PRIME

Prevention and Remediation of Insulin Multimorbidity in Europe

H2020 – 847879

D1.2.– Report on the association of compulsive traits and/or cognitive rigidity with insulin signalling markers and/or somatic insulin-related disorders in participants of the UK Biobank

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Abbreviations

AUC	Area under the curve
BMI	Body mass index
CAD	coronary artery disease
HDL	high-density lipoproteins
LDL	low-density lipoproteins
RT	Reaction time
T2DM	Type 2 diabetes mellitus
WHR	waist-to-hip ratio

Table of Contents

1. Executive Summary

In PRIME we are interested in investigating whether altered insulin signaling may be a key mechanism underlying the multimorbidity of somatic insulin-related disorders and mental disorders and traits. In WP1 we are investigating the prevalence of these multimorbidities and traits. For this specific task, we sought to investigate the association of highly prevalent somatic insulin-related conditions that cause considerable health and socioeconomic burden, such as obesity, type 2 diabetes mellitus (T2DM), cardiovascular disease, and metabolic syndrome, with cognitive traits in participants of the UK Biobank study, a very large (N~500k) and information-rich population-based cohort. Given the availability of several individual published studies assessing the link between different facets of insulin resistance and the performance on distinct cognitive tasks in the UK Biobank, our aim was to review the previous literature in order to provide an overall view of the association findings involving somatic insulin-related conditions and cognitive traits in participants of the UK Biobank study. For this task we performed a search on PubMed (August 2021) using a list of key-words for several diseases/traits related to insulin resistance and cognitive traits, as well as the UK Biobank cohort, as query for title and/or abstract of indexed publications. The literature search yielded 68 publications, of which eleven were deemed suitable for this review. We found that there is ample evidence associating cardio-metabolic diseases and traits and general worse performance on various cognitive domains. This effect seems to be independent of the use of medications and possible socio-economic and demographic confounding factors. Possible mediating roles of depressive symptoms and brain structural and connectivity/integrity factors have been suggested, as well as potential implication of immune-inflammation markers.

2. Deliverable report

An electronic search of the literature was conducted to identify studies that have investigated the relationship between insulin-related traits/disease and cognition in the population-based UK Biobank cohort. The Medline/PubMed database was searched for paper published until August 2021. We used search terms related to insulin-related traits and diseases as well as terms related to the neuropsychological tasks used to measure several cognitive domains in the UK Biobank. We also added "UK biobank", "UKb", and "UKbb" as search terms in order to restrict to studies conducted using the UK biobank cohort. Two reviewers (GF and NRM) independently screened the results obtained through the search query to identify potentially relevant studies. Studies were included if they investigated the relationship between cognition and insulin resistance-related traits/diseases in the UK biobank cohort.

Results

The initial literature search yielded 68 results. After independent inspection by two researchers, 11 pertinent studies were identified and reviewed. The main overall findings are presented below.

Obesity and obesity-related measures

Higher body mass index (BMI), a quantitative measure used to diagnose and categorize obesity, was significantly associated with worse cognitive performance in processing speed, short-term memory, verbal-numerical and nonverbal reasoning, and executive functions (Haagenaars et al.,2017, Olivo et al., 2019, Ferguson et al., 2020). Individuals diagnosed with overweight (BMI: 25 kg/m2 to 29.9 kg/m2) and obesity (BMI≥ 30 kg/m2) showed worse cognitive performance compared to normal weight individuals (BMI: 18.5 kg/m2 to 24.9 kg/m2) (Olivo et al., 2019). Furthermore, the association between BMI and executive function was found to be partially mediated by specific structural brain variations (Ferguson et al., 2020). A subsequent study found that obesity affects systemic inflammation, diabetes, dyslipidemia and hypertension, which in turn mediate the negative association of obesity and

obesity-related measures with markers of cerebrovascular disease and brain morphometry, which ultimately mediate the link between obesity and cognitive dysfunction (Morys et al., 2021). Despite the above associations, psychiatric disorders such as depression and anxiety, remain better predictors of cognitive ability (area under the curve (AUC) of 0.63-0.68) than cardiometabolic diseases (AUC of 0.56-0.60) (Li et al., 2020).

Diabetes

Diabetes mellitus was associated with worse performance in several cognitive domains (e.g. fluid intelligence, reaction time, and visual and numeric memory) (Lyall et al., 2017; Hagenaars et al., 2017, Talboom et al 2021, Whitelock et al., 2021). These effects were independent of depression, socioeconomic and demographic variables, medication use and BMI (Lyall et al., 2017). Prediabetes (HbA1c=42-48 mmol/mol) and type 2 diabetes (T2DM) have also been shown to elevate the risk of cognitive decline over time and were associated with higher white matter hyperintensity and lower hippocampal volumes (Garfield et al., 2021). The association between T2DM and cognitive performance was found to be partially mediated (10-59%) by cardiovascular disease (i.e., hypertension, thromboembolism, stroke, coronary artery disease (CAD)), depressive symptoms, and to a lesser extent by visceral obesity (Whitelock et al., 2021).

Metabolic syndrome and cardiovascular disease

Metabolic syndrome is characterized by a cluster of at least three conditions including increased waist-to-hip ratio (WHR), hypertension, hyperglycaemia, hypertriglyceridemia, and low HDL cholesterol levels. Increased WHR was associated negatively with working memory and fluid intelligence (Morys et al., 2021). A history of hypertension (i.e. average systolic blood pressure - SBP >=140 mmHg and diastolic blood pressure - DBP >=90) and CAD were also linked to poorer performance in fluid intelligence, reaction time, and visual and numeric memory (Lyall et al., 2017, Feng et al., 2020, Talboom et al., 2021). The association between hypertension and numeric memory was partially mediated by reduced functional connectivity of the hippocampus and, to a lesser extent, other areas of the cortex (Feng et al., 2020).

Consistently, when taken as a continuous measure, higher SBP was associated with worse executive functions (Veldsman et al 2020) and verbal–numerical reasoning (Hagenaars et al., 2017, Ferguson et al., 2020) and a mediating role of alterations in brain morphometry and integrity was highlighted for the latter association (Ferguson et al., 2020).

3. Conclusion

The present review aimed to summarize previous evidence on a possible relationship between somatic diseases/traits linked to insulin-resistance and cognition from studies conducted in the large population-based cohort from the UK Biobank study. Overall, there is consistent evidence of a general negative influence of cardio-metabolic diseases and traits on various cognitive domains, which is independent of the use of medications and possible socio-economic and demographic confounding factors. Some studies indicate that these associations could be partially mediated by alterations in brain morphometry and connectivity/integrity and/or depressive symptoms while others suggest a possible role of immune-inflammation markers.

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