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Genetic variants associated with fasting glucose levels in the Brazilian population: a review of studies of European-identified polymorphisms

Variantes genéticas associadas aos níveis de glicose em jejum na população brasileira: uma revisão de estudos de polimorfismos identificados em europeus

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ABSTRACT

Objective

Impaired fasting glucose is a well-known risk factor for diabetes, and has been linked to other conditions, such as cardiovascular and Alzheimer's disease. Whether these associations imply causation remains to be established. Observational studies are often afflicted by confounding and reverse causation, making them less than ideal for demonstrating causal relationships. Genetically-informed methods like Mendelian randomization, which are less susceptible to these biases, can be implemented. Mendelian randomization uses genetic variants as proxies (or instrumental variables) for modifiable exposures, testing their association with disease outcomes. However, since most genetic proxies have been described in European populations, applying Mendelian randomization in the Brazilian population necessitates the identification of locally relevant instruments. We investigated genetic variants associated with fasting glucose that were discovered in genome-wide association studies of Europeans and have also been examined in Brazil. The aim of our study was to define whether these variants served as proxies for fasting glucose in Brazil too.

Methods

We carried out an exhaustive literature search using databases of published research articles and a repository of Brazilian theses and dissertations.

Results

We examined a total of 38 papers and 27 dissertations/theses, published between 1997 and 2022, involving 21888 participants. We found few results for impaired fasting glucose, as opposed to many reports on the association of the selected genetic variants with diabetes. The genes *GCK* and *TCF7L2* prevailed in the analyses, although studies on *GCK* were mainly related to Maturity-Onset Diabetes of the Young rather than to common diabetes conditions.

Conclusion
Additional studies with improved reporting of findings are imperative to elucidate the genetic predictors of fasting glucose (and possibly other risk factors) in Brazil.

Keywords: Brazil. Diabetes Mellitus. Genome-wide association studies. Mendelian randomization. Single nucleotide polymorphisms.

RESUMO

Objetivo
A glicose em jejum alterada é um fator de risco bem conhecido para o diabetes, mas também tem sido associada a outras doenças, como as cardiovasculares e o mal de Alzheimer. Ainda não se sabe se essas associações são causais. Os estudos observacionais são afetados por fatores de confusão e causalidade reversa e, portanto, não são ideais para estabelecer relações causais. Pelo contrário, os métodos geneticamente informados, como a randomização mendeliana, são menos suscetíveis a esses vieses. A randomização mendeliana usa variantes genéticas como proxies (ou variáveis instrumentais) de exposições modificáveis, testando sua associação com desfechos de interesse. Entretanto, como a maioria dos proxies genéticos foi descrita em populações europeias, a aplicação da randomização mendeliana na população brasileira requer a identificação de instrumentos localmente relevantes. Foi investigado as variantes genéticas associadas à glicemia de jejum que foram descobertas em estudos de associação genômica ampla em europeus e foram examinadas no Brasil. O objetivo do estudo foi definir se essas variantes eram proxies para a glicemia de jejum também no Brasil.

Métodos
Realizamos uma pesquisa exaustiva da literatura cientifica usando bases de dados de artigos publicados e uma coleção de teses e dissertações brasileiras.

Resultados
Examinamos 38 artigos e 27 dissertações/teses, publicados entre 1997 e 2022, envolvendo 21.888 participantes. Encontramos poucos artigos sobre a glicemia de jejum, em comparação com os numerosos trabalhos sobre a associação das variantes genéticas selecionadas com o diabetes. Os genes GCK e TCF7L2 prevaleceram nas análises, embora os estudos sobre o GCK estivessem relacionados principalmente ao diabetes MODY (Maturity-Onset Diabetes of the Young), e não a diabetes crônica multifatorial.

Conclusão
São necessários estudos adicionais e uma melhor documentação dos resultados para identificar os preditores genéticos dos níveis de glicose em jejum (e possivelmente outros fatores de risco) no Brasil.

***Palavras-chave**: Brasil. Diabetes Mellitus. Estudos de associação genômica ampla. Randomização mendeliana. Polimorfismos de nucleotídeo único.*

INTRODUCTION

Identifying the causes of disease is a key pursuit in epidemiology, which also motivates many other activities and disciplines in human research. In epidemiology the the relationship of an exposure or risk factor with an outcome is achieved via observational or experimental studies, although only the latter provide strong enough evidence to support claims of causality. Observational studies are often affected by biases such as confounding and reverse causation as well as measurement error, and consequently, the detected associations cannot be unequivocally considered causal. Genetically-informed techniques have been developed to overcome these drawbacks, by attempting to untangle genetic and environmental factors affecting the outcome [1]. Genetically-informed methods include family-based designs as well as designs that utilize genetic variation in unrelated individuals such as Mendelian Randomization (MR) [2].

MR incorporates the fundamentals of instrumental variable (IV) theory from econometrics and Mendel's laws of segregation and independent assortment, to estimate an unbiased causal

effect of an exposure on an outcome of interest [3]. This is done through the use of genetic variants that are strongly associated with the risk factor (exposure), and therefore act as proxies or IVs for that exposure. The choice of genetic variants as IVs is based on the fact that genotypes segregate independently of other genetic or environmental factors and, consequently, are unlikely to be associated with confounding factors of the relationship between exposure and outcome. In addition, since genotypes are randomly set at conception, they are less vulnerable to reverse causation (i.e. unlikely to be influenced by the outcome). The strength of an IV is measured with R^2 (the amount of variability in the exposure that is explained by the instrument) and the F-statistic, both obtained from the regression of the exposure on the IV when individual-level data are available [4].

The expansion of genomic technology, the reduction in genotyping and sequencing costs, and the increasing practice of data sharing have made possible the growing popularity of MR in the last decade. MR has been applied to address a variety of research questions of epidemiological interest, assessing the causal effect of an increasingly large number and diverse range of exposures on a wide selection of traits and diseases [5].

However, as demonstrated by the Genome-Wide Association Study (GWAS) catalog [6], the overwhelming majority of individuals and studies where the association of genetic variants with exposures has been investigated belongs to populations of European origin. Hispanic or Latin American individuals represent only 1.3% of the subjects, 2.2% of the studies and 4% of the associations reported in GWAS. In order to be able to apply MR in the Brazilian population it is then important to have access to adequate IVs, i.e. IVs that reflect the association of genetic variants with exposures in the local population.

In addition to its use in MR analysis, identifying genetic variants that are robust determinants of disease risk factors locally will also help with the creation of appropriate Polygenic Risk Scores (PRSs). A PRS consists of summing the number of risk alleles across independent Single Nucleotide Polymorphisms (SNPs) carried by an individual, a sum that is often weighted by the effect of these alleles on the risk factor, obtained from a previous large-scale study [7]. A PRS can be calculated using all SNPs from a GWAS or only the SNPs associated with the trait at a particular p-value threshold. However, PRSs are frequently generated using just a small number of SNPs, e.g. [8,9], especially when resources for genome-wide genotyping are scarce or nonexistent.

The aim of this study was to ascertain genetic variants identified as strong IVs for fasting glucose levels, a risk factor for diabetes, in Europeans, which were also tested in Brazil. Fasting glucose was chosen as the target exposure, instead of diabetes itself, because as an intermediate phenotype for diabetes the association with genetic determinants of hyperglycaemia may be stronger. In addition, fasting glucose has been associated with other disorders, like cardiovascular and Alzheimer's disease [10,11], so IVs for fasting glucose could be used to test its causal association with these outcomes. According to the International Diabetes Federation (IDF) Diabetes Atlas, in Brazil in 2021 the age-adjusted comparative prevalence of diabetes was ~9%, and that of impaired fasting glucose was ~10% (https://diabetesatlas.org/data/en/country/27/br.html). This represents almost 16 million people with disease and about 21.5 million people with a risk factor for disease, numbers expected to increase to 19 and 24 million, respectively, by 2030. Since performing a GWAS of fasting glucose levels in the Brazilian population, which would be ideal to discover genetic proxies of local significance, is beyond our means, we examined existing literature to determine whether these European variants are likely to work as IVs in Brazil as well [12]. In that way, researchers intending to apply MR or create a PRS to investigate the association of fasting glucose with an outcome of

interest in Brazil will be able to make an informed decision about the feasibility of such a study using proxies derived from Europeans.

METHODS

We used the GWAS catalog to uncover SNPs associated with fasting serum glucose, using the term "fasting glucose" to run the search, and selected 21 SNPs with a P value < $5x10^{-8}$ (Table 1). We then searched the scientific literature databases PubMed, the *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS, Latin American and Caribbean Literature on Health Sciences), the Brazil Scientific Electronic Library Online (SciELO), and the *Biblioteca Digital Brasileira de Teses e Dissertações* (BDTD, Brazilian Digital Library of Theses and Dissertations), to identify publications that tested the association of those SNPs with circulating levels of fasting glucose in Brazil. In these databases, the search was conducted using the SNP rs code or the name of the gene where the SNP is located together with the terms "Brazil" and "fasting glucose" (for example, 'rs1799884 and "fasting glucose" and Brazil', or '*TCF7L2* and "fasting glucose" and Brazil'). Due to limited success using this strategy, we changed the terms to rs code or gene name, "Brazil" and "diabetes" (e.g. 'rs1799884 and diabetes and Brazil' or '*TCF7L2* and diabetes and Brazil'), and we found 69 publications (papers, dissertations or theses, from here on referred collectively as 'articles'). Both authors participated in the article selection process, which was not carried out blindly. Disagreements were solved by further extensive discussion between the authors. Searches were performed during the second semester of 2021 and the first semester of 2022.

After assessing the content of the abstract and removing the duplicated articles, 60 publications remained to be examined in depth. The inclusion criteria for the articles were: (a) study conducted in the Brazilian population; and (b) study that ascertained SNPs or genes previously shown in the GWAS catalog as strongly associated with fasting glucose concentrations. For each selected article we extracted the following information: study, bibliographic database where the article was found, authors, studied population, region/city/town, gene of interest, SNPs or mutations in this gene, effect allele, effect of this allele on the protein, prevalence of diabetes in the studied population, age at diabetes diagnosis, age at sample collection, N, sex, ethnicity, fasting glucose level in mg/dl, Odds Ratios (OR) and 95% Confidence Interval (CI) for diabetes, p-value for the association of the SNP with diabetes or fasting glucose, Hardy-Weinberg equilibrium test p-value, correction for population stratification, and study type .

We kept studies that, although clearly using the same or an overlapping dataset, did not report exactly the same results. This situation mainly occurred with theses and dissertations from which papers were published, and with articles that originated in the same research group. In several

Table 1 – Single nucleotide polymorphisms (SNPs) strongly associated with fasting glucose levels in genome-wide association studies (GWAS) reported in the Genome-wide Association Study (GWAS) catalog.

Genetic variant	Risk allelle	p-value	Risk Allele Frequency	Beta[a]	Unit	95% CI	Mapped gene	Chromosome	Location[b]	Study accession
rs10830963	G	$3x10^{-50}$	0.280	0.070	mmol/l increase	[0.06-0.08]	MTNR1B	11	92975544	GCST000276
rs10830963	G	$6x10^{-175}$	0.300	0.067	mmol/l increase	[0.061-0.073]	MTNR1B	11	92975544	GCST000568
rs10830963	C	$2x10^{-100}$	0.706	0.079	unit decrease	[0.072-0.087]	MTNR1B	11	92975544	GCST005186
rs10830963	?	$6x10^{-26}$	NR	n/a	n/a	n/a	MTNR1B	11	92975544	GCST006404
rs10830963	G	$5x10^{-89}$	0.240	0.072	unit increase	[0.065-0.079]	MTNR1B	11	92975544	GCST007899
rs10830963	?	$9x10^{-32}$	NR	0.134	unit increase	[0.11-0.16]	MTNR1B	11	92975544	GCST008032
rs10830963	G	$7x10^{-26}$	0.440	0.105	unit increase	[0.085-0.125]	MTNR1B	11	92975544	GCST011587
rs10830963	C	$1x10^{-98}$	0.697	0.074	unit decrease	[0.067-0.081]	MTNR1B	11	92975544	GCST012076
rs10830963	C	$4x10^{-100}$	0.697	0.078	unit decrease	[0.071-0.086]	MTNR1B	11	92975544	GCST012077

Table 1 – Cont.

Genetic variant	Risk allelle	p-value	Risk Allele Frequency	Beta[a]	Unit	95% CI	Mapped gene	Chromosome	Location[b]	Study accession
rs10830963	C	$1x10^{-211}$	0.697	0.077	unit decrease	[0.072-0.082]	MTNR1B	11	92975544	GCST012078
rs10885122	G	$7x10^{-18}$	0.862	0.027	unit increase	[0.021-0.033]	BTBD7P2/ADRA2A	10	111282335	GCST012078
rs11558471	A	$7x10^{-18}$	0.679	0.030	unit increase	[0.023-0.036]	SLC30A8/ZNT8	8	117173494	GCST005186
rs11558471	G	$5x10^{-24}$	0.281	0.035	unit decrease	[0.028-0.041]	SLC30A8/ZNT8	8	117173494	GCST007899
rs11558471	A	$1x10^{-24}$	0.671	0.032	unit increase	[0.026-0.038]	SLC30A8/ZNT8	8	117173494	GCST012076
rs11558471	A	$5x10^{-35}$	0.671	0.027	unit increase	[0.023-0.031]	SLC30A8/ZNT8	8	117173494	GCST012078
rs11605924	A	$1x10^{-26}$	0.489	0.023	unit increase	[0.019-0.027]	CRY2	11	45851540	GCST012078
rs11708067	A	$7x10^{-22}$	0.780	0.027	mmol/l increase	[0.021-0.033]	ADCY5	3	123346931	GCST000568
rs11708067	A	$5x10^{-22}$	0.771	0.023	unit increase	[0.018-0.027]	ADCY5	3	123346931	GCST012078
rs11920090	T	$2x10^{-18}$	0.868	0.027	unit increase	[0.021-0.033]	SLC2A2	3	170999732	GCST012078
rs13387347	?	$2x10^{-36}$	NR	0.114	unit increase	[0.096-0.132]	SPC25	2	168898336	GCST002586
rs1387153	T	$2x10^{-36}$	0.290	0.070	mmol/l increase	[0.05-0.08]	MTNR1B/SNRPGP16	11	92940662	GCST000291
rs1799884	A	$2x10^{-19}$	0.190	0.062	mg/dl increase	[0.049-0.075]	GCK	7	44189469	GCST001233
rs1799884	?	$2x10^{-25}$	NR	0.117	unit increase	[0.095-0.139]	GCK	7	44189469	GCST008032
rs1799884	T	$8x10^{-27}$	0.190	0.136	unit increase	[0.11-0.16]	GCK	7	44189469	GCST011587
rs2191349	T	$3x10^{-44}$	0.520	0.030	mmol/l increase	[0.024-0.036]	GTF3AP5	7	15024684	GCST000568
rs2191349	T	$2x10^{-20}$	0.526	0.028	unit increase	[0.022-0.034]	GTF3AP5	7	15024684	GCST005186
rs2191349	G	$2x10^{-18}$	0.478	0.025	unit decrease	[0.02-0.031]	GTF3AP5	7	15024684	GCST012076
rs2191349	G	$8x10^{-25}$	0.478	0.032	unit decrease	[0.026-0.038]	GTF3AP5	7	15024684	GCST012077
rs2191349	G	$4x10^{-40}$	0.478	0.027	unit decrease	[0.023-0.031]	GTF3AP5	7	15024684	GCST012078
rs2232326	C	$4x10^{-77}$	0.050	0.457	unit decrease	[0.41-0.51]	G6PC2/SPC25	2	168907981	GCST011587
rs4506565	A	$8x10^{-24}$	0.694	0.022	unit decrease	[0.018-0.026]	TCF7L2	10	112996282	GCST012078
rs4607517	A	$1x10^{-25}$	0.180	0.060	mmol/l increase	[0.05-0.07]	GCK	7	44196069	GCST000276
rs4607517	A	$7x10^{-92}$	0.160	0.062	mmol/l increase	[0.054-0.07]	GCK	7	44196069	GCST000568
rs4607517	A	$6x10^{-52}$	0.167	0.064	unit increase	[0.056-0.072]	GCK	7	44196069	GCST005186
rs4607517	A	$1x10^{-50}$	0.156	0.063	unit increase	[0.054-0.071]	GCK	7	44196069	GCST007899
rs4607517	?	$2x10^{-21}$	NR	0.114	unit increase	[0.091-0.138]	GCK	7	44196069	GCST008032
rs4607517	G	$3x10^{-46}$	0.839	0.058	unit decrease	[0.05-0.066]	GCK	7	44196069	GCST012076
rs4607517	G	$7x10^{-44}$	0.839	0.059	unit decrease	[0.051-0.068]	GCK	7	44196069	GCST012077
rs4607517	G	$4x10^{-97}$	0.839	0.059	unit decrease	[0.053-0.065]	GCK	7	44196069	GCST012078
rs540524	G	$9x10^{-27}$	0.400	0.113	unit decrease	[0.091-0.135]	SPC25	2	168900420	GCST011587
rs560887	C	$9x10^{-218}$	0.700	0.075	mmol/l increase	[0.069-0.081]	SPC25/G6PC2	2	168906638	GCST000568
rs560887	A	$4x10^{-23}$	0.300	0.060	mmol/l decrease	[0.05-0.08]	SPC25/G6PC2	2	168906638	GCST000205
rs560887	C	$1x10^{-57}$	0.700	0.060	mmol/l increase	[0.05-0.07]	SPC25/G6PC2	2	168906638	GCST000276
rs560887	C	$2x10^{-75}$	0.291	0.244	mmol/l increase	[0.22-0.27]	SPC25/G6PC2	2	168906638	GCST004206
rs560887	C	$6x10^{-68}$	0.291	0.224	mmol/l increase	[0.2-0.25]	SPC25/G6PC2	2	168906638	GCST004206
rs560887	T	$3x10^{-99}$	0.299	0.072	unit decrease	[0.065-0.078]	SPC25/G6PC2	2	168906638	GCST005186
rs560887	A	$4x10^{-87}$	0.258	0.079	unit decrease	[0.072-0.087]	SPC25/G6PC2	2	168906638	GCST007899
rs560887	?	$9x10^{-35}$	NR	0.164	unit increase	[0.14-0.19]	SPC25/G6PC2	2	168906638	GCST008032
rs560887	C	$1x10^{-30}$	0.970	0.319	unit increase	[0.26-0.37]	SPC25/G6PC2	2	168906638	GCST011587
rs560887	C	$8x10^{-92}$	0.685	0.067	unit increase	[0.061-0.074]	SPC25/G6PC2	2	168906638	GCST012076
rs560887	C	$4x10^{-81}$	0.685	0.069	unit increase	[0.062-0.076]	SPC25/G6PC2	2	168906638	GCST012077
rs560887	C	$7x10^{-190}$	0.685	0.069	unit increase	[0.064-0.074]	SPC25/G6PC2	2	168906638	GCST012078
rs730497	?	$8x10^{-27}$	NR	0.121	unit increase	[0.099-0.143]	GCK	7	44184122	GCST002586
rs730497	?	$1x10^{-23}$	NR	0.112	unit increase	[0.09-0.134]	GCK	7	44184122	GCST008032
rs780094	C	$6x10^{-38}$	0.620	0.029	mmol/l increase	[0.023-0.035]	GCKR	2	27518370	GCST000568
rs780094	T	$3x10^{-24}$	0.400	0.032	unit decrease	[0.026-0.038]	GCKR	2	27518370	GCST005186
rs780094	A	$9x10^{-23}$	0.361	0.032	unit decrease	[0.025-0.038]	GCKR	2	27518370	GCST007899
rs780094	C	$3x10^{-26}$	0.610	0.031	unit increase	[0.025-0.037]	GCKR	2	27518370	GCST012076
rs780094	C	$4x10^{-22}$	0.610	0.030	unit increase	[0.024-0.037]	GCKR	2	27518370	GCST012077
rs780094	C	$1x10^{-49}$	0.610	0.031	unit increase	[0.027-0.035]	GCKR	2	27518370	GCST012078
rs7944584	A	$2x10^{-18}$	0.750	0.021	mmol/l increase	[0.015-0.027]	MADD	11	47314769	GCST000568
rs7944584	A	$3x10^{-24}$	0.732	0.024	unit increase	[0.02-0.029]	MADD	11	47314769	GCST012078
rs895636	T	$7x10^{-25}$	0.420	0.110	unit increase	[0.088-0.132]	KRTCAP2P1/SIX3	2	44961214	GCST011587
rs917793	T	$1x10^{-28}$	0.183	0.175	mmol/l increase	[0.14-0.21]	YKT6	7	44206254	GCST004206
rs917793	T	$3x10^{-24}$	0.183	0.156	mmol/l increase	[0.13-0.19]	YKT6	7	44206254	GCST004206
rs983309	G	$2x10^{-21}$	0.864	0.029	unit decrease	[0.023-0.035]	RNU6-526P/ RNU6-1151P	8	9320222	GCST012078

Note: [a]Beta: Effect of the risk allele on fasting glucose levels; [b]Mapped to genome assembly GRCh38.p13. NR: Not reported; n/a: Not available.

cases, a smaller set of findings was published in journals.. For example, not all SNPs analysed as part of the postgraduate work were included in the peer-reviewed publication. When the peer-reviewed and the postgraduate publication described identical results, only the former was considered.

Linkage disequilibrium (LD) between SNPs in *GCK*, *TCF7L2*, and *SLC30A8* was estimated using the LDmatrix tool in the LDlink suite, with Puerto Rico and Colombia as reference populations.

RESULTS

The articles in our study, 38 papers and 27 dissertations/theses, were published between 1997 and 2022 and involved 21888 participants. The mean age of the participants varied considerably among the studies, as did the biological sex ratios, although there were several studies that consisted exclusively of women (it was not the same for men). Twenty-five articles described genetic variants in the glucokinase (*GCK*) gene [13–37], whilst 28 publications focused on the transcription factor 7 like 2 gene (*TCF7L2*) [26,38–64]. The genes *SLC30A8* and *GCKR* were ascertained in four and three articles, respectively [26,55,65–69]. All the SNPs analysed are shown by study and gene in Table 2.

GCK

The *GCK* gene is located on chromosome 7p13, codes for a hexokinase enzyme, which catalyses the phosphorylation of glucose to glucose-6-phosphate, and regulates insulin secretion in the pancreatic beta cell [70]. The SNPs in this gene were first detected in association with fasting glucose levels in a GWAS of Europeans published in 2010 [71].

In our search, the majority of articles addressing variation in *GCK* concerning diabetes investigated mutations likely to cause monogenic forms of the disease, such as the Maturity-Onset Diabetes of the Young (MODY) (Table S1 – All supplementary material is available at https://docs.google.com/spreadsheets/d/15TM-UyqBD24oiXkuR_-eHVBpu5nVaGZP/edit#gid=38352188). For that reason, most of the studies we found consisted of families or related individuals, did not include a control group, used sequencing as a genotyping method, and were mainly descriptive, i.e. did not run a statistical analysis to test for association between the genetic variant and the disease or glucose levels. It was inferred that *GCK* mutations present in family members with MODY or hyperglycaemia, and absent in family members without those traits, were probably causing the phenotypes. Table S2 lists all *GCK* mutations described in Brazil in the literature that we examined.

Only seven articles portrayed studies assessing SNPs, namely the variants rs13306388, rs144723656, rs1799884, rs2268574, rs2268575, rs2908274 and rs35670475, usually in a case-control design (Table S3). These SNPs showed low levels of LD with each other in LDlink (Table S4). One study found evidence of association of rs1799884 with circulating fasting glucose amongst controls ($p<0.01$), with the A allele correlated with higher concentrations, as expected based on European data [17,18]. Additionally, allele frequencies of SNP rs2268574 were reported to differ significantly between women with gestational diabetes and control women [24,26].

The fact that mutations in *GCK* could explain rare diabetes conditions suggests that common variants in the same gene may underlie chronic diabetes disorders and accordingly, deserve to be further investigated in this context.

Table 2 – Fasting glucose-associated SNPs reported in the Brazilian population by study and gene.

Authors	Population	City, state	Gene	SNPs	EA	EA frequency (cases/controls)	N	Database
Santos (2010) [17]	Women diagnosed with gestational diabetes and healthy pregnant women	Curitiba, PR	GCK	rs1799884	A	0.240/0.200	750	BDTD
Santos et al. (2010) [18]	Unrelated Euro-Brazilian pregnant women	Curitiba, PR	GCK	rs1799884	A	0.240/0.200	750	PUBMED
Frigeri et al. (2012) [19]	Women diagnosed with gestational diabetes and healthy pregnant women	Curitiba, PR	GCK	c.43331A>G; rs2268574; rs2908274; rs13306388	G; C; T; A	n/a	200	PUBMED
Frigeri et al. (2014) [24]	Euro-Brazilian women diagnosed with gestational diabetes and healthy pregnant women	Curitiba, PR	GCK	rs2268574	T	0.384/0.483	227	PUBMED
Frigeri (2015) [26]	Biorepository samples	Curitiba, PR	GCK	rs144723656; rs2268574; rs2268575	T; T; G	0.014/0.008; 0.429/0.450; 0.220/0.223	227	BDTD
Frigeri et al. (2016) [29]	Unrelated Euro-Brazilian women	Curitiba, PR	GCK	rs144723656; rs2268574; rs2268575	T; T; G	0.014/0.008; 0.429/0.450; 0.220/0.223	271	PUBMED
Lepore (2016) [28]	Pregnant women diagnosed with diabetes mellitus and their newborns	Ribeirão Preto, SP	GCK	rs35670475; rs2268574; rs144723656	T; T; T	n/a	201	BDTD
Bride et al. (2021) [63]	Elderly volunteers from SABE health survey	São Paulo, SP	TCF7L2	rs7903146	T	0.27-0.40	1023	PUBMED
Cirelli et al. (2021) [64]	Individuals treated at the Periodontology Department, Universidade Estadual Paulista	Araraquara, SP	TCF7L2	rs7903146	T	0.26	931	PUBMED
Wunsch et al. (2019) [61]	European patients that underwent coronary angiography	Lajeado, RS	TCF7L2	rs12255372; rs7903146	T; T	0.31; 0.32	647	PUBMED
Ferreira et al. (2018) [60]	Patients with T2D	São Paulo, SP	TCF7L2	rs7903146	T	n/a	162	PUBMED
Anghebem-Oliveira et al. (2017) [58]	Unrelated Euro-Brazilian pregnant women	Curitiba, PR	TCF7L2	rs7901695	C	0.336; 0.390	252	PUBMED
Anghebem-Oliveira (2015) [55]	Patients with T1D, T2D or GD	Curitiba, PR	TCF7L2	rs7901695	T	0.664; 0.610	967	BDTD
de Melo et al. (2015) [56]	Unrelated Euro-Brazilian women	Curitiba, PR	TCF7L2	rs7903146; rs12255372	T; T	0.295/0.360; 0.303/0.320	400	PUBMED
Barros et al. (2014) [53]	Unrelated individuals from the general population	Parnaíba, PI	TCF7L2	rs7903146; rs12255372	T; T	0.28/0.29; 0.28/0.22	220	PUBMED
Assmann et al. (2014) [54]	T2D patients and non-diabetic subjects	Porto Alegre, RS	TCF7L2	rs7903146	T	0.38; 0.31	1488	PUBMED
Vaquero et al. (2012) [45]	Smooth muscle cells from human mammary artery segments	São Paulo, SP	TCF7L2	rs7903146	T	0.288	92	PUBMED
Franco et al. (2011) [44]	Individuals recruited from the Japanese-Brazilian Diabetes Study Group	Bauru, SP	TCF7L2	rs7903146; rs12255372	T; T	0.051/0.055; 0.032/0.035	222	PUBMED
Sousa et al. (2009) [40]	Individuals referred for cardiac catheterization for the diagnosis of CAD; MASS II study	São Paulo, SP	TCF7L2	rs7903146	T	0.319; 0.416	1455	PUBMED
Sousa (2011) [43]	Individuals undergoing cardiac catheterization and individuals with coronary artery disease from the MASS II study	São Paulo, SP	TCF7L2	rs7903146	T	0.319; 0.416; 0.470	1455	BDTD
Marquezine et al. (2008) [38]	Patients with documented multi-vessel coronary artery disease and normal left ventricular function (MASS II trial); general population of Vitoria, ES	São Paulo, SP; Vitoria, ES	TCF7L2	rs7903146	T	0.416; 0.333	2143	PUBMED
Marquezine (2009) [39]	Vitoria urban population; 33 districts of Ouro Preto; school children and their parents from Itapetininga; patients with coronary artery disease (MASS II)	Vitória, ES; Ouro Preto, MG; Itapetininga, SP	TCF7L2	rs7903146	T	n/a	4579	BDTD
Barra et al. (2012) [46]	Subjects seen at the Brasilia University Hospital	Brasilia, DF	TCF7L2	rs7903146	T	0.358; 0.270	252	SCIELO
Oliveira (2019) [62]	Individuals with T2D or without previous diagnosis of any type of diabetes	Belém, PA	TCF7L2	rs7901695	C	0.496 (0.505/0.476)	147	BDTD
Pinto (2018) [59]	Adolescents enrolled in state public schools	Vitória, ES	TCF7L2	rs7903146	T	0.385	312	BDTD
Catena (2016) [57]	Patients from two cohorts, subdivided into newborns and adults	João Pessoa, PB; Recife, PE	TCF7L2	rs7901695; rs7903146; rs12255372	C; T; T	0.389; 0.319; 0.277	149	BDTD
Costa (2014) [50]	Patients with T2D and healthy individuals	Porto Alegre, RS	TCF7L2	rs7903146; rs12255372	T; T	0.36; 0.30/0.34; 0.31	579	BDTD

Table 2 – Cont.

Authors	Population	City, state	Gene	SNPs	EA	EA frequency (cases/controls)	N	Database
da Rocha (2014) [51]	Individuals with T2D	Vale do Taquari, RS	TCF7L2	rs7903146; rs12255372	T; T	0.402; 0.391	46	BDTD
Cezar (2013) [48]	Patients with GD and pregnant women with no history of GD	Ribeirão Preto, SP	TCF7L2	n/a	n/a	n/a	28	BDTD
Ferreira (2013) [49]	T2D patients and individuals without diabetes and without T2D family history from the DNA bank at University of São Paulo	São Paulo, SP	TCF7L2	rs7903146	T	0.335	302	BDTD
Moraes (2013) [47]	Individuals recruited at the University Hospital of the University of São Paulo	São Paulo, SP	TCF7L2	rs7903146	T	0.354; 0.321	429	BDTD
Silva (2011) [42]	Diabetic and healthy individuals	Triunfo, PE	TCF7L2	rs7901695; rs7903146; rs11196205; rs12255372	C; T; C; T	0.528/0.435; 0.344/0.306; 0.587/0.626; 0.398/0.323	340	BDTD
da Silva Filho (2010) [41]	Diabetics and non-diabetics	Triunfo, PE	TCF7L2	rs7901695; rs7903146; rs11196205; rs12255372	C; T; C; T	0.528/0.435; 0.344/0.306; 0.587/0.626; 0.398/0.323	340	BDTD
Frigeri (2015) [26]	Biorepository samples	Curitiba, PR	TCF7L2	rs7901695	C	0.338; 0.387	313	BDTD
Welter (2014) [52]	T2D patients and healthy individuals	Curitiba, PR	TCF7L2	rs7903146; rs12255372	T; T	0.340/0.310; 0.330/0.280	241	BDTD
Welter et al. (2015) [77]	Unrelated Euro-Brazilian subjects	Curitiba, PR	ADRA2A	rs10885122	T	0.20/0.19	241	PUBMED
Welter (2014) [52]	T2D patients and healthy individuals	Curitiba, PR	ADRA2A; SLC2A2	rs10885122; rs5393	T; C	0.20/0.19; 0.21/0.20	241	BDTD
Weiss (2014) [76]	Pregnant women	Curitiba, PR	ADRA2A; SLC2A2	rs10885122; rs5393	T; G	0.210/0.200; 0.190/0.180	814	BDTD
Anghebem-Oliveira et al. (2017) [58]	Unrelated Euro-Brazilian pregnant women	Curitiba, PR	GCKR	rs780094	T	0.307/0.384	252	PUBMED
Anghebem-Oliveira (2015) [55]	Healthy individuals, patients with T1D, T2D or GD, samples from the UFPR Clinical Biochemistry Laboratory	Curitiba, PR	GCKR	rs780094	C	0.693/0.616	967	BDTD
Junior (2014) [75]	Pregnant women healthy and with GD	Curitiba, PR	MTNR1B	rs10830963	G	0.276/0.202	442	BDTD
von Kostrisch (2016) [78]	Mothers and their children	Bauru, SP	MTNR1B	rs10830963; rs1387153	G; T	n/a	400	BDTD
Lima (2018) [69]	Volunteers with T2D	Aracaju, SE	SLC30A8	rs11558471	A	0.768	110	BDTD
Gomes et al. (2017) [67]	T1D patients and healthy controls	São Paulo, SP	SLC30A8	rs2466295; rs16889462	G; A	n/a	1280	PUBMED
Teleginski et al. (2017) [68]	Unrelated Euro-Brazilian pregnant women	Curitiba, PR	SLC30A8	rs13266634	A; T	0.366/0.403; 0.235/0.278	314	PUBMED
Bandeira (2016) [65]	T2D patients	São Paulo, SP	SLC30A8	rs13266634	T	0.280	82	BDTD
Frigeri (2015) [26]	Biorepository samples	Curitiba, PR	GCKR; SLC30A8	rs780094; rs13266634	T; T	0.396/0.394; 0.227/0.255	313	BDTD

Note: BDTD: *Biblioteca Digital Brasileira de Teses e Dissertações,* EA: Effect allele, GD: Gestational Diabetes, MASS: Medicine, Angioplasty or Surgery Study, SABE: *Saúde, Bem-estar e Envelhecimento,* T1D: Type 1 Diabetes, T2D: Type 2 Diabetes, UFPR: *Universidade Federal do Paraná,* UNESP: *Universidade Estadual Paulista*, USP: *Universidade de São Paulo*.

TCF7L2

The *TCF7L2* gene lies on chromosome 10q25.2-q25.3, and encodes a protein that is involved in the Wnt signalling pathway, which is a key player in the pathogenesis of several human diseases [72]. This gene was first associated with impaired fasting glucose in a study conducted in the Finnish population [73].

Unlike what happened with the analysis of *GCK*, all articles considering *TCF7L2* tested SNPs rather than mutations, in individuals affected by common types of diabetes. The studied populations consisted of unrelated individuals, generally in outpatient settings. The considered SNPs, rs7903146, rs7901695, rs12255372 and rs11196205, were associated with type 2 diabetes in the GWAS catalog and the Phenoscanner database [74]. No study included the SNP rs4506565, the main signal for the association with fasting glucose within *TCF7L2* (Table 1), but it is expected that all investigated SNPs are in strong LD with it (r^2>0.50; Table S5). Eleven articles out of 28 showed an association between SNPs in the gene and type 2 or gestational diabetes ($p \leq 0.05$) and in these cases, the allele that increased the risk of the disease in Europeans also did so in Brazilians (Table S6). A few publications investigated the relationship of SNP genotypes with fasting glucose levels in the control group (and occasionally in the patient group), without finding convincing evidence of association [38,40,43,47,49,50]. We did not carry out a meta-analysis for *TCF7L2* due to the low number of independent studies.

Other genes

The *GCK* and *TCF7L2* genes were the most cited in the surveyed literature. Other genes and SNPs that also appeared, although less frequently, are shown together in Table S7. We found 12 articles describing studies of variation in the genes *ADRA2A*, *GCKR*, *MTNR1B*, *SLC2A2*, and *SLC30A8 (ZNT8)*, and diabetes as a common disease [26,52,55,65–69,75–78]. The Linkage disequilibrium levels between *SLC30A8* SNPs are depicted in Table S8. Six studies, not all independent, showed evidence of association of the SNPs with gestational, type 1 or type 2 diabetes, five of them in the same direction as in European populations.

DISCUSSION

In this study, we investigated the extent to which genetic determinants of fasting glucose blood levels had been explored in Brazilians, with the aim of promoting their use in future MR and PRS analyses in the local population. We revealed a heterogeneous set of studies linking genetic variation with diabetes, that for the most part analysed SNPs emerging from diabetes GWAS or MODY-related mutations across diverse Brazilian groups, predominantly in the South and Southeastern regions of the country (see Table 2). MODY is the most frequent form of monogenic diabetes, making up about 2-5% of diabetes cases worldwide. It is usually diagnosed before the age of 25 years, has an autosomal dominant inheritance pattern and is unrelated to autoantibodies. Key genes related to MODY are *GCK* and *HNF4A*, which harbour mutations that affect pancreatic beta cell functions. The main difference between MODY and type 1 and type 2 diabetes relates to the fact that the pathophysiology of the latter two involves several genes and environmental factors, while MODY arises from a deficiency of a single identified gene [79,80].

Few studies have been conducted in Brazil specifically testing the association of SNPs with fasting glucose levels, despite most studies using this parameter as a marker for the presence of diabetes. In fact, the majority of investigations focused on MODY, type 2 and gestational diabetes. Available data showed an agreement between the direction of allelic effects on diabetes in European and Brazilian populations, indicating that some of the variants examined might function as IVs for diabetes liability in Brazil (for example, rs2268574 in *GCK*, rs7903146 in *TCF2L7*, rs780094 in *GCKR*, rs13266634 and rs2466295 in *SLC30A8*, and rs10830963 in *MTNR1B*). Nonetheless, conducting a more extensive search for IVs is necessary if the goal is to perform an MR (or PRS) analysis using diabetes as an exposure. On the other hand, it has been suggested that instrumentalizing glycated haemoglobin (HbA1c) rather than diabetes in MR studies on the effects of hyperglycaemia on health outcomes may produce results less likely to be affected by weak instrument bias[4]. We conducted a quick search of the term HbA1c in the GWAS catalog and found among the top 50 associated SNPs there were variants in the genes *GCK* and *SPC25/G6PC2*, which were also associated with fasting glucose (Table 1). Polymorphisms in the *HK1* gene (rs16926246 and rs17476364) showed the strongest association with HbA1c, but neither has been described in Brazil.

A recent multiethnic study of 39 GWAS loci for fasting glucose identified in Europeans, replicated ~80% of them in African Americans, Asian and Pacific Islanders, and/or American Indians/Alaskan Natives [81]. Among the 31 replicated loci, we identified 8 genes (*GCK*, *TCF7L2*, *ADRA2A*, *CDKAL1*, *GCKR*, *MTNR1B*, *SLC2A2* and *SLC30A8*) and 3 SNPs (rs780094, rs11558471 and rs10830963) in our study of the Brazilian population, suggesting a fairly broad generalizability for at least some of them.

The studies reviewed presented several limitations that precluded us from extracting more definite conclusions with respect to the transferability of instruments between Europe and Brazil. These limitations include: lack of statistical power due to small sample sizes, not performing or not reporting Hardy-Weinberg equilibrium tests, absence of control for population stratification, limited or reduced ethnic diversity within and across studies (with a majority of White subjects in most of them), and insufficient information on the population sample utilized. Furthermore, limitations of our own study include the possibility of overlooking SNPs associated with fasting glucose that may not be among the top 21 in the GWAS catalog but are important in Brazil, as well as the omission of relevant literary sources from unexplored databases.

Among the strengths, it's noteworthy that this study is the first to investigate genetic predictors of fasting glucose in a Latin American population, where we have performed a fairly exhaustive literature search and identified important gaps in our knowledge of non-European groups. Additionally, by identifying the shortcomings and highlighting limitations in the few studies carried out aims to encourage a more comprehensive and adequate sharing of results that leads to their inclusion in future meta-analyses. We hope our work could promote more quality research to find strong genetic proxies for modifiable exposures of public health significance.

CONCLUSION

Our attempt to review studies examining the association of genetic variants with fasting glucose levels in the Brazilian population was not successful due to the lack of appropriate reports. Replacing fasting glucose with diabetes identified 60 studies that fit the inclusion criteria, focused on the genes *GCK* and *TCF7L2*. However, the information provided in these studies was somewhat lacking and not complete enough to be used in a meta-analysis. Addressing these weaknesses will

enable us to better plan, conduct, and report genetic association studies in Brazil and other Latin American countries, allowing us to combine data from which evidence to carry out genetically-informed causal inference methods could ultimately be obtained.

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