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The link between cognition and somatic conditions related to insulin resistance in the UK Biobank study cohort: a systematic review

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ABSTRACT

Clinical and genomic studies have shown an overlap between neuropsychiatric disorders and insulin resistance (IR)-related somatic conditions, including obesity, type 2 diabetes, and cardiovascular diseases. Impaired cognition is often observed among neuropsychiatric disorders, where multiple cognitive domains may be affected. In this review, we aimed to summarise previous evidence on the relationship between IR-related diseases/traits and cognitive performance in the large UK Biobank study cohort. Electronic searches were conducted on PubMed, Scopus, and Web of Science until April 2022. Eighteen articles met the inclusion criteria and were qualitatively reviewed. Overall, there is substantial evidence for an association between IR-related cardiometabolic diseases/traits and worse performance on various cognitive domains, which is largely independent of possible confoundings. The most consistent findings referred to IR-related associations with poorer verbal and numerical reasoning ability, as well as slower processing speed. The observed associations might be mediated by alterations in immune-inflammation, brain integrity/connectivity, and/or comorbid somatic or psychiatric diseases/traits. Our findings provide impetus for further research into the underlying neurobiology and possible new therapeutic targets.

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1. Introduction

The main feature of somatic diseases and traits linked to insulin resistance (IR) is a deficient response to insulin in peripheral tissues. IR is prominently involved in the pathophysiology of obesity, type 2 diabetes mellitus, and cardiovascular diseases (e.g., atherosclerosis, hypertension, coronary artery disease), as well as related traits, such as elevated glycated haemoglobin levels, high body mass index (BMI), and increased systolic blood pressure (Mancusi et al., 2020; Ormazabal et al., 2018). These conditions frequently coexist and are considered modern-day epidemics due to their increasingly high prevalence as a result of, amongst others, unhealthy diet and sedentary lifestyle (Seidell, 2000). While the role of IR in these somatic diseases and traits is well established (DeFronzo and Ferrannini, 1991; Mancusi et al., 2020; Ormazabal et al., 2018), it is becoming clearer that insulin also plays an important role in the central nervous system. For example, insulin is involved in important brain processes like neurotransmission, synaptic plasticity, and neuroprotection (Klinedinst et al., 2019). A growing body of studies have shown evidence of both clinical and genetic overlap between IR-related somatic diseases and neuropsychiatric disorders (Bralten et al., 2020; Fanelli et al., 2022; Wimberley et al., 2022). For example, many studies have linked Alzheimer's disease to altered insulin signalling, and some people even refer to Alzheimer's disease as type 3 diabetes mellitus (Kroner, 2009). In addition, studies in rat models have shown that local administration of insulin in the hippocampus modulates cognitive function, including spatial memory, and that selective blockade of the insulin signalling pathway leads to dysfunction of memory abilities, as also occurs following IR induced by a high-fat diet (McNay et al., 2010). These observations indicate a potential role for insulin-related processes on cognitive phenotypes, like cognitive impairment and dementia. Cognitive impairment and IR-related somatic diseases are important contributors to reduced quality of life and life expectancy and constitute major health and economic burdens for society (Kazukauskiene et al., 2021). Another relevant issue is that cognitive deficits are commonly seen in individuals with neuropsychiatric disorders and are seldom alleviated by currently available pharmacotherapies, usually persisting even in individuals who show a good overall response to treatment (Hori et al., 2020; Vinasi et al., 2021).

The recent availability of very large, population-based, well-phenotyped cohorts makes it possible to extend analyses beyond clinically defined phenotypes, allowing for a better investigation of the relationship of IR with cognition in humans. The largest of these cohorts addressing cognition and IR-related conditions is the UK Biobank cohort, which is a deeply phenotyped, large prospective study aimed at studying the general health of middle-aged and older people ($\geq$ 40 years old) across the United Kingdom (UK) (Sudlow et al., 2015). From 2006 to 2010, approximately 500,000 individuals were recruited for baseline assessments, which included detailed characterisation of sociodemographic, lifestyle, environmental factors, medical history, physical measures, and cognition. The richness of this data collection makes the UK Biobank study particularly useful to address the relationship of IR-related somatic diseases and traits with cognition. Cognitive function was initially measured by the pairs matching and reaction time tests using fully automated, unsupervised touchscreen questionnaires. Additional cognitive tests were later added to the baseline assessment and therefore administered only to a subsample of participants, namely the prospective memory, numeric memory, and fluid intelligence tests. A subset of 20,000 participants was invited to repeat the assessment of baseline measures (between 2012 and 2013), which included the same baseline tests as cognitive measures, excluding the numeric memory test. Several cognitive function tests (i.e., fluid intelligence, pairs matching, and numeric memory tests) were later re-implemented as web-based questionnaires (completed between 2014 and 2015 by around 110,000 participants), and two additional tests were included, the trail making and the symbol digit substitution tests. Starting in 2016 and with ongoing recruitment, a subsequent imaging assessment visit has been introduced, where participants are also assessed on additional cognitive domains by tests such as the tower rearranging, the matrix pattern completion, and the trail making tests, for example. A further detailed description of the UK Biobank cognitive tests can be found in Lyall et al. (2016) and Table 1.

With UK Biobank making its collected data available to the research community, many studies had the ability to investigate the cognitive phenotypes in this cohort in combination with somatic IR-related diseases and traits. While multiple studies included parts of this exploration in their analyses, the literature still lacks a good overview of the gathered information. Therefore, we performed a literature review to identify and summarise the studies that investigated the relationship between IR-related diseases and traits and different cognitive domains in the UK Biobank study cohort, the largest population cohort addressing both a wide range of cognitive measures as well as diverse IR-traits and diseases on the same individuals.

2. Methods

2.1. Study protocol

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (Page et al., 2021). The full review protocol was registered on PROSPERO: International prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero, PROSPERO ID: CRD42022335139).

2.2. Searching strategy

An electronic search of the literature was conducted on the PubMed, Scopus, and Web of Science databases looking for studies investigating the relationship between IR-related diseases/traits and cognitive functioning in the UK Biobank study cohort. We used the Polyglot Search Translator tool to transform the PubMed query into formats appropriate to other databases (Clark et al., 2020). We included papers published until April 2022, when the databases were last searched. We used search terms related to cognition and to IR-related traits and diseases, including terms encompassing glycaemic and lipidaemic control/homoeostasis, diabetes mellitus, obesity and obesity-related measures, metabolic syndrome, cardiovascular disease, Cushing's syndrome, and polycystic ovary syndrome. The search was restricted to studies conducted using the UK Biobank study cohort and where any of the search terms appeared in the title or abstract. The full search queries used are provided in the Supplementary materials. Duplicates were removed using EndNote 20.2 (Clarivate, Philadelphia, PA).

Two reviewers (GF and NRM) independently screened the results retrieved from the search query to identify potentially relevant studies by evaluating titles and abstracts. The full text of the selected studies and those of uncertain relevance were obtained and thoroughly evaluated to ascertain the pertinence of each study. In the event of disagreement during the study selection process, a decision was made through open discussion, and in the case of persistent inconsistency of judgement, with the involvement of a third reviewer (JB).

2.3. Inclusion and exclusion criteria

Studies were included if: 1) they investigated the phenotypic relationship between cognition and IR-related diseases/traits; 2) the analyses were conducted within the population-based UK Biobank cohort; 3) they were written in English. Reasons for exclusion were: 1) being a meta-analysis or review; 2) being a preprint (not yet peer-reviewed); 3) being a commentary, a letter, a congress abstract, or an editorial; 4) not having the outcomes of interest measured/reported.

Table 1
Description of the cognitive function tests administered throughout the UK Biobank study. Further information on how each test was conducted can be found at: https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100026.

UK Biobank cognitive tests	Cognitive domains[1]	UK Biobank Field ID(s) used by reviewed studies	Cognitive assessment time point (number of participants with valid data)[2]
Prospective memory	Prospective memory	Field ID: 20018 Prospective memory result	Baseline (subsample: N = 117,517) Repeat (subsample: N = 20,329) Imaging (subsample: N = 48,178)
Trail Making Test, part A (TMT-A)[§]	Executive function, divided attention, visual scanning, processing speed	Field ID: 6348 Duration to complete numeric path (trail #1)	Imaging (subsample: N = 35,663)
Trail Making Test, part B (TMT-B)[§]	Executive function (and more specifically, set shifting/cognitive flexibility, and working memory (short-term memory)), divided attention, visual scanning, conceptual tracking, processing speed	Field ID: 6350 Duration to complete alphanumeric path (trail #2)	Imaging (subsample: N = 35,663)
Tower rearranging	Executive function (and more specifically, planning, working memory (short-term memory), problem solving, and response inhibition), visuospatial memory, procedural and skill learning	Field ID: 21004 Number of puzzles correct	Imaging (subsample: N = 34,933)
Numeric memory	Working memory (short-term memory), attention	Field ID: 4282 Maximum digits remembered correctly	Baseline (subsample: N = 51,799) Imaging (subsample: N = 36,535)
Pairs matching	Visual declarative memory (short-term memory)	Field ID: 399 Number of incorrect matches in round	Baseline (subsample: N = 497,791) Repeat (subsample: N = 20,344) Imaging (subsample: N = 48,202)
Fluid intelligence	Verbal and numerical reasoning	Field ID: 20016 Fluid intelligence score (i.e., sum of the correct answers given)	Baseline (subsample: N = 165,430) Repeat (subsample: N = 20,110) Imaging (subsample: N = 47,291)
Matrix pattern completion	Non-verbal reasoning	Field ID: 6373 Number of puzzles correctly solved	Imaging (subsample: N = 35,243)
Reaction time	Processing speed	Field ID: 20023 Mean time to correctly identify matches Field ID: 404[3] Duration to first press of snap-button in each round	Baseline (subsample: N = 496,590) Repeat (subsample: N = 20,254) Imaging (subsample: N = 47,878) Baseline (subsample: N = 493,160) Repeat (subsample: N = 20,265) Imaging (subsample: N = 47,926)
Symbol digit substitution	Processing speed, attention	Field ID: 23324 Number of symbol digit matches made correctly	Imaging (subsample: N = 35,264)

[a] Different cognitive tests may correlate with one another because they can measure the same cognitive domain or general cognitive ability. Definitions of associated cognitive domains to each test are according to Fawns-Ritchie and Deary (2020) and Lezak (2012).
[b] Baseline (N = 502,536), repeat assessment (N = 20,346), and/or imaging assessment visit (tot N = 37,102). Maximum sample size (N) for each cognitive assessment visit and test according to UK Biobank data Showcase: https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100026).
[c] Used only by Morys et al. (2021), Talboom et al. (2021).
[§] The Trail Making Test difference (TMT part B - part A) score removes the speed and completion time component from the evaluation of shifting ability; the Trail Making Test B/A ratio score (TMT part B/part A) better captures set-switching ability.

2.4. Study quality and risk of bias assessment

The Newcastle-Ottawa Scale (NOS) for cohort studies (Wells et al., 2000) and its version adapted for cross-sectional studies (Herzog et al., 2013) were used to assess the quality and risk of bias of each included study (longitudinal or cross-sectional, respectively) by two independent reviewers (GF and NRM) (Herzog et al., 2013). A maximum score of 9 points (NOS for cohort studies) or 10 points (NOS adapted for cross-sectional studies) could be assigned to a study. Studies with 0 to 4 points were deemed to be of unsatisfactory quality, 5 to 6 points to be of adequate quality, 7 to 8 points to be of good quality, and 9 to 10 points to be of very good quality. Regardless of the NOS score, all studies were considered for qualitative synthesis. Any disagreements were settled through consensus among reviewers.

3. Results

The initial literature search yielded 244 results; these articles were screened to determine whether they met the inclusion criteria. After removing 156 duplicates, the remaining 88 studies were screened for possible inclusion. After the title and abstract inspection, 28 studies were selected as potentially relevant to our research topic and their full texts were collected. Finally, after careful assessment of full texts and discussion between reviewers, 18 pertinent studies matching the inclusion criteria were identified and reviewed (Fig. 1). The quality of the included studies, according to the NOS assessment tool (Herzog et al., 2013; Wells et al., 2000), ranged from adequate to very good, indicating a low risk of bias (Table 2).

Results are reported in detail in the following paragraphs, grouping evidence regarding obesity, diabetes mellitus, and cardiovascular diseases and their related traits. With regard to diabetes mellitus, most of the studies included in this review did not make a clear distinction between type 2 diabetes mellitus and other (much less prevalent) types of diabetes, such as type 1 diabetes mellitus and gestational diabetes mellitus, among others. Only three reviewed studies (Garfield et al., 2021; Hagenaars et al., 2017; Whitelock et al., 2021) report having applied additional algorithms and/or filtering inclusion criteria in order to retain as cases mainly those with type 2 diabetes mellitus, for example by excluding cases diagnosed before a certain age or those that started insulin therapy soon after diagnosis (features more commonly associated with type 1 diabetes mellitus). However, despite the lack of clear distinguishing measures by the other studies, it should be taken into consideration that it has been reported that 90% of all confirmed cases of diabetes mellitus in the UK population are type 2 diabetes mellitus, about 8% are type 1 diabetes mellitus, and the other forms account for the remaining 2% (Whicher et al., 2020). Therefore, for practical and readability reasons, hereafter we will refer to findings involving either type 2 diabetes mellitus or diabetes mellitus not otherwise specified simply as 'diabetes'.

3.1. Obesity and related measures

BMI is the most used quantitative measure to diagnose and classify obesity. BMI was significantly associated with performance in several

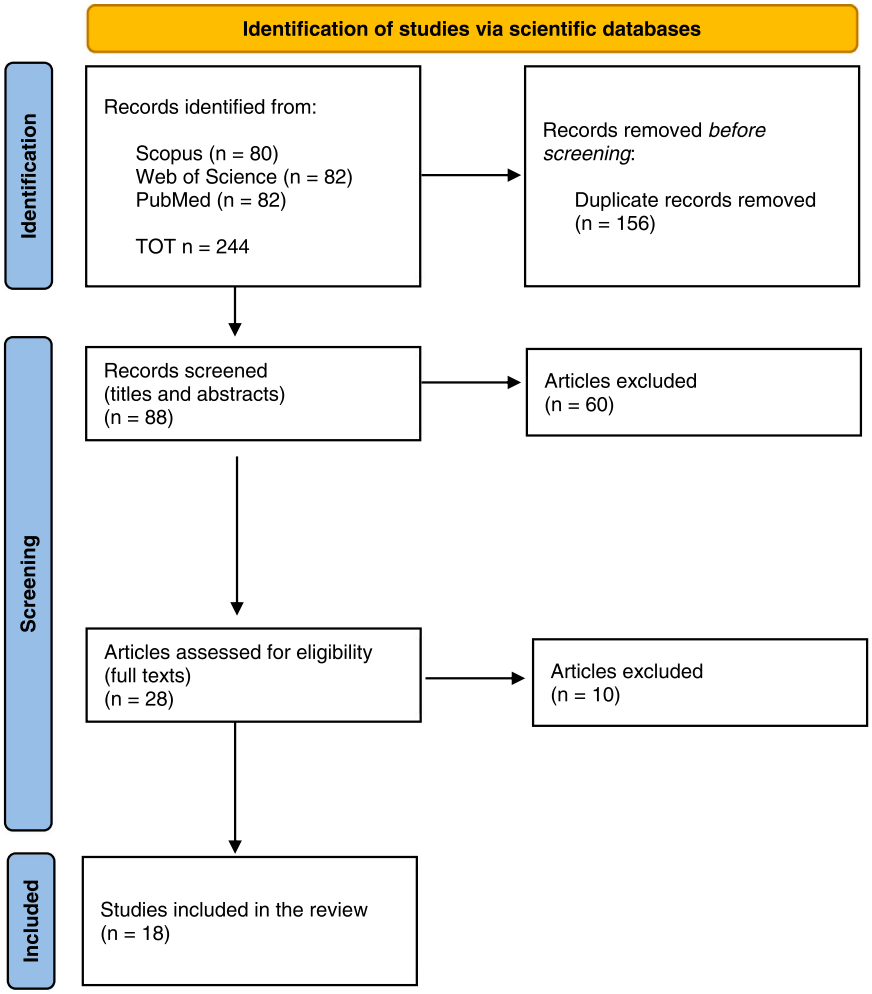

Fig. 1. PRISMA flow diagram of the systematic review process.

cognitive domains in the UK Biobank study. Higher BMI has been associated with worse performance on fluid intelligence (Ferguson et al., 2020; Hagenaars et al., 2017; Olivo et al., 2019, but not by Morys et al., 2021), numeric memory (Morys et al., 2021; Olivo et al., 2019), matrix pattern completion (Ferguson et al., 2020), trail making (i.e., higher Trail Making Test B/A ratio; Olivo et al., 2019), and symbol digit substitution tests (Ferguson et al., 2020). On the other hand, no association between BMI and prospective memory was found (Morys et al., 2021). Interestingly, the association between BMI and numeric memory was partially mediated (9%) by brain white matter hyperintensity (WMH) load (Morys et al., 2021). Similarly, the association between BMI and symbol digit substitution was found to be mediated (approximately 19%) by WMH, along with grey matter volume and a general factor of mean diffusivity (Ferguson et al., 2020).

Results were mixed for the association between BMI and slower reaction time, with one study finding an association (Ferguson et al., 2020), and another one not (Morys et al., 2021). Similarly, no consistent results were found regarding BMI and pairs matching and tower rearranging tests. While one study found increasing BMI associated with worse performance in the pairs matching test at the baseline assessment (Olivo et al., 2019), two studies examined the data collected during the imaging assessment visit, available only from a subset of participants, and found that BMI was associated with better performance on this test (Ferguson et al., 2020; Morys et al., 2021). Regarding the tower rearranging test, while one study found no association with BMI (Ferguson et al., 2020), another, using more limited sample size, found increasing BMI associated with better performance (Morys et al., 2021).

When BMI was used to categorise individuals, those with overweight (BMI: 25–29.9 kg/m^2) or obesity (BMI $\geq$ 30 kg/m^2) showed worse cognitive performance compared to normal-weight individuals (BMI: 18.5–24.9 kg/m^2). In particular, both overweight and obesity were associated with poorer performance on fluid intelligence, numeric memory, and pairs matching, while only obesity (but not overweight) was associated with worse performance on the trail making (Trail Making Test B/A ratio (Olivo et al., 2019)). Severe obesity (BMI $\geq$ 40 kg/m^2) was associated with worse performance on reaction time, Trail Making Test part B (but not part A), fluid intelligence, and symbol digit substitutions (Lyall et al., 2019). The presence of obesity, when combined with diabetes, hypertension, and frequent alcohol use, was associated with worse performance on the pairs matching task, and this association was found to be partially mediated by lower grey matter volume in the posterior cingulate cortex (Suzuki et al., 2019).

Considering other continuous obesity-related measures, increasing waist-to-hip ratio (WHR) has been associated with worse performance on fluid intelligence and numeric memory tasks, but no association was found with reaction time, prospective memory, pairs matching, and tower rearranging tasks (Morys et al., 2021). The authors suggested that the association between WHR and numeric memory and fluid intelligence were partially mediated by brain WMH load (7% and 12%, respectively). No association was found between WHR and a continuous latent variable representing executive function (i.e., predicting reaction time and pairs matching performances) (Veldsman et al., 2020). Body fat percentage, in turn, has been associated with worse numeric memory and better pairs matching performance, while no association was found

Table 2
Summary of included studies investigating the association of diseases and traits linked to IR and cognition in the UK Biobank study cohort.

Reference [Study Quality Assessment[a]]	Sample size[b] (and assessment time point)	Insulin resistance-related somatic phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Cross-sectional studies					
Feng et al. (2020) [***]	N = 42,392–133,439 (baseline)	Hypertension	Fluid intelligence, prospective memory, and numeric memory	Age, sex, Townsend deprivation index, alcohol use, smoking status, and educational qualifications	History of hypertension was associated with reduced performance in fluid intelligence, and in prospective and numeric memories.
Ferguson et al. (2020) [***]	N = 28,412 (imaging assessment visit)	BMI and SBP	Fluid intelligence, pairs matching, matrix pattern completion, symbol digit substitution, tower rearranging, and reaction time	Age, sex, assessment centres, Townsend deprivation index, self-reported medication (for dyslipidaemia, heart rate rhythm, oral contraceptive, or insulin), apolipoprotein ε4 genotype, ever-smoking, population stratification, and genotypic array	BMI was associated with reduced fluid intelligence, matrix pattern completion, symbol digit substitution, and reaction time performance, as well as with better pairs matching performance. SBP was associated with reduced intelligence and matrix pattern completion performances.
Garfield et al. (2021) [**]	N = 449,973 (baseline)	Diabetes (considering prediabetes, undiagnosed, and known diabetes status)	Reaction time and pairs matching	Age, sex, ethnicity, Townsend deprivation index, educational attainment, smoking status, BMI, baseline cardiovascular disease, and antihypertensive medication and statin use	Prediabetes, undiagnosed and known diabetes were associated with slower reaction time compared to normoglycaemia. Known diabetes was associated with better pairs matching performance.
Hagenaars et al. (2017) [**]	N = up to 36,035 (baseline)	BMI, SBP, CAD, and diabetes	Fluid intelligence	Age, sex, genetic batch and array, and population stratification	All somatic IR-related phenotypes tested were associated with worse performance on fluid intelligence.
Lyall et al. (2017) [**]	N = 158,631–474,129 (baseline)	Diabetes, CAD, and hypertension	Fluid intelligence, reaction time, and pairs matching	Age, sex, ethnicity, Townsend score, education, depression, smoking status, alcohol intake, cholesterol/blood pressure/insulin medication use, and BMI	Diabetes, CAD, and hypertension, alone or in comorbidity, were associated with worse fluid intelligence and reaction time performances. Non-comorbid CAD and comorbid CAD + hypertension and diabetes + hypertension (but not non-comorbid hypertension or diabetes) were associated with worse pairs matching performance. Overall, an increasing number of somatic IR-related diseases had an additive deleterious dose effect on the cognitive measures.
Lyall et al. (2019) [***]	N = 70,988–324,725 (baseline, for fluid intelligence and reaction time; imaging assessment, for TMT A and B, and symbol digit substitution)	Severe obesity (BMI ≥ 40)	Fluid intelligence, reaction time, TMT A and B, symbol digit substitution	Age, sex, genotypic array (also CAD, hypertension, diabetes, education, and Townsend deprivation index for the fully adjusted model)	Severe obesity was associated with worse reaction time, worse TMT part B, worse fluid intelligence, and worse symbol digit substitutions performances in the partially adjusted model; these associations were no longer significant after additional covariates (i.e., CAD, hypertension, diabetes, education - university college degree -, Townsend deprivation index) were added to the model.
Newby et al. (2021) [***]	N = 155,151–437,794 (baseline) N = 18,801–29,628 (imaging assessment visit)	Hypertension	Fluid intelligence, pairs matching, reaction time, difference between TMT part B and part A (TMT B–A), matrix pattern completion, symbol digit substitution, tower rearranging	Age, sex, education, ethnicity, assessment centres, BMI, smoking status, diabetes, hyperlipidaemia, and interactions between sex and age and age^2 (non-linear effects: sex * age and sex * age^2)	Hypertension was associated with worse performance on fluid intelligence (both on baseline and imaging assessment data), and on reaction time and pairs matching (only on baseline data) tests.

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Table 2 (*continued*)

Reference [Study Quality Assessment[a]]	Sample size[b] (and assessment time point)	Insulin resistance-related somatic phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Newby and Garfield (2022) [**]	N = 24,402–36,323 (imaging assessment visit)	Diabetes (irrespective of comorbidity status), non-comorbid diabetes and hypertension, and comorbid diabetes + hypertension	Fluid intelligence, pairs matching, reaction time, TMT B–A, matrix pattern completion, symbol digit substitution, and tower rearranging	Age, sex, Townsend deprivation index, educational attainment, ethnicity, smoking, BMI, hypertension, and high cholesterol	Diabetes was associated with worse performance on fluid intelligence, reaction time, TMT B–A, matrix pattern completion, and symbol digit substitution. Individuals with diabetes, both with and without comorbid hypertension, performed worse on reaction time and symbol digit substitution than individuals with non-comorbid hypertension or none of these diseases. Individuals with non-comorbid diabetes had better performance on fluid intelligence than individuals with comorbid diabetes + hypertension.
Olivo et al. (2019) [***]	N = 42,102–167,730 (baseline)	BMI, overweight, and obesity	Fluid intelligence, numeric memory, pairs matching, and TMT	Age, sex, education, ethnicity, smoking status, alcohol consumption, physical activity	Increasing BMI was associated with worse performance on fluid intelligence, numeric memory, pairs matching, and TMT. Overweight and obesity were associated with worse performance on fluid intelligence, numeric memory, and pairs matching tests, while only obesity (but not overweight) was similarly associated with TMT.
Shen et al. (2020) [**]	N = 19,364 (imaging assessment visit)	"Vascular burden" latent variable that included BMI, diabetes, hypercholesterolaemia, hypertension, and smoking	"Cognition" latent variable, that included fluid intelligence, pairs matching, reaction time, prospective memory, and numeric memory scores	Age, sex, Townsend deprivation index, education, ethnicity, and white matter hyperintensity	Vascular burden was no longer associated with the cognition latent variable after controlling for global efficiency (i.e., a measure of brain network integration). Mediation analysis further supports the (partially) mediating role of global efficiency in the relationship between vascular burden and cognition.
Suzuki et al. (2019) [**]	N = 8,312 (imaging assessment visit)	Number of following conditions present: obesity, diabetes, hypertension, and frequent alcohol use	Fluid intelligence, reaction time, and pairs matching	Age, sex, and ethnicity	Participants reporting the presence of all four conditions studied had worse performance on pairs matching test than those without any of those conditions; this association was partially mediated by lower grey matter volume in the posterior cingulate cortex.
Talboom et al. (2021) [**]	N = 158,245 (baseline)	Diabetes, stroke, and hypertension	Reaction time	Age, sex, diabetes, handedness, stroke, hypertension, smoking status, dizziness, educational attainment, and a first-degree family history of Alzheimer's disease	Diabetes, stroke, and hypertension were associated with slower reaction time.
van Gennip et al. (2021) [***]	N = 87,075 (baseline)	Diabetes	Reaction time and pairs matching	Age, sex, and education	Diabetes was associated with worse reaction time performance.
Veldsman et al. (2020) [**]	N = up to 22,059 (imaging assessment visit)	Diabetes, use of antihypertensive medication, use of cholesterol-lowering medication, WHR, and SBP	Continuous latent variable representing executive function (predictive of performance in the reaction time and the pairs matching tests)	Age and Townsend deprivation index	Diabetes, use of antihypertensive medication, and increasing SBP were associated with worse performance on the continuous latent variable.

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Table 2 (*continued*)

Reference [Study Quality Assessment[a]]	Sample size[b] (and assessment time point)	Insulin resistance-related somatic phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Whitelock et al. (2021) [**]	N = 47,468 (baseline)	Diabetes	fluid intelligence, reaction time, pairs matching, numeric memory, prospective memory	Age, sex, ethnicity, Townsend deprivation index, smoking status, alcohol consumption, physical activity, and antidiabetic medications use	Diabetes was associated with worse performance on numeric memory.
Longitudinal studies					
Garfield et al. (2021) [*]	N = 18,809 (for cognitive decline; repeat cognitive assessment)	Diabetes (considering prediabetes, undiagnosed, and known diabetes status)	Cognitive decline, which was derived from the follow-up assessment of the pairs matching task	Age, sex, years of education, and time between the two assessments	Prediabetes and known diabetes were associated with an increased risk of cognitive decline.
Klinedinst et al. (2019) [*]	N = 4,431 (baseline plus two additional assessments at 2-year intervals)	Visceral adipose mass, non-visceral adipose mass, and lean muscle mass	Fluid intelligence - changes in performance over a 6-year period	Education, socio-economic status (average total household income)	More visceral and non-visceral adipose mass independently predicted fluid intelligence decline, while more lean muscle mass predicted gains in fluid intelligence performance over time.
Li et al. (2020) [**]	N = 1,175 (baseline, 5-year follow-up and imaging assessment visit)	Cardiovascular disease and diabetes	Reaction time intraindividual variability	Age, sex, BMI, lifestyle factors (smoking, alcohol, fruit/vegetables consumption), socio-economic factors (employment, education, ethnicity, income)	The model including 'diabetes and cardiovascular diseases' had a significant, although weak, performance in predicting reaction time intraindividual variability over time.
Morys et al. (2021) [*]	N = 6,803–17,094 (baseline, for obesity and blood measures; imaging assessment visit, for cognitive tests)	BMI, WHR, and body fat percentage	Fluid intelligence, pairs matching, reaction time, numeric memory, tower rearranging, and prospective memory	Age, sex, average household income, Townsend deprivation index, education, depression, frequency of drinking alcohol, physical activity, and smoking status	BMI associated with worse numeric memory, and better pairs matching and tower rearranging test performances. WHR was associated with worse fluid intelligence and numeric memory performances. Body fat percentage was associated with worse numeric memory and better pairs matching performances.

Abbreviations: body mass index (BMI), coronary artery disease (CAD), diastolic blood pressure (DBP), glycated haemoglobin (HbA1c), high-density lipoprotein (HDL), insulin resistance (IR), systolic blood pressure (SBP), trail making test (TMT), waist-to-hip ratio (WHR).

[a] Study Quality Assessment according to the Newcastle-Ottawa Scale (NOS) for cohort studies (Wells et al., 2000) or its adapted version for cross-sectional studies (Herzog et al., 2013): *** indicates very good (9–10 points), ** indicates good (7–8 points), and * indicates adequate (5–6 points) qualities.

[b] For some studies, the sample size is presented as a range instead of a single numeric value. This can happen due to the varying number of participants that completed each individual cognitive task. See the Section 1 for a more detailed description of the cognitive assessment procedure in UK Biobank.

with fluid intelligence, reaction time, prospective memory, and tower rearranging (Morys et al., 2021). The associations found with body fat percentage were found to be partially mediated (9%) by WMH load.

Adipose mass is another quantitative measure related to obesity. A longitudinal study found that more visceral and non-visceral adipose mass independently predicted a decline in fluid intelligence performance over a period of six years, both in men and women (Klinedinst et al., 2019). Conversely, the presence of greater lean muscle mass favoured gains in fluid intelligence across time. Interestingly, they showed important immune system-related mediation effects as the association between visceral adipose mass and fluid intelligence was either partially (men) or fully (women) mediated by changes in leukocyte subpopulation counts (Klinedinst et al., 2019).

3.2. Diabetes and related measures

Diabetes has been associated with worse performance on fluid intelligence, both at baseline (Lyall et al., 2017) and on follow-up data from the imaging assessment visit (Newby and Garfield, 2022). Others, however, did not find such an association (Whitelock et al., 2021). Intriguingly, when comorbidity with hypertension was considered, individuals with only diabetes had worse performances on fluid intelligence than those with comorbid diabetes and hypertension (Newby and Garfield, 2022).

Diabetes has also been repeatedly associated with slower reaction time (Garfield et al., 2021; Lyall et al., 2017; Talboom et al., 2021; van Gennip et al., 2021), although this was not always the case (Whitelock et al., 2021). These results were shown to be independent of possible confounders, such as socio-economic and demographic variables, depression, medications use, and BMI (Garfield et al., 2021; Lyall et al., 2017). Furthermore, diabetes has also been associated with worse performance on a latent executive function continuous variable, representing reaction time and pairs matching test scores (Veldsman et al., 2020). In addition to participants with known diabetes (i.e., self-reported, diagnosed by a doctor and/or hypoglycaemic medications use), those classified with either prediabetes (i.e., HbA1c $42 \leq 48$ mmol/mol) or undiagnosed diabetes (i.e., HbA1c ≥ 48 mmol/mol) at baseline also showed slower reaction time than normoglycaemic participants (i.e., HbA1c ≥ 35 and <42 mmol/mol; Garfield et al., 2021). The association between diabetes and worse reaction time performance has been replicated using data from the imaging visit assessment and individuals with comorbid diabetes+hypertension showed worse performance than individuals with non-comorbid hypertension or neither diabetes nor hypertension (Newby and Garfield, 2022). Noteworthy, another study showed that the higher the number of cardio-metabolic risk variables found within the normal ranges (i.e., HbA1c, blood pressure, and BMI), the least reaction time impairment difference was found between individuals with and without diabetes (van Gennip et al., 2021). A machine learning approach was used to examine whether diabetes and cardiovascular disease could predict

reaction time intraindividual variability (RT-IIV) over time (i.e., across baseline and two follow-up assessments). This was considered a sensitive measure of cognitive change over time, with greater RT-IIV used as an indicator of longitudinal cognitive decline. Although it was outperformed by alternative models whose variables captured psychiatric phenotypes (i.e., anxiety and depression models, with an area under the curve (AUC) of 0.68 and 0.63, respectively), the 'diabetes and cardiovascular' model showed a significantly better classification performance than randomness (AUC = 0.60; Li et al., 2020).

The results about the relationship between diabetes and the pairs matching test, however, have been less consistent. While some reported an association between known diabetes and better baseline performance on this test (Garfield et al., 2021), others found an association with worse performance only when diabetes was comorbid with hypertension (no association otherwise) (Lyall et al., 2017), and others reported no association in smaller sample sizes from baseline (van Gennip et al., 2021; Whitelock et al., 2021) or imaging assessment visit data (see Table 2) (Newby and Garfield, 2022).

Interestingly, the same study that showed an outperformance of individuals with diabetes in the pairs matching task at baseline, further combined this data with the scores obtained during the UK Biobank follow-up assessment to address cognitive decline (i.e., measured by regressing the follow-up scores on the baseline scores). This longitudinal analysis indicated that participants with prediabetes and known diabetes might be subject to a faster deterioration rate of pairs matching abilities than normoglycaemic individuals, suggesting a higher risk for cognitive decline (Garfield et al., 2021).

Using baseline data, Whitelock et al. (2021) found that participants with diabetes showed worse performance on numeric memory compared to those without diabetes, while they did not differ in terms of prospective memory performance. No differences between those with and without diabetes at the imaging assessment visit were found on tower rearranging performance either (Newby and Garfield, 2022).

At the imaging assessment visit, participants with diabetes performed worse on symbol digit substitution, trail making (i.e., Trail Making Test B–A), and matrix pattern completion than those without diabetes (Newby and Garfield, 2022). When comorbidity with hypertension was considered, both the group of participants with only diabetes and those with comorbid diabetes+hypertension performed worse on symbol digit substitution compared to those with only hypertension or none of these diseases (Newby and Garfield, 2022). Interestingly, when cardiovascular confounders were considered (i.e., smoking, BMI, hypertension, high cholesterol), the associations between diabetes and worse cognitive performance were attenuated, in particular matrix pattern completion and symbol digit substitution performances (Newby and Garfield, 2022). On this note, others have shown that the association between diabetes and cognitive performance was partially mediated (between 10% and 59%) by cardiovascular diseases (i.e., hypertension, thromboembolism, stroke, coronary artery disease (CAD)), depressive symptoms, and to a lesser extent by visceral obesity (i.e., WHR), possibly via immune-inflammatory dysregulation that is commonly present in each of these three conditions (Whitelock et al., 2021).

Lastly, the effect of diabetes and other cardio-metabolic diseases on cognition was found to be additive, meaning that an increasing number of concomitant cardio-metabolic diseases was associated with greater cognitive impairment (Lyall et al., 2017). Furthermore, a latent variable composed of BMI, diabetes, hypercholesterolemia, hypertension, and smoking, was found to be associated with a cognition latent variable (composed of fluid intelligence, pairs matching, reaction time, prospective memory, and numeric memory scores). However, this association was no longer significant after controlling for brain global efficiency, a measure of brain network integration (Shen et al., 2020). Further investigation through mediation analysis supported the (partially) mediating role of global efficiency in the relationship between vascular burden and cognition (Shen et al., 2020).

3.3. Cardiovascular diseases and traits

CAD, defined as (self-reported) presence of angina and/or myocardial infarction diagnosis, was associated with poorer performance on the fluid intelligence (Hagenaars et al., 2017; Lyall et al., 2017), pairs matching, and reaction time tests (Lyall et al., 2017). These associations remained significant independently from the presence of other cardio-metabolic diseases (i.e., diabetes and/or hypertension) and after the adjustment for socio-economic and demographic variables, depression, medication use, and BMI (Lyall et al., 2017). In addition, stroke was also associated with worse processing speed on the reaction time test (Talboom et al., 2021).

Hypertension has also been repeatedly associated with worse cognitive performance. Although hypertension may have diverse underlying pathophysiology, it has been estimated that 60–70% of hypertension cases during adulthood may be directly attributed to adiposity and IR (Jameson et al., 2018). Furthermore, IR has been shown to contribute to hypertension by impairing vascular peripheral resistance and endothelial function (Mancusi et al., 2020). A history of hypertension (i.e., self-reported having previously received hypertension diagnosis by a doctor) has been associated with poorer performance in fluid intelligence (Lyall et al., 2017) and slower reaction time (Lyall et al., 2017; Talboom et al., 2021). Regarding the pairs matching task, no association was found with a history of non-comorbid hypertension, but associations with worse performance were observed when hypertension was comorbid with either diabetes or CAD (Lyall et al., 2017). When taking multiple combined measures to define hypertension (i.e., SBP $\geq$ 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg and/or use of blood pressure medication and/or self-reported history of a hypertension diagnosis by a doctor), results replicated the associations with fluid intelligence and reaction time and in turn also revealed an association with worse performance on the pairs matching task (Newby et al., 2021). However, no association was found with symbol digit substitution, matrix pattern completion, tower rearranging, and trail making (difference between Trail Making Test part B and part A) tasks, for which data was acquired during the imaging assessment visit and thus was only available from a subset of UK Biobank participants (Newby et al., 2021). Data from hospital admission records for hypertension treatment has also been used to classify UK Biobank participants regarding hypertension. A history of hospitalisation for hypertension treatment was associated with lower fluid intelligence scores, corroborating previous findings. Additionally, it was associated with reduced prospective and numeric memories (Feng et al., 2020). Of note, this association with prospective memory was found to be partially mediated by reduced brain functional connectivity, which explained 11.5% of the association between hypertension and these cognitive task results (Feng et al., 2020).

When assessing the effect of systolic blood pressure as a continuous measure rather than a dichotomous hypertension diagnosis, higher SBP was associated with lower fluid intelligence (Ferguson et al., 2020; Hagenaars et al., 2017) and matrix pattern completion (Ferguson et al., 2020) scores, while no significant association was found with reaction time, symbol digit substitution, tower rearranging, and pairs matching tests (Ferguson et al., 2020). It was suggested that the association between SBP and fluid intelligence was, at least partially, mediated by differences in brain morphometry and connectivity/integrity (Ferguson et al., 2020). Furthermore, increasing SBP was associated with a graded reduction in performance on a continuous latent variable representing executive function (i.e., corresponding to reaction time and pairs matching tasks) in participants not taking antihypertensive medication (Veldsman et al., 2020). This was especially true for mid-aged participants (44–69 years) and less so for older ones (> 70 years). For the participants taking antihypertensive medications (which can be considered as a proxy for hypertension diagnosis), however, executive performance was stable for the SBP range < 140 mmHg, while increasing SBP above this threshold was associated with a decline in

performance (Veldsman et al., 2020).

4. Discussion

This systematic literature review aimed to summarise previous evidence on the relationship between somatic diseases and traits linked to insulin resistance and cognitive performance across several domains based on studies conducted in the large population-based UK Biobank study cohort. Overall, we found substantial evidence for an association between IR-related cardio-metabolic diseases and traits and general worse performance on various cognitive domains, which was largely independent of possible confounding factors, such as general socio-economic and demographic factors and the use of medications.

4.1. Worse fluid intelligence performance consistently associated with IR-related diseases/traits

The most consistent finding across studies within the UK biobank cohort is the association between the presence of IR-related diseases and traits with worse performance on fluid intelligence. This test was designed to evaluate verbal and numerical reasoning, which refers to the ability to derive logical inferences and solve novel problems through evaluation, abstraction, and integration of information and hypothesis testing. Fluid intelligence was initially assessed on a subsample of UK Biobank participants at baseline, with follow-up assessments at different time points. Despite encompassing a smaller sample size compared to other tasks (Table 1), it shows largely consistent findings for all the IR-related phenotypes reviewed (i.e., obesity, diabetes, cardiovascular disease, and their related traits), independent of the methods and corrections for confounders applied. Verbal and numerical reasoning have been linked to the activity of the dorsolateral and medial prefrontal cortex (which is part of the frontal lobe) and the posterior parietal cortex in previous studies in samples other than UK Biobank (Kolb and Wishaw, 2012). In line with this evidence, Ferguson and colleagues reported a mediating effect of frontal lobe volumes in the association between high SBP and poor verbal and numerical reasoning (Ferguson et al., 2020). Noteworthy, impairment in this cognitive domain has been associated with higher psychopathological severity across psychiatric disorders, a recent diagnosis of specific phobia, bipolar disorder and impulse-control disorders among adolescents (Keyes et al., 2017), and depressive symptoms in elderly individuals (Murray et al., 2013). Moreover, fluid intelligence deficits significantly contribute to worse performance in executive tasks among patients with Parkinson's disease, fronto-temporal dementia, and schizophrenia (Roca et al., 2014).

4.2. Slower reaction time also associated with IR-related phenotypes

Similarly, the associations between IR-related phenotypes and slower reaction time have been quite consistent in the UK Biobank literature. The reaction time task constitutes one of the tasks with the largest sample size in the UK Biobank, being assessed in the whole baseline cohort, in addition to the follow-up assessments. The reaction time task measures processing speed, which is the ability to quickly perform a variety of cognitive, perceptual, and motor processes, whose impairment has been linked to white matter integrity (Papanicolaou, 2017). Processing speed deficit is an important characteristic of Parkinson's disease and several psychiatric disorders, such as autism spectrum disorder, mood disorders, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, obsessive-compulsive disorder, and panic disorder (Millan et al., 2012), which in turn have been shown to overlap (clinically and genetically) with IR-related somatic diseases (Fanelli et al., 2022; Wimberley et al., 2022).

4.3. Better pairs matching performance: a counterintuitive finding?

A less consistent but perhaps more intriguing finding concerns the associations of IR-related somatic phenotypes with better performance on the pairs matching test, which was assessed at baseline for the whole cohort and included in all cognitive reassessments. The pairs matching test assesses visual short-term memory, which is the ability to retain information from a visual stimulus for a short period of time after the stimulus has ceased, allowing the comparison of perceptual information of objects separated in time and space (Hollingworth and Luck, 2008). Impairment in visual memory is a typical characteristic of Alzheimer's disease, and it is also commonly present in ADHD, although it has been less strongly reported in other neuropsychiatric disorders (Millan et al., 2012). The seemingly counterintuitive association with pairs matching outperformance was found for higher BMI (Ferguson et al., 2020; Morys et al., 2021), body fat percentage (Morys et al., 2021), and diabetes (Garfield et al., 2021). Although others have not replicated these findings (see the Results section), the repeated association of IR-related diseases and traits with better cognitive performance seems to be unique for pair matching, but a pathophysiological explanation behind such finding does not appear to be obvious at present. Noteworthy is the fact that the pairs matching task did not present a good test-retest reliability between baseline and a repeat assessment (in a subsample of 20,000 participants) about four years apart (Lyall et al., 2016). Furthermore, an intriguing finding arises from a longitudinal study showing that, despite a baseline association with better performance on this test, individuals with diabetes had a steeper decline in performance on follow-up assessment compared to individuals without diabetes (Garfield et al., 2021).

4.4. Possible underlying mechanisms linking IR and cognition

Several mechanisms have been suggested as possibly underlying the link between IR and cognition, including the insulin modulation of some neurotransmitter systems (among others, the cholinergic and glutamatergic systems, which have a major role in cognition), immune-inflammation and oxidative stress, and altered hypothalamus-pituitary axis function (Butterfield and Halliwell, 2019; De Felice et al., 2022). In particular, insulin has been implicated in the modulation of synaptic plasticity and memory through its effects on the expression and presentation of glutamatergic receptors on the plasma membrane (De Felice et al., 2022). Furthermore, insulin is responsible for glucose uptake in the hippocampus and some cortical areas through the membrane translocation of glucose transporter type 4 (GLUT4) (Koepsell, 2020), whose inhibition was shown to hinder the procognitive action of insulin on working memory in rats (De Felice et al., 2022). It is also important to consider that obesity and diabetes lead to a state of systemic inflammation with an increase in proinflammatory cytokines that is also reflected in the brain (Lyra et al., 2019). Here, microglia activation results in the production of proinflammatory cytokines, such as interleukin (IL)-6, tumour necrosis factor-α, IL-1β, which may interfere with insulin signalling (Kullmann et al., 2016). Interestingly, a UK Biobank study showed that the association between fluid intelligence and lean muscle or visceral adipose mass was mediated by the levels of different leukocyte subpopulations (Klinedinst et al., 2019). It has also been suggested that accumulation of amyloid-β oligomers, which is a hallmark of Alzheimer's disease neuropathology, may lead to cognitive impairment through defective brain insulin signalling (Tumminia et al., 2018). Animal studies have shown that impairments in insulin signalling following intracerebroventricular infusion of amyloid-β oligomers were accompanied by memory deficits in several behavioural tasks. In turn, IR may accelerate amyloid-β production and brain accumulation (Tumminia et al., 2018). IR may also result in microcirculation damage and atherosclerosis, leading to brain reduced oxygen supply and tissue suffering, as also revealed by the widespread white matter and functional connectivity alterations, as well as the regional brain volumes variations seen in individuals with diabetes or obesity, also in UK Biobank (Ferguson et al., 2020; Garfield et al., 2021; Hsu et al., 2012; Morys et al., 2021; Suzuki et al., 2017). These neuroimaging correlates and

cardiovascular alterations may mediate the relationship between IR and worse cognitive performance, as repeatedly reported by some authors (Feng et al., 2020; Ferguson et al., 2020; Morys et al., 2021; Suzuki et al., 2017; Whitelock et al., 2021). In fact, recent studies further suggest that white matter integrity may mediate the link between cognitive performance and both variations in HbA1c levels (Repple et al., 2021) and genetic liability to type 2 diabetes mellitus (Repple et al., 2022).

Interestingly, one study in the UK Biobank also suggested that depressive symptoms may mediate the relationship between diabetes and cognitive function (Whitelock et al., 2021). Of note, depression and diabetes are both predisposing factors for each other, and common molecular pathways have been proposed (Nguyen et al., 2018). In addition, oral hypoglycaemic medications used in diabetes, such as liraglutide, have shown clinical usefulness in improving cognitive function in people with depression (Fanelli and Serretti, 2022). As a result, it is possible to speculate that biological factors common to diabetes and depression may have an influence on cognition.

4.5. Strengths and limitations

This review should be considered in light of clear strengths and limitations. The UK Biobank represents the largest population-based cohort where both cognitive measures and IR-related somatic diseases and traits have been deeply phenotyped. While large-scale Danish/Scandinavian population-based registries include information on clinical diagnoses and prescribed medication to identify cardio-metabolic and psychiatric conditions, they do not contain information on cognitive measures (Schmidt et al., 2019) or only do so for a very limited subsample derived from smaller clinical/follow-up studies on specific patient groups (e.g., patients with dementia or diabetes) that are then linked to national registries (Fereshtehnejad et al., 2015; Wium-Andersen et al., 2019). The richness of the phenotypes measured in UK Biobank allows going beyond clinical comparisons and addressing the full spectrum of phenotypes as a continuum in the general population. In order to allow cognitive assessment of an unprecedented number of individuals under the same protocol, some of the most widely used and clinician-rated cognitive instruments were specifically adapted for the UK Biobank study. Thus, a possible limitation is that the cognitive measures under the UK Biobank protocol were obtained by concise, unsupervised touchscreen assessments and not under traditional standardised conditions (Sudlow et al., 2015). It is important, however, to also weigh in as a clear strength of this approach the possibility of addressing several facets of cognition in a short period of time and that, despite the adapted nature of this protocol, the UK Biobank tests showed overall good validity, demonstrating moderate-to-high test-retest reliability and substantial correlation with the reference tests from which they were derived (Fawns-Ritchie and Deary, 2020). However, it is worth considering that the UK Biobank sample population was recruited on a voluntary basis and is not fully representative of the general UK population. In fact, participants were generally healthier, less likely to smoke or consume alcohol, and resided in less socio-economically deprived areas than non-participants (Fry et al., 2017). Nevertheless, because of its large sample size and variety of exposure measurements, it can still provide valid scientific inferences about the link between exposures and health outcomes that are generalisable to other populations (Fry et al., 2017). Another possible point of attention is that the derivation of the diabetes phenotype was heterogeneous across studies, sometimes pooling type 1 and type 2 diabetes mellitus, or even other types of diabetes, which have partially or entirely different aetiopathogenetic mechanisms. This may have added noise to the results of individual studies, contributing to some of the inconsistent findings described in this review. Last but not least, the study design was cross-sectional in most of the reviewed studies, limiting any interpretation of a temporal and/or causal link between IR-related diseases and cognitive changes. Cardio-metabolic diseases may have a deleterious impact on cerebral blood flow and, consequently, on cognitive function, while individuals with poorer cognitive abilities may be less likely to engage in healthy lifestyles and behaviours that prevent cardio-metabolic diseases. Although a causal relationship between IR-related cardio-metabolic diseases and impaired cognitive function is likely, data from the UK Biobank calls for caution for the time being. Studies on independent cohorts are required to clarify any causal relationship.

4.6. Directions for future research

In addition to focusing on better understanding the causal relationship between cognitive impairment and cardio-metabolic diseases linked to IR, both at the genomic and clinical levels, future research should also examine the potential contribution of immune-inflammatory, oxidative, and central insulin signalling mechanisms. Genomic research examining the pleiotropic effect of genes implicated in insulin signalling, immune-inflammation, and HPA axis modulation on both cognition and IR-somatic diseases might aid in unravelling the mechanisms behind the phenotypic associations highlighted in this review. Additional studies are also needed to further investigate the possible underlying mechanisms (and/or alternative explanations) for the seemingly counterintuitive findings associating IR-related conditions and better performance on visual memory tasks. Functional analyses, possibly including (animal) modelling, could provide further answers to the underlying pathological mechanisms involved in the differential effects observed for specific cognitive domains. Future research could benefit from a more homogeneous classification of participant diagnostic groups (e.g., better distinction between type 2 diabetes mellitus cases from those with other types of diabetes) to allow better interpretation of the findings and/or uncovering of possible underlying biology. Furthermore, despite the lack of clear knowledge on the causal relationship between IR-related conditions and cognitive performance nor the identification of (possible) shared underlying factors so far, growing evidence suggests a potential future use of hypoglycaemic drugs, such as metformin, proliferator-activated receptor-γ (PPAR-γ) agonists, and glucagon-like peptide 1 receptor agonists (GLP1RA), in the treatment of cognitive deficits seen in various neuropsychiatric disorders (Fanelli and Serretti, 2022; Zhang et al., 2020). However, large-scale randomised clinical trials are required to confirm their safety and efficacy, which could possibly also inform on the shared pathophysiological mechanisms. Cognitive impairment is still one of the most challenging symptom domains to tackle with available pharmacological therapy (Fanelli and Serretti, 2022). As a result, gaining a deeper understanding of the processes underlying the reported links between IR and cognitive impairment will be critical in identifying potential new targets for pharmacological and/or behavioural intervention in patients with neuropsychiatric disorders.

5. Conclusion

In conclusion, this literature review of UK Biobank studies found substantial evidence for an association between an overall worse performance on various cognitive domains and cardio-metabolic traits and diseases related to insulin resistance, such as obesity, type 2 diabetes mellitus, hypertension, and CAD, in the general adult population. The most consistent findings are related to a detrimental influence on measures of verbal and numerical reasoning, as well as processing speed, while results for visual short-term memory have been mixed or indicated enhanced performance. It has been suggested that these associations might be mediated by alterations in immune-inflammation or white matter integrity/connectivity or brain volumes. Considering the worldwide increasing levels of multimorbidity and public health concerns about rising rates of cognitive decline, our findings offer important suggestions for future research in this crucial field and draw the attention of clinicians to the importance of primary and secondary prevention in people with cardio-metabolic diseases.

Declarations of interest

AS is or has been consultant/speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boheringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. BF discloses having received educational speaking fees from Medice GmbH. CF was a speaker for Janssen. GP is director of Drug Target ID (DTID), Ltd. All other authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104927.

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