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RESEARCH PAPER

The brain insulin receptor gene network and associations with frailty index

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Abstract

Objective: To investigate longitudinal associations between variations in the co-expression-based brain insulin receptor polygenic risk score and frailty, as well as change in frailty across follow-up.
Methods: This longitudinal study included 1605 participants from the Helsinki Birth Cohort Study. Biologically informed expression-based polygenic risk scores for the insulin receptor gene network, which measure genetic variation in the function of the insulin receptor, were calculated for the hippocampal (hePRS-IR) and the mesocorticolimbic (mePRS-IR) regions. Frailty was assessed in at baseline in 2001–2004, 2011–2013 and 2017–2018 by applying a deficit accumulation-based frailty index. Analyses were carried out by applying linear mixed models and logistical regression models adjusted for adult socioeconomic status, birthweight, smoking and their interactions with age.
Results: The FI levels of women were 1.19%-points (95% CI 0.12–2.26, $P = 0.029$) higher than in men. Both categorical and continuous hePRS-IR in women were associated with higher FI levels than in men at baseline ($P < 0.05$). In women with high hePRS-IR, the rate of change was steeper with increasing age compared to those with low or moderate hePRS-IR ($P < 0.05$). No associations were detected between mePRS-IR and frailty at baseline, nor between mePRS-IR and the increase in mean FI levels per year in either sex ($P > 0.43$).
Conclusions: Higher variation in the function of the insulin receptor gene network in the hippocampus is associated with increasing frailty in women. This could potentially offer novel targets for future drug development aimed at frailty and ageing.

Keywords: insulin receptor (IR), frailty, hippocampal (hePRS), frailty index (FI), insulin receptor, older people

Key Points

- Frailty index levels of women in late adulthood are higher than men.
- Higher variation in the function of the insulin receptor gene network is associated with increasing frailty index in women.
- This is indicative of an increased state of frailty and a more pronounced incline in frailty progression.

Introduction

As the body ages, there is a gradual decline in the physiological reserve. In frailty, this decline is accelerated, which leads to failure of the homeostatic mechanisms [1]. Frailty constitutes a state of enhanced vulnerability resulting from an ageing-associated, multisystem decline in reserve and function, compromising the ability to cope with every day or acute stressors [2]. According to estimations, around 10% of people older than 65 years and about 25–50% of people older than 85 years are frail [3], and this prevalence is rising [4]. As frailty and co-morbidity go hand in hand [5], frail individuals exploit a significant amount of health care resources, thus increasing the economic burden [6].

A consensus is yet to be reached regarding the definition of frailty; however, two approaches are most commonly applied. Frailty has been defined as a phenotype consisting of five indicators: unintentional weight loss, slow gait speed, reduced grip strength, exhaustion and physical inactivity [7]. Although this definition is important and offers stronger clinical reproducibility [8], the use of a frailty index (FI) of deficits captures the risk of adverse outcomes more accurately [9]. In a study comparing the two approaches, the FI identified a greater number of individuals as frail, indicating its potential to offer improved discrimination within the lower to middle range of the frailty continuum [10]. The FI score is based on accumulation of health deficits with increased score representing increased frailty.

Frailty arises as a result of multiple interrelated physiological systems. A review identified six biological processes related to frailty [11]: (i) brain changes, more accurately reduction of grey matter and brain-derived neurotrophic factors; (ii) endocrine dysfunction with reduction of IGF-1, oestradiol, testosterone and DHEA-S as well as increase of cortisol; (iii) enhanced inflammatory response; (iv) immune dysregulation, specifically elevated levels of IL-6 and CRP; (v) metabolic imbalance including changes in insulin and glucose metabolism as well as weight loss and (vi) oxidative stress.

Regarding peripheral metabolism, increased fasting and 2-hr oral glucose tolerance test (OGTT) levels of glucose [12, 13], higher levels of HbA_{1c} and insulin [14] and presence of insulin resistance [15] have been linked to frailty. The underlying mechanisms of abnormal glucose and insulin metabolism in frailty remain unclear; however, they might be due to the association between disturbances in glucose–insulin homeostasis and elevation of inflammation markers, which lead to muscle loss [16]. Insulin resistance is also directly associated with perturbances in skeletal muscle metabolism [17] and activation of muscle proteolysis [18], ultimately resulting in loss of muscle and the hallmarks of frailty.

The brain changes including loss of grey matter have been linked to slow gait speed, physical inactivity and reduced handgrip [19]. Especially, the hippocampus is key to maintaining a balanced stress response; thus loss of neurons in this area could be vital in the development of frailty [20–22]. In addition, the hippocampus has been identified as an important mediator in the pathophysiology of cognitive decline and Alzheimer's disease (AD) [23]. Energy and glucose homeostasis in the hippocampus constitute a pivotal neuroprotective part in neurodegenerative and neuropsychiatric diseases [24]. Glucose uptake in the hippocampus is dependent on insulin receptor–stimulated translocation of the glucose transporter GLUT4 [25, 26]. The crucial involvement of insulin receptor mediated signalling in the brain is underscored by multiple connections to its neuroprotective function in AD [27, 28] Parkinson's disease [29, 30] and major depression [31]. An independent link between dementia and frailty has also been reported [32].

In the Helsinki Birth Cohort Study (HBCS), we have previously applied biologically informed polygenic risk scores calculated for the insulin receptor gene co-expression network in the hippocampal (hePRS-IR) and the mesocorticolimbic area (mePRS-IR) of the brain [33], which were originally calculated to predict AD and neurocognitive disorders. These novel ePRSs take into account that genes operate in networks and reflect tissue-specific biologic functions more accurately than traditional PRSs. They reflect the concept that genes code for biological processes rather than diseases, and by doing so, they describe individual variation in the function of the central insulin receptor gene network. Variation in gene expression constitutes a fundamental source of biological diversity, both within and among populations, with a substantial impact on phenotypic diversity [34]. By employing the ePRS-IRs to examine individual variations in central insulin action, we detected associations between the hePRS-IR and lower health-related quality of life and type of depression [35] as well as impaired glucose and insulin regulation and unfavourable cardiometabolic health in women (in press).

While peripheral insulin and glucose metabolism have been examined in relation to frailty, as far as we know no studies have investigated the association between central insulin action and frailty. In this longitudinal study, we aim to investigate whether variation in the function of the insulin receptor network in the brain is associated with frailty and change in frailty across a 17-year follow-up, by applying an FI and the ePRS-IRs.

Material and methods

Participants

The Helsinki Birth Cohort consists of 13,345 individuals, of which 8760 were born in 1934–1944 at the Helsinki University Central Hospital [36]. Supplementary File 1 presents a flowchart over the study population. Of these, 2902 individuals were randomly invited to a baseline clinical examination in 2001–2004 ($n = 2003$; mean age = 61.5 years; SD = 2.7 years) and follow-up visits in 2011–2013 ($n = 1082$; mean age = 71.1 years; SD = 2.7 years) and 2017–2018 ($n = 815$; mean age = 75.9 years; SD = 2.7 years). After excluding missing values, FI data were available on 1982

individuals from the baseline examination, 1072 individuals from the follow-up visit in 2011–2013 and 803 individuals from the visit in 2017–2018. After excluding individuals with missing data on genetics and covariates, the final study sample comprised 1605 individuals. The study was approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa and that of the National Public Health Institute, Helsinki and follows the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

The ePRS-IRs

Genotyping and ePRS-IR calculation were carried out as previously described [33]. DNA was extracted from blood samples measured during the baseline examination as per standard protocols, and genotyping was executed with the modified Illumina 610k chip by the Wellcome Trust Sanger Institute, Cambridge, UK. Genomic coverage was extended by imputation using the 1000 Genomes Phase I integrated variant set (v3/April 2012; NCBI build 37/hg19) as the reference sample and IMPUTE2 software. Quality control filters were applied before imputing by setting SNP clustering probability for each genotype at >95%, call rate at >95% for individuals and markers (99% for markers with minor allele frequency (MAF) < 5%), MAF at >1%, and the *P*-value for the Hardy–Weinberg Equilibrium exact test $P > 1 \times 10^{-6}$. Additionally, heterozygosity and gender and relatedness checks were performed and any discrepancies removed. The total number of SNPs in the imputed data was 39,282,668 (Supplementary Files 2 and 3).

For the ePRS calculation, lists of genes co-expressed with the insulin receptor in the mesocorticolimbic system or hippocampus were constructed based on RNA sequencing data from mice. Human homologues genes from these networks were identified. Single-nucleotide polymorphisms (SNPs) from these gene networks were mapped, and the list of SNPs was submitted to linkage disequilibrium clumping. In HBCS, the clumped list of SNPs was weighted with the betas from the Genotype-Tissue Expression (GTeX) [37], a resource database and tissue bank for studying the relationship between genetic variation and gene expression in human tissues, by applying data from each respective brain region. The selection of the SNPs within a given clumping window was based on the lowest *P*-value. Thus, biologically informed mesocorticolimbic (mePRS-IR) and hippocampal (hePRS-IR) specific co-expression based polygenic scores for the insulin receptor (IR) gene network were calculated. For the analyses, both hePRS-IR and mePRS-IR were standardised and reported as *z*-scores. For the analyses, the PRS-IRs were standardised and reported both as a continuous and a categorical variable (0 = low = <−0.5 SD, 1 = moderate = −0.5 to 0.5 SD and 2 = high = >0.5 SD).

The HBCS-FI

The HBCS-FI was created according to standard procedures [38] based on the Rockwood deficit accumulation model [39] and calculated for each of the three measurement occasions as previously described [40]. We considered symptoms, diseases, disabilities, clinical measurements and laboratory test results. We excluded deficits that saturated early, had a prevalence <1% or had more than 10% data missing from any single deficit from any of the three measurement occasions. 41 relevant deficits were created (Supplementary File 4). The original 41-deficit FI contains two insulin-related parameters, i.e. 'diabetes diagnosed by a doctor' and 'abnormal fasting glucose', which were excluded in the 39-deficit FI (Supplementary File 5). In both FI scores, included are individuals with information on at least 33 deficits (i.e. deficit count >80% available [38]; 99.6% or $n = 1982$ at baseline; 99.9% or $n = 1072$ in 2011–2013; 99.1% or $n = 806$ in 2017–2018). Individual FI levels were calculated by dividing the total number of deficits for an individual by the total number of deficits considered. The FI × 100 level of ≥25 was used to indicate frail state [8, 41]. The HBCS-FI has been found to share similar characteristics with other published studies applying the FI [40].

Co-variates

Co-variates included smoking, adult socioeconomic factor (SES) and birth weight. Smoking and SES were selected based on previous literature [40], while birthweight was chosen due to its possible impact on ePRS-IR. Smoking was coded as never, former and current. Socioeconomic status was obtained from Statistics Finland and coded as high official, low official, self-employed and manual workers [42]. The participants' birth weight was retrieved from hospital birth records [43].

Statistical analysis

The data are reported as means (standard deviation or 95% confidence intervals) or counts (percentage). All analyses were calculated for both the 41-deficit and the 39-deficit FI. Linear regression analyses tested associations between the categorical and continuous ePRS-IR and baseline FI. Linear mixed models examined associations between the ePRS-IRs and FI levels at the youngest age in the data (57 years) and the rate of change in FI levels from late midlife into old age. Age was used as the underlying time scale and centred at 57 years. The linear mixed models investigated associations between time and the rate of change in FI. Potential U-shaped associations between the variables and FI levels were tested by incorporating a quadratic term and its interaction with age into the models. All models were adjusted for SES, birthweight, smoking and their interactions with age. An ePRS-IR × sex interaction term investigated the differences in slope between men and women and detected a significant sex term interaction. Logistic regression analyses examined the cross-sectional association between categorical ePRS-IR and frailty status (no frailty = FI <0.25 and frailty = FI ≥0.25). The regression analyses were stratified by sex because of the interaction detected in the mixed models. To enhance the comprehensibility of our model estimates, the FI were multiplied by 100 and handled as percentages. Estimates of

Table 1. The participants' characteristics

	All (n = 1605)			Women (n = 905)			Men (n = 700)		
Characteristics	n			n			n		
Age (years), means (SD)	1605	61.5	(2.9)	905	61.6	(3)	700	61.4	(2.8)
Maximum SES adulthood, n(%)									
High official	1605	229	(14)	905	84	(9)	700	145	(21)
Low official	1605	691	(43)	905	509	(26)	700	182	(26)
Self-employed	1605	157	(10)	905	80	(11)	700	77	(11)
Labourers	1605	528	(33)	905	232	(42)	700	296	(42)
Smoking, n(%)									
Never	1605	685	(43)	905	496	(55)	700	189	(27)
Quite	1605	525	(33)	905	221	(24)	700	304	(43)
Current	1605	395	(25)	905	188	(21)	700	207	(30)
Birth weight (kg), mean (SD)	1605	3407.5	(482.1)	905	3344.5	(461.8)	700	3488.9	(495.7)
hePRS-IR × 103 (AU), mean (SD)	1605	−5.38	(0.34)	905	−5.37	(0.34)	700	−5.39	(0.35)
mePRS-IR × 103 (AU), mean (SD)	1605	3.24	(0.44)	905	3.27	(0.44)	700	3.21	(0.44)
hePRS-IR, n(%)									
<−0.5 SD	1605	482	(30)	905	260	(28.7)	700	222	(31.7)
≥ −0.5 SD – ≤0.5 SD	1605	627	(39.1)	905	365	(40.3)	700	262	(37.4)
>0.5 SD	1605	496	(30.9)	905	280	(30.9)	700	216	(30.9)
mePRS-IR, n(%)									
<−0.5 SD	1605	509	(31.7)	905	612	(38.1)	700	484	(30.2)
≥ −0.5 SD – ≤0.5 SD	1605	270	(29.8)	905	338	(37.4)	700	297	(32.8)
>0.5 SD	1605	239	(34.1)	905	274	(39.1)	700	187	(26.7)
41-Deficit frailty index (%), mean (SD)									
Baseline (2001–2004)	1605	20.4	(10.1)	905	20.6	(10.3)	700	20	(9.8)
2011–2013	859	21.5	(10.1)	512	22.9	(10.3)	347	19.4	(9.5)
2017–2018	640	23.3	(10.8)	384	24.4	(11.1)	256	21.7	(10.2)
41-Deficit frailty index >0.25, n(%)									
Baseline (2001–2004)	1605	460	(29)	905	280	(31)	700	180	(26)
2011–2013	859	272	(32)	512	192	(38)	347	80	(23)
2017–2018	640	240	(38)	384	162	(42)	256	78	(30)
39-Deficit frailty index (%), mean (SD)									
Baseline (2001–2004)	1597	22.5	(10.1)	897	23	(10.5)	700	21.7	(9.6)
2011–2013	852	23.1	(10.2)	505	24.9	(10.3)	347	20.5	(9.5)
2017–2018	633	23.8	(10.8)	377	25.3	(11.0)	256	21.4	(10.0)
39-Deficit frailty index >0.25, n(%)									
Baseline (2001–2004)	1597	557	(35)	897	343	(38)	700	214	(31)
2011–2013	852	321	(38)	505	230	(46)	347	91	(26)
2017–2018	633	252	(40)	377	176	(47)	256	76	(30)

SES, socioeconomic status; hePRS-IR, hippocampal polygenic risk score for the insulin receptor; mePRS-IR, mesocorticolimbic polygenic risk score for the insulin receptor.

the FI level represent percentage (%) of lower/higher levels of frailty while estimates of the rate of change in FI levels represent percentage point (PP) differences of change per year. A P-value <0.05 was considered to be statistically significant. Statistical analyses were carried out using Stata/MP version 17.0 (Stata Corporation, College Station, TX, USA).

Results

Participant characteristics

The characteristics of the participants are shown in Table 1.

FI level at baseline (2001–2004) and association with the ePRS-IRs

When applying the 41-deficit FI score at baseline, the adjusted mean FI level (FI × 100) was 20.37% points (95% CI 19.89–20.86). The FI levels of women were 1.19%-points (95% CI 0.12–2.26, P = 0.029) higher than in men.

Women in the higher hePRS-IR category had significantly higher FI levels (P for linearity = 0.0004, Figure 1). No association was found in men (P for hePRS-IR × sex interaction = 0.09). Similarly, when hePRS-IR was treated as a continuous variable, we detected a significant association in women (B = 1.1% points 95% CI 0.4–1.7, P = 0.001, Figure 2), but not in men (P = 0.61) (P for hePRS-IR × sex interaction = 0.033). No associations were detected between the mePRS-IR and the FI levels at baseline. When applying the 39-deficit FI, these results did not significantly change (Supplementary Files 6 and 7).

As displayed in Supplementary File 8, when employing the 41-deficit FI, compared to low hePRS-IR, moderate and high hePRS-IR were associated with increased odds of frailty status at baseline in women (OR for moderate

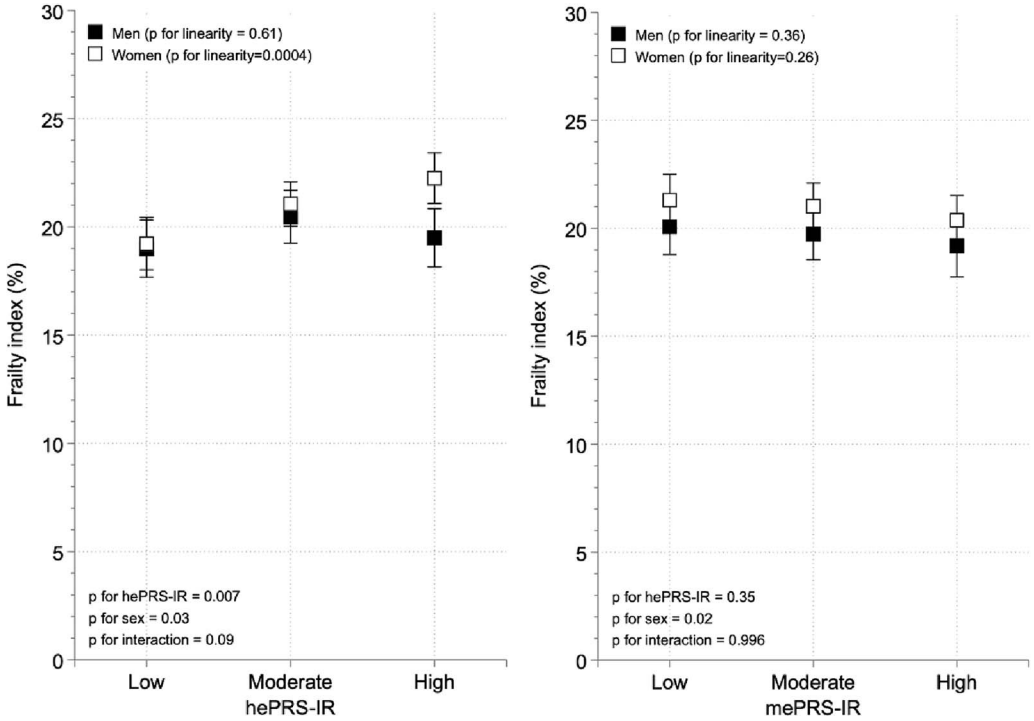

Figure 1. Association between categorical hePRS-IR and mePRS-IR variables and FI level at baseline. The models are adjusted for socioeconomic status, smoking and birth weight. hePRS-IR, hippocampal polygenic risk score for the insulin receptor; mePRS-IR, mesocorticolimbic polygenic risk score for the insulin receptor.

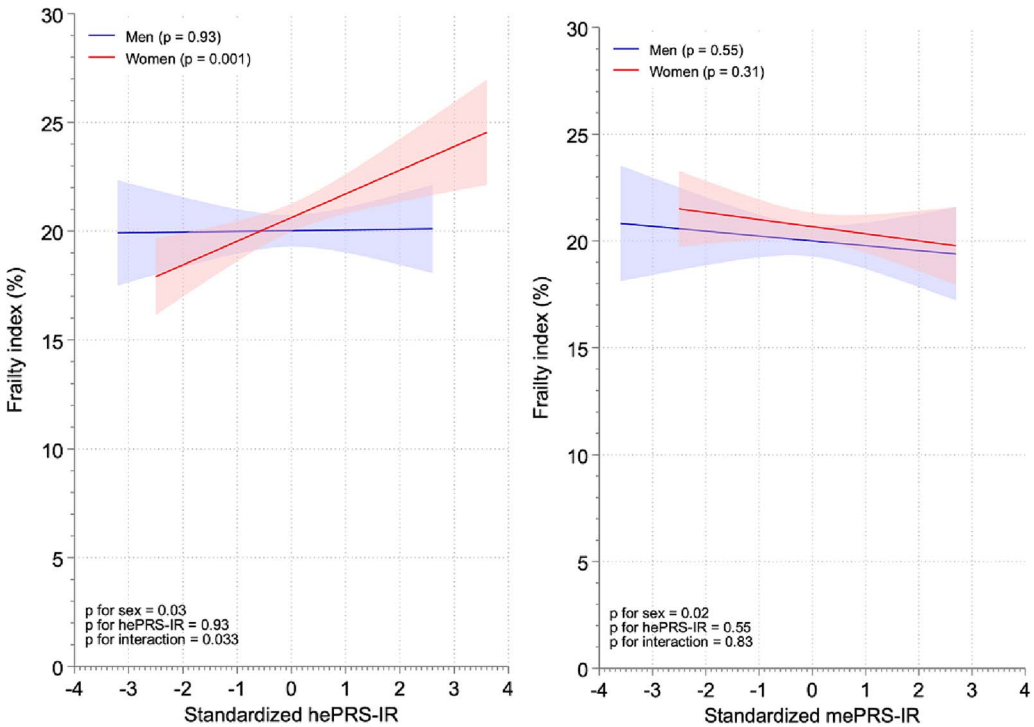

Figure 2. Association between FI levels and hePRS-IR as a continuous variable at baseline. The models are adjusted for socioeconomic status, smoking and birth weight. hePRS-IR, hippocampal polygenic risk score for the insulin receptor; mePRS-IR, mesocorticolimbic polygenic risk score for the insulin receptor.

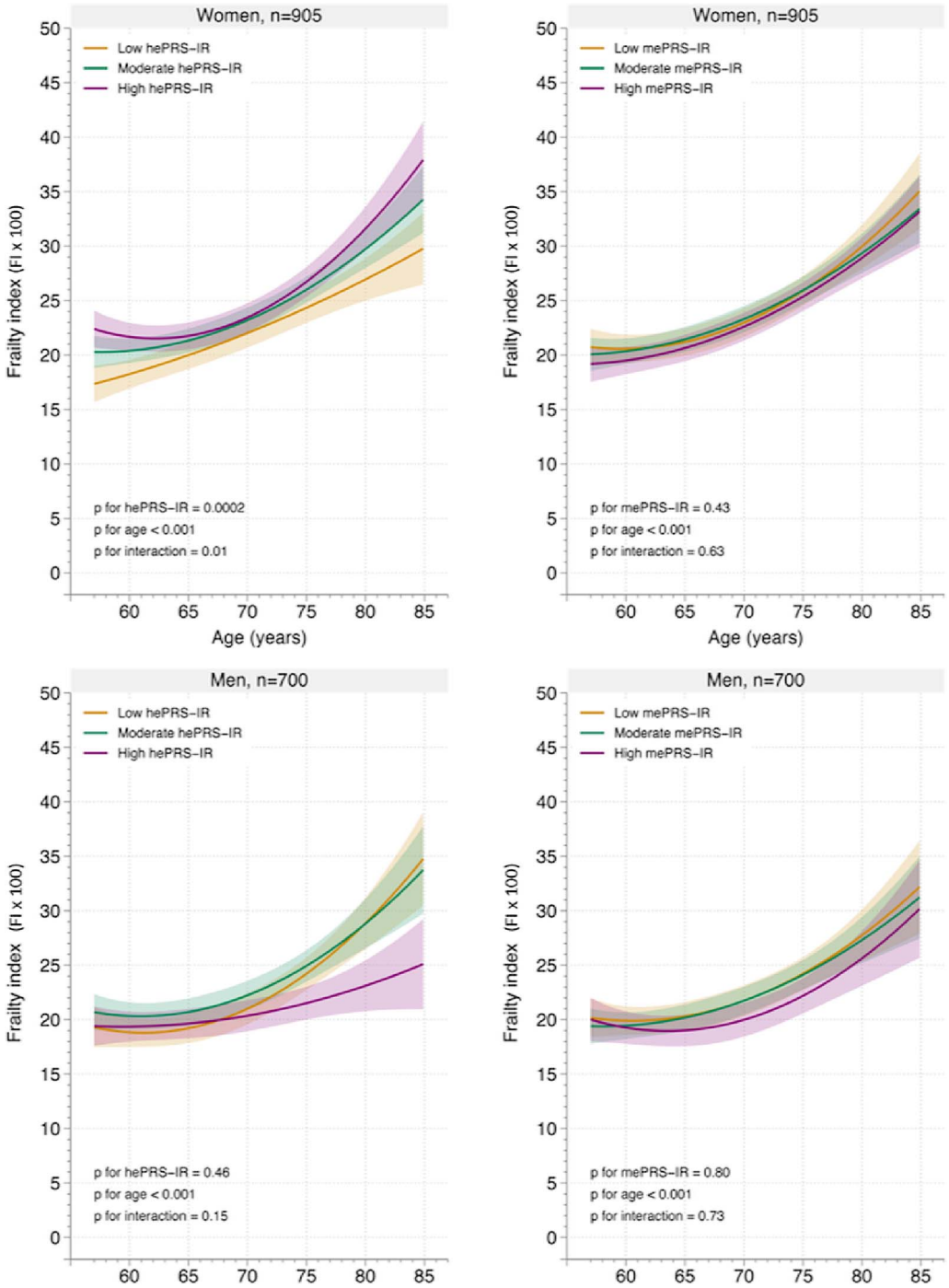

Figure 3. Mean FI levels (FI × 100) as a function of age shown in the hePRS-IR and the mePRS. In these analyses, the ePRS-IRs were categorical (0 = low = <−0.5 SD, 1 = moderate = − 0.5 to 0.5 SD and 2 = high = >0.5 SD). hePRS-IR, hippocampal polygenic risk score for the insulin receptor; mePRS-IR, mesocorticolimbic polygenic risk score for the insulin receptor.

hePRS-IR = 1.68, 95% CI 1.17–2.42, $P = 0.005$ and OR for high hePRS-IR = 1.75, 95% CI 1.18–2.56, $P = 0.005$) but not in men. This association was also detected when applying the 39-deficit FI (Supplementary File 9). No association was found between the categorical mePRS-IR and frailty status at baseline in either sex.

The ePRS-IRs and the rate of change in FI levels from midlife into old age

As illustrated in Figure 3, in women, hePRS-IR modified the association between age and the rate of change in FI levels (P for hePRS-IR × age interaction = 0.01) when utilising the 41-deficit FI. Over the years, FI levels increased at

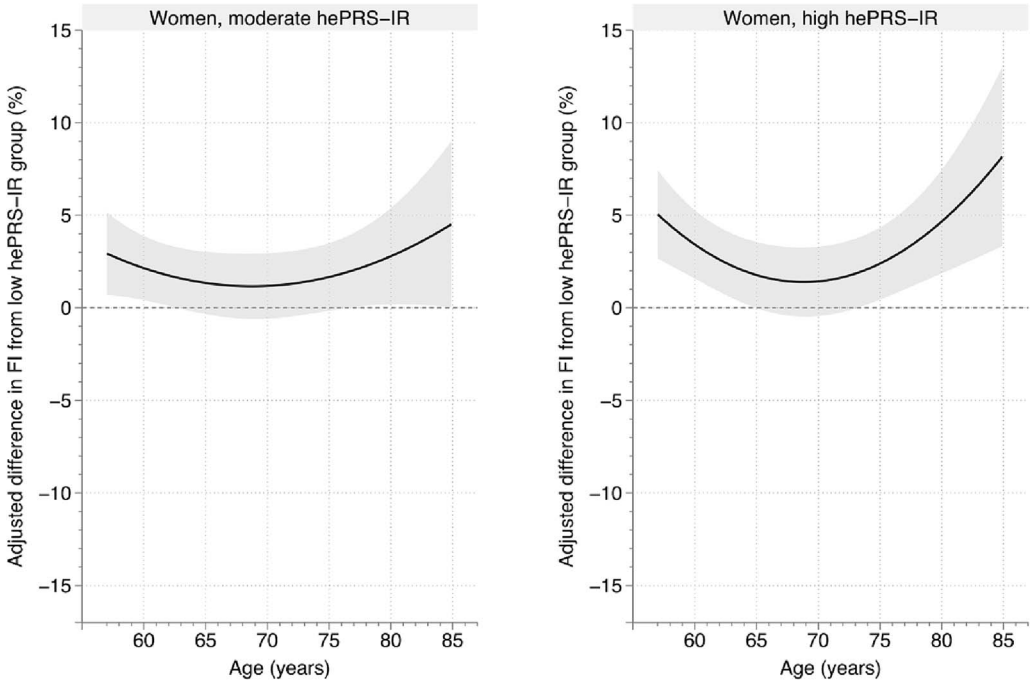

Figure 4. Adjusted differences in frailty index in women in moderate and high hippocampal insulin receptor network expression based polygenic risk score (hePRS-IR) compared to low hePRS-IR as a function of age. Adjustments are made for socioeconomic status, smoking and birth weight. hePRS-IR, hippocampal polygenic risk score for the insulin receptor; mePRS-IR, mesocorticolimbic polygenic risk score for the insulin receptor.

greater rate among women with high hePRS-IR compared to the women in the low hePRS-IR-group (Figure 4). This effect was detected especially after 73 years of age. The same modifying influence was identified when employing the 39-deficit FI (Supplementary Files 10 and 11). No significant interaction between the hePRS-IR and age was found in men (P for interaction = 0.15), nor between the mePRS-IR and rate of change in FI in either sex ($P \geq 0.43$).

Discussion

Frailty is characterised by decrease in physiological reserves across multiple systems, resulting in brain alterations and altered peripheral glucose and insulin metabolism. We observed that susceptibility for higher variation in the expression of the insulin receptor gene network in the hippocampus is associated with higher FI and frailty status in women. The FI rose with increasing age, and the slope was steeper in women with high expression of the hippocampal insulin receptor gene network. This constitutes a state of faster biological aging since the FI score is suggested to measure frailty on an individual level [44]. None of these associations were observed in men nor for the mesocorticolimbic insulin receptor gene network. The results were not significantly altered when applying the 39-deficit FI excluded of insulin-related parameters, which provide further evidence that the associations detected between ePRS-IRs and the FI are not driven by the endocrine dysfunction measured within the FI.

According to our results, only the hePRS-IR was associated with increased frailty. Previously, the hePRS-IR has displayed an association with AD and the mePRS with impulsivity and tendency to substance abuse [33]. The hippocampus plays a crucial part in memory, cognition processes and stress balance [45]. Dementia, in turn, is closely linked with poorer physical performance and declining physical health, a hallmark of frailty [46]. In light of this, it would be expected that disturbances in hippocampal insulin metabolism relate to increased frailty, as our results display. The lack of associations between the mePRS-IR and frailty might further be explained by the higher level of gene expression of insulin receptors in the hippocampus than the mesocorticolimbic area [47].

We have previously reported associations between the hePRS-IR and lower health-related quality of life, impaired glucose regulation and unfavourable cardiometabolic health in women [48] (in press). Another study using the same study population reported prediction of accelerated age-associated deficits by unfavourable body composition [49]. Taken together, our current results point to the hePRS-IR being associated with frailty partly through an adverse body composition profile. Moreover, as we have previously shown, the hePRS-IR is associated with impaired peripheral glucose and insulin regulation (in press), which has also been attributed to frailty [13, 14].

According to our results, central insulin receptor function is associated with higher FI but only in women. This might be due to post-menopausal women suffering more

frequently from conditions related to adverse glucose and insulin metabolism than men [50] as a result of the loss of the protective effect of oestrogen [51, 52] and because of sex differences in body composition [53]. In addition, one of the proposed mechanisms behind frailty is thought to relate to brain changes, especially in the hippocampus. Altered function in the hippocampus is also thought to be an underlying pathway to the development of AD. Women display higher incidence of AD than men, which might be reflected in our results [54]. Moreover, only in women have changes in hippocampal volumes been detected to affect the progression to AD [55].

Brain changes have been described in frail people, as have peripheral insulin resistance and impaired glucose tolerance [12, 14, 15]. The underlying mechanisms are yet to be fully understood; however, evidence points to pathways resulting in loss of muscle [16–18], a significant attribute of frailty. Physical fitness and glucose homeostasis share a bidirectional relationship. Muscle gain and exercise have a beneficiary effect on central insulin levels and insulin resistance [56, 57] while insulin resistance has been proposed as a contributor to muscle loss [58]. Disturbances in glucose–insulin homeostasis and elevation of inflammatory markers culminating in muscle loss might also contribute [16].

There are strengths as well as weaknesses in our study. The HBCS is a well-characterised cohort study with reliable measurements from clinical examinations and a long follow-up period. The ePRSs could potentially enhance disease diagnostics and treatment when applied in combination with other clinical risk factors and disease manifestations. The FI predicts disadvantageous outcomes more accurately and at a younger age compared to the frailty phenotype definition, presumably due to the FI reflecting a complex and continuous measure [10, 59]. The HBCS–FI encompasses more than the minimally required 30 deficits. Roughly every sixth participants had died by the last measurement occasion, which potentially undermines longitudinal associations found in the study as they likely exhibited higher levels of frailty. In addition, the participants were all born in Helsinki, Finland, which may affect generalisability and applicability of our results.

To conclude, women exhibiting a susceptibility for higher individual variation in the co-expression of the insulin receptor gene network in the hippocampus display a greater FI, indicative of an increased state of frailty, and a more pronounced incline in frailty progression. Our findings extend on existing evidence of the association between insulin metabolism and frailty and could offer novel drug targets focused on tackling frailty.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Declaration of Conflicts of Interest: None.

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Data Availability: The data analysed during the current study are available from the corresponding author on reasonable request.

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