be taken into account. First, three studies [3,13,19] were not included in the meta-analysis because data on the association between GAD65 antibodies and Type 2 Diabetes Mellitus incidence was not shown and could not be provided afterwards upon request, possibly leading to selection bias. A second limitation is that no data was available on other diabetes autoimmunity parameters that are often used in addition to GAD65 antibody levels, such as Insulin Autoantibody-2A (IA-2A) and Zinc Transporter 8 (ZnT8). Consequently, although studies with specified incident LADA or incident Type 1 Diabetes Mellitus were excluded from the review, there is a possibility there were also LADA and Type 1 Diabetes Mellitus cases among those now defined as incident Type 2 Diabetes Mellitus. However, as the average age in each study included in the review was over 40 years of age, we believe this to be a very low number. Third, a low score for the methodological quality assessment may not necessarily correspond to a low quality of the study. It could be a consequence of lack of reporting, for example because some papers did not study the association between GAD65 antibodies and diabetes as a primary aim. Finally, the included studies were characterized by heterogeneity due to different risk estimates and study populations and designs. In addition, due to the limited number of studies included, one estimate may have strong effects on our results. Nevertheless, several sensitivity analyses, including the one where we excluded one study at the time, provided broadly consistent results and showed that the heterogeneity was mainly driven by the studies with high risk populations, of which one study [14] acted as an outlier. We believe this approach provided a general summary of the literature, but for the examination of specific differences, individual studies should be examined.

5. Conclusions

In conclusion, GAD65 antibody positivity is associated with an increased risk of developing Type 2 Diabetes Mellitus. The findings of this review suggest that diabetes autoimmunity, as reflected by GAD65 antibody positivity, predicts incident Type 2 Diabetes Mellitus.

Declaration of Interest

The authors have nothing to disclose. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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Data Accessibility

Data from the Hoorn study are available for researchers who meet the criteria for access to confidential data. Please contact hoornstudy@vumc.nl to request access.

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Author Contributions

ADMK performed the literature search, study selection, data extraction, quality assessment and data synthesis, and drafted the manuscript, tables and figures. MG performed study selection and quality assessment, assessed data extraction and made major revisions to the manuscript. EV, SR, AAvdH and TMcD provided support in design and execution of the review and meta-analyses, and made major revisions to the manuscript. JWB provided support in design and execution of the review and meta-analyses, and made major revisions to the manuscript. FR performed study selection and quality assessment, made major revisions to the manuscript, is the guarantor of this work and takes responsibility for the integrity of the work and analyses. This manuscript has not been submitted elsewhere and it is original.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.03.001.

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