

THE LONGEVITY ASSOCIATED SH2B3 (LNK) GENETIC VARIANT: SELECTED AGING PHENOTYPES IN 379,758 SUBJECTS

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Abstract

Human *SH2B3* is involved in growth factor and inflammation signaling. A *SH2B3* missense variant (rs3184504) is associated with cardiovascular diseases plus breast, colorectal and lung cancers, with highly correlated variants across the *ATXN2/SH2B3/BRAP* locus linked to parental age at death, suggesting a geroscience common mechanism of aging and disease. To better understand the *SH2B3*-related aging pathway and its potential as an intervention target, we undertook a phenotype-wide association study (PheWAS) of 52 aging traits. Data were from 379,758 European-descent UK Biobank participants, aged 40 to 70 at baseline: 27% of participants were CC homozygotes and 23% TT at rs3184504. Parental extreme longevity (mothers aged ≥ 98 years, fathers ≥ 96) was more common in CC versus TT (Odds Ratio =1.18, 95% CI: 1.07 to 1.29) with an additive per allele effect. The C allele associated with better cognitive function and white blood cell counts were more likely to be normal. The C allele reduced risks of coronary heart disease (OR= 0.95, 95% CI: 0.93 to 0.96) but was also associated with a modestly higher cancer rate (OR=1.03, 95% CI: 1.02 to 1.04), suggesting a trade-off across aging outcomes and limiting its potential as an anti-aging target.

Key Words: centenarian, anti-aging, IGF-1, cancer, UK Biobank

Introduction

The geroscience hypothesis argues that shared underlying mechanisms drive many diseases of aging (1), but few such mechanisms have been proven in humans (2). A missense variant (rs3184504) in *SH2B3* has been linked to many common diseases in genome-wide association studies, including several autoimmune and cardiovascular disorders, hypertension (3) and myeloproliferative cancers (4), plus breast, colorectal and lung cancers (5). In a genome-wide analysis of parental longevity in UK Biobank (6), we found that 11 highly correlated genetic variants in the wider *SH2B3/ATXN2/BRAP* locus (including rs3184504) were associated with parent's attained age, and this longevity association has been replicated in other cohorts (7). Given this involvement in many human diseases and longevity, *SH2B3* may shed light on biological mechanisms that contribute to the aging process. Drug targets supported by genetic evidence are twice as likely to succeed in human trials (8).

However, the impact of this *SH2B3* variant on many aging phenotypes is unknown.

The *SH2B3* gene in humans codes for the lymphocyte adaptor protein *LNK*. Initially characterized as a hematopoiesis and lymphocyte-specific differentiation regulator, *LNK* is widely expressed in the human body (4), and is involved in transduction and regulation of growth factor and (inflammation-related) cytokine receptor-mediated signaling (9). The rs3184504 T allele missense variant is predicted to disrupt the subcellular localization and functioning of *LNK* (10).

As noted, the above variation in *SH2B3* appears highly relevant to geroscience, but little is known about associations with aging-related traits, including muscle weakness, frailty, chronic pain, cognitive measures, blood measured (e.g., of inflammation, with high white cell counts) and several relevant disease diagnoses. We aimed to undertake a phenome-wide association study (PheWAS) of 52 aging traits, to clarify the health outcomes of common variation in *SH2B3*, as marked by rs3184504. UK Biobank offers a large sample of community volunteers with baseline self-reports of parental age at death, morbidity, and physical measures, plus a follow-up in national hospital, cancer registry, and death certificate data.

Methods

UK Biobank is a volunteer cohort, with 502,642 participants aged 40-70 seen between 2006 and 2010. A range of questionnaire, physiological, and disease data are available, including hospital admissions (up to 10 years follow-up) (11). Genotype information was available on 488,377 participants. Genotype imputation was successful in 487,442 UK Biobank participants and increased the number of available genetic variants to ~96 million (12).

Analyses were restricted to European-descent participants ($n = 451,433$), as numbers from the other ancestry groups in UK Biobank are unfortunately too small to provide sufficiently powered estimates for this PheWAS. European-descent participants were identified based on genetic principal components analysis as described in more detail in Thompson et al.(13). To avoid inflated effects from inclusion of closely related family members, only one subject in 3rd-degree or closer pairs were included in analyses (based on the kinship analysis), leaving 379,758 participants aged 40 to 70 at baseline. None of the included samples were identified by UK Biobank as outliers in heterozygosity and missing rates, which would indicate poor-quality genotypes for these samples (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=531>).

rs3184504 UK Biobank utilized two Affymetrix microarrays (the BiLEVE array in ~50,000 participants, and the Axiom array in ~440,000 participants, >95% shared marker content) (12). We analyzed the 10 SNPs in linkage disequilibrium (LD, $R^2 > 0.8$) with rs3184504, associated with parents' attained age ($p < 5 \times 10^{-8}$) in our 2017 GWAS (14). See Supplementary Figure 1 for LocusZoom plot of the region (± 250 kb). None of the 10 SNPs were conditionally associated with parents' attained age given rs3184504 was in the model ($p > 0.05$) (Supplementary Table 1). The results suggested that the common variation in *SH2B3* was marked by rs3184504 for the association with parents' attained age. We here conducted a PheWAS to study *SH2B3* via rs3184504 and aging. rs3184504 (chr12, b37 111,884,608) was directly genotyped on the arrays, and for analyses was coded as 0, 1 or 2 copies of the C (lifespan-extending) allele. The C allele frequency was 0.52 and the

genotype distribution (23% TT, 50% CT, and 27% CC) was not significantly deviant from Hardy-Weinberg equilibrium ($p=0.642$).

Parental extreme longevity

Parental age at death was assessed by survey questions, administered to participants and updated with data from follow-up visits. We derived at least one parent top 1% survival, which was 98 for mothers and 96 for fathers, determined by parental age at death in UK Biobank. Parents who attained the top 1% survival were compared to short-lived parents who both died before the age of 80. Parents who died prematurely (more than 1 standard deviation below the modal age of death: mothers <57 years, fathers <46 years) were excluded from analyses (15).

Baseline phenotypes

Baseline phenotypes included depression, chronic pain (back, hip, and knee pains), falls, muscle weakness, Fried defined frailty status, a cumulative morbidity frailty index, cognitive function, and physiological biomarkers.

Depression, chronic pain, and falls in the last year were assessed by the survey questions: “Over the past two weeks, how often have you felt down, depressed or hopeless?” with the responses grouped into several days and longer or not at all; “In the last year, have you had any falls?” with the responses grouped into any fall or no falls”; “Have you had back pains for more than 3 months?” with the responses grouped into yes or no”; “Have you had hip pains for more than 3 months?” with the responses grouped into yes or no”; and “Have you had knee pains for more than 3 months?” with the responses grouped into yes or no.

Low muscle mass (8.87 kg/m^2 for men and 6.42 kg/m^2 for women) and low hand grip strength (30 kg for men and 20 kg for women) were defined from the European Working Group on Sarcopenia in Older People (EWGSOP) (16).

For cognitive function, we analyzed reaction time and visual memory errors. “Reaction time” was calculated as the average time taken to correctly identify a match in a symbol matching game similar

to the snap card game. “Visual memory errors” was measured as the number of errors that a participant made to complete a pairs matching task where 6 pairs of cards were presented for 3 seconds beforehand. Both were log transformed to correct skewness of the distributions. Visual memory errors were right shifted by 1 to avoid infinite values from zero errors.

Fried frailty status (frail or not frail) was frail if meeting 3 or more of the five conditions: self-reported exhaustion, weight loss, and slow walking pace, plus measured grip strength and physical activity at the lowest 20% where physical activity was measured by the short version of International Physical Activity Questionnaire (IPAQ) (17).

Physiological biomarkers included lung function measures of Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and FEV1/FVC; heel bone mineral density and blood pressures. Albumin-creatinine ratio ≥ 3 mg/mmol was used as a biomarker of renal impairment for diagnosing chronic kidney disease, which was associated with hypertension and cardiovascular mortality (18).

We also examined associations with hematological measures, due to previously known links between *SH2B3* and bone marrow activation (4). We compared raised or lowered values to reference ranges quoted by manufacturer (<https://biobank.ctsu.ox.ac.uk/crystal/docs/haematology.pdf>).

Disease outcomes

At the baseline assessment, participants self-reported prevalent doctor diagnosed diseases. These were combined with hospital admission data to identify participants with diagnoses of multiple relevant diseases. The disease status was confirmed regardless of prevalent or incident cases. Common diseases were included such as cancers, diabetes, respiratory diseases, bone diseases, and cardiovascular diseases. We derived “any cancer” excluding non-melanoma skin cancers and “any-cause anemia” that was mild or more severe. Additionally, we included the frailty index by Williams et al. (19), which scored 49 deficits mostly pains and diseases (range 0-49).

Statistical Analysis

A logistic regression model was performed to associate a binary outcome and the rs3184504 genotype, adjusted for age at measurement (age at baseline or age at the last follow-up), sex, genotyping microarray, assessment center, and principal components 1-5 to account for ancestry composition. A linear regression model was used instead for a continuous outcome, which was z-transformed to standardize the scale. We highlighted associations with p-values smaller than the Bonferroni-corrected level ($p < 0.05/52 = 0.00096$) and reported 95% confidence intervals. All the statistical analyses were performed in R 3.4.1.

Sensitivity analyses

We performed subgroup analyses for baseline phenotypes and disease outcomes by sex or using subjects aged 60 and older at measurement (baseline or the last follow-up) to exclude possibly atypical cases. Parental extreme longevity traits are parental traits determined by both parents; therefore, were not included in subgroup analyses. We also linked the 10 SNPs in LD with rs3184504 to traits associated with rs3184504, and tested their effects conditioning on rs3184504.

Power analysis

Denote by f (=0.52) the C allele frequency of rs3184504. The effect size (ES) defined as $2 \times \beta^2 \times f(1-f)$ is the percent of trait variance explained by rs3184504 assuming Hardy-Weinberg equilibrium and an additive polygenic model where β is the standard deviation (SD) change per C allele in a continuous trait (20). Given the sample size of each trait assuming the Bonferroni-correct significance level ($0.05/52 = 0.00096$), power to detect a 0.1 or -0.1 standard deviation change ($\beta = 0.1$ or -0.1 , ES = 0.50%) in a continuous trait was calculated using G*Power (21). Power to detect a relative risk of 1.2 or 0.83 (multiplicative inverse of 1.2) assuming a multiplicative model for a binary trait was calculated using the R package `statapps/power.ctepd` (22) where the case-control ratio and the prevalence were estimated from the sample. Power for all studied phenotypes was >80%, except for

parental extreme longevity (69% power), type 1 diabetes (44% power), renal failure (75% power), and some hematological measures (see Supplementary Table 2 for details).

Ethics

UK Biobank received an approval from the UK Biobank Research Ethics Committee (REC) (REC reference 11/NW/0382). All the participants provided written informed consent to participate in the study and for their data to be used in future research. This research was conducted using UK Biobank resource, under application 14631.

Results

379,758 European-descent participants in UK Biobank were included in analyses (mean age 56.7, Standard Deviation=8.0, range: 40 to 73), with a mean follow-up of 7.8 years (SD=1.0). The studied sample (54% women) included n=168,310 aged 60 plus at baseline interview (n=261,837 aged 60 and older by the end of follow-up). Overall, 11,014 subjects died during follow-up. A summary of aging traits, overall and by rs3184504 genotypes, was provided in Supplementary Table 2, where traits associated with the SNP ($p < 0.00096$) were marked by grey background.

Associations with p-values smaller than the Bonferroni-corrected level ($p < 0.00096$) were discussed below. Complete association results using all mid-age and older adults, 60 or older adults only, and men, or women only were provided in Supplementary Table 3.

Associations with parental extreme longevity

Extreme parental longevity (at least one parents top 1% survival in UK Biobank) was more common for CC compared to TT homozygotes (OR=1.18, 95% CI: 1.07 to 1.29), with an additive per allele effect (per C allele OR=1.08, 95% CI: 1.03 to 1.14, Figure 1).

Associations with baseline phenotypes

rs3184504 C allele was associated with a reduced prevalence of low muscle mass (per C allele OR=0.97, 95% CI: 0.96 to 0.98, Figure 1), lower systolic and diastolic blood pressures (systolic SD change

= -0.020, 95% CI: -0.024 to -0.015, diastolic SD change = -0.037, 95% CI: -0.042 to -0.033). Also, in cognitive testing, reaction times were shorter (SD change in log scale = -0.012, 95% CI: -0.017 to -0.008) (Figure 2). To ensure relevance to aging in men and women, we undertook specific analyses in 60 plus year old, including separate estimates for men and women: effect sizes as odds ratios or SD changes were similar in all mid-age and older adults, 60 or older adults only, and men, or women only (Figures 1 and 2). There was no association ($p > 0.00096$) with visual memory errors (to measure cognitive function), chronic pain, depression, Fried frailty (comparing frail versus not frail), falls, grip strength, heel bone mineral density, lung function biomarkers (FEV1, FVC, and FEV1/FVC), and the urinary biomarker, albumin-creatinine ratio (≥ 3 mg/mmol) (Figures 1 and 2).

Analyses of baseline hematological measures (Figure 3) showed associations between rs3184504 C allele and lower risks of being above white cell count clinical reference ranges, including total white cell count (OR=0.90, 95% CI: 0.89 to 0.92), neutrophils (OR= 0.95, 95% CI: 0.93 to 0.98), lymphocytes (OR= 0.84, 95% CI: 0.79 to 0.91), eosinophils (OR= 0.87, 95% CI: 0.82 to 0.93) and basophils (OR= 0.94, 95% CI: 0.91 to 0.97). rs3184504 C allele was also associated with lower risks of being above reference ranges of platelets (OR= 0.78, 95% CI: 0.75 to 0.81), reticulocytes (OR= 0.88, 95% CI: 0.86 to 0.90), and total red blood cell count (OR= 0.88, 95% CI: 0.84 to 0.93). The effect sizes for lymphocytes, platelets, and red cell count, were stronger in women than in men. Clinically low hemoglobin concentrations (below sex-specific reference ranges) were slightly less common in C allele carriers, overall, in men, and in women but didn't reach statistical significance.

Associations with disease outcomes (binary) and the multi-morbidity-based frailty index

The rs3184504 C allele increased the risk of any-cause anemia (mild or more severe, OR=1.09, 95% CI: 1.08 to 1.11); however, reduced the risks of hypothyroidism (OR= 0.81, 95% CI: 0.80 to 0.83), and type I diabetes (OR= 0.88, 95% CI: 0.83 to 0.93) (Figure 4). Positive associations were found with breast cancer (OR= 1.05, 95% CI: 1.03 to 1.08), and any cancer (excluding non-melanoma skin cancers, OR= 1.03, 95% CI: 1.02 to 1.04), coronary heart disease (OR= 0.95, 95% CI: 0.93 to 0.96), and hypertension (OR= 0.94, 95% CI: 0.93 to 0.94). Except for the association with any-cause anemia (mild or more severe, mainly present in women), the effect sizes overall were similar to those in the

subgroups of 60 and older, men only, and women only (Figure 4). While not highlighted at the Bonferroni-corrected level ($p < 0.00096$), the C allele was modestly associated with colorectal cancer (OR= 1.05, 95% CI: 1.00 to 1.09) and protective for renal failure (OR= 0.95, 95% CI: 0.91 to 1.00), rheumatoid arthritis (OR= 0.95, 95% CI: 0.91 to 0.98), stroke (OR= 0.96, 95% CI: 0.93 to 0.99), and type 2 diabetes (OR= 0.97, 95% CI: 0.95 to 0.99) (Figure 4). rs3184504, however, was not associated ($p > 0.00096$) associated with the 49-item frailty index (Figure 2).

In additional analysis for each rs3184504-associated trait, we examined the association for the 10 SNPs in LD with rs3184504 at the same locus. Overall, effect sizes and p-values were very similar, and in conditional analyses, none showed independence from rs3184504 except a SNP for reaction time ($p < 0.00094$) but the effect size was minimal (see Supplementary Table 4).

Discussion

The *SH2B3* missense variant rs3184504 has been linked to several chronic diseases and cancers, and highly correlated variants in the wider *SH2B3/ATXN2/BRAP* locus (including rs3184504) were associated with parental age at death. Here we aimed to provide a phenotype scan of 52 aging-related traits, to better understand the *SH2B3*-related aging pathway and to test the variant's potential as a target for anti-aging interventions. We showed that rs3184504 is associated with substantially increased chances of having at least one parent top 1% survival in UK Biobank. We also showed that the C allele was associated with lower blood pressures, shorter reaction time (cognitive measure), and healthier muscle mass and hematological measures: i.e., lower prevalence of low muscle mass and lower prevalence of abnormally high blood white cell counts. In addition, we found associations between the C allele and reduced rates of hypothyroidism, hypertension and cardiovascular disease. However, a modest excess in cancer risk was present: rs3184504 was associated with any cancer (excluding non-melanoma skin cancers) and breast cancer, plus the expected association with colorectal cancer, although this appeared to be modest. Our findings thus suggest that modulation of *SH2B3*-related pathways may be subject to trade-offs between aging outcomes.

Our PheWAS results for those traits that have been previously studied are consistent with the published literature: rs3184504 has been reported to be associated with coronary heart disease (CHD) risk (23), increased blood pressure (24), type-1 diabetes (25), and platelet counts and leukocytosis (especially neutrophil counts) (26), in the same direction as our results. Similarly, several links have been shown between *SH2B3* and cancers, including rs3184504 associations with colorectal cancer (27). Longevity associations were also identified by Fortney *et al.* in the New England Centenarian Study using an “informed GWAS” approach (28), and highly correlated SNPs across the *SH2B3/ATXN2/BRAP* locus were associated with parental longevity in the LifeGen cohorts (29). We found no association between rs3184504 and a number of age-related traits, including cognitive function (visual memory errors), chronic pain, and frailty. This is consistent with published GWAS (where available in the GWAS catalog) and is unexpected given the association with longevity, although the pleiotropic effect of the variant on cancer and cardiovascular disease may explain this. This PheWAS cannot address mechanism directly, but there is extensive published evidence suggesting the likely mechanisms driving these associations. The lifespan decreasing T (missense) allele of rs3184504 in *SH2B3* is predicted to disrupt normal *SH2B3/LNK* functioning in facilitating transduction and regulation of growth factor and (inflammation-related) cytokine receptor-mediated signaling (9). Inflammation has been suggested as a factor accounting for the association between *SH2B3* variants and lung, bowel and breast cancer in GWAS studies (5). Several other links have been shown between *SH2B3* and cancers, including the presence of activating mutations in acute lymphoblastic leukemia cells (30,31). The rs3184504 C (lifespan-increasing) allele is associated with reduced levels of vascular cell adhesion protein 1 (VCAM-1) (32), which has major roles in development in the spread of cancers (33) plus white cell recruitment in the cellular immune response and in angiogenesis. Similarly there are several suggested mechanisms linking *LNK/SH2B3* with cardiovascular disease and hypertension (10), partly through increased production of IFN γ , a pro-inflammatory cytokine. *SH2B3* is also a crucial mediator of post myocardial infarction inflammation and fibrosis (34). A trade-off between chronic diseases and cancer in aging has been suggested (35), based on the hypothesis that more apoptosis of damaged cells might prevent cancers but could also

result in less regrowth and repair thus promoting chronic diseases, and vice versa: more regrowth may prevent chronic disease while promoting cancer. More work is clearly needed to fully define *SH2B3* aging mechanisms in humans.

Incidentally, in *Drosophila*, the *SH2B* gene is involved in insulin-like growth factor (*IGF1*) and other energy balance-related signaling, and a *Drosophila SH2B* loss of function mutant had increased lifespan under starvation conditions through increased carbohydrate stores (36). In mice and humans, several *SH2B* homologues exist, with *SH2B1* and *SH2B2* also involved in *IGF1* signaling (37), but no GWAS associations have thus-far been reported for human longevity in these genes. As discussed above, *SH2B3* is associated with human longevity but is not thought to be an important driver of *IGF1* signaling (37).

There are inevitably limitations to this analysis: UK Biobank is a volunteer study and the sample tended to be healthier at baseline than the general population, but the sample did include a wide range of exposures (38). We have studied only European ancestry participants, as numbers for other ancestry groups were relatively small. Several phenotype measures are available at baseline only. Follow-up data are limited to discharge hospital records and death certificates, so may underestimate incident diagnoses. The data used from UK Biobank was included in several previous studies of specific diseases and parental age at death, but these associations have been replicated in independent samples, and our focus here on aging phenotypes extends the existing literature.

Conclusion

The human *SH2B3* locus harbors common variation associated with human longevity, several chronic diseases and cancers, and may represent a geroscience hypothesized common mechanism of aging. In a large aging PheWAS of 52 relevant traits, common variation marked by rs3184504 was associated with a substantial increase in the chances of having at least one parent top 1% survival. There was also evidence for this variant being associated with better cardiovascular health and better cognition. However, modestly higher cancer rates were found, confirming previous reports. Therefore, despite

being associated with parental extreme longevity, common variation in *SH2B3* may be subject to trade-offs between aging outcomes, which will limit its potential as an anti-aging intervention target.

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Conflict of Interest Statement

None declared

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Figure legends

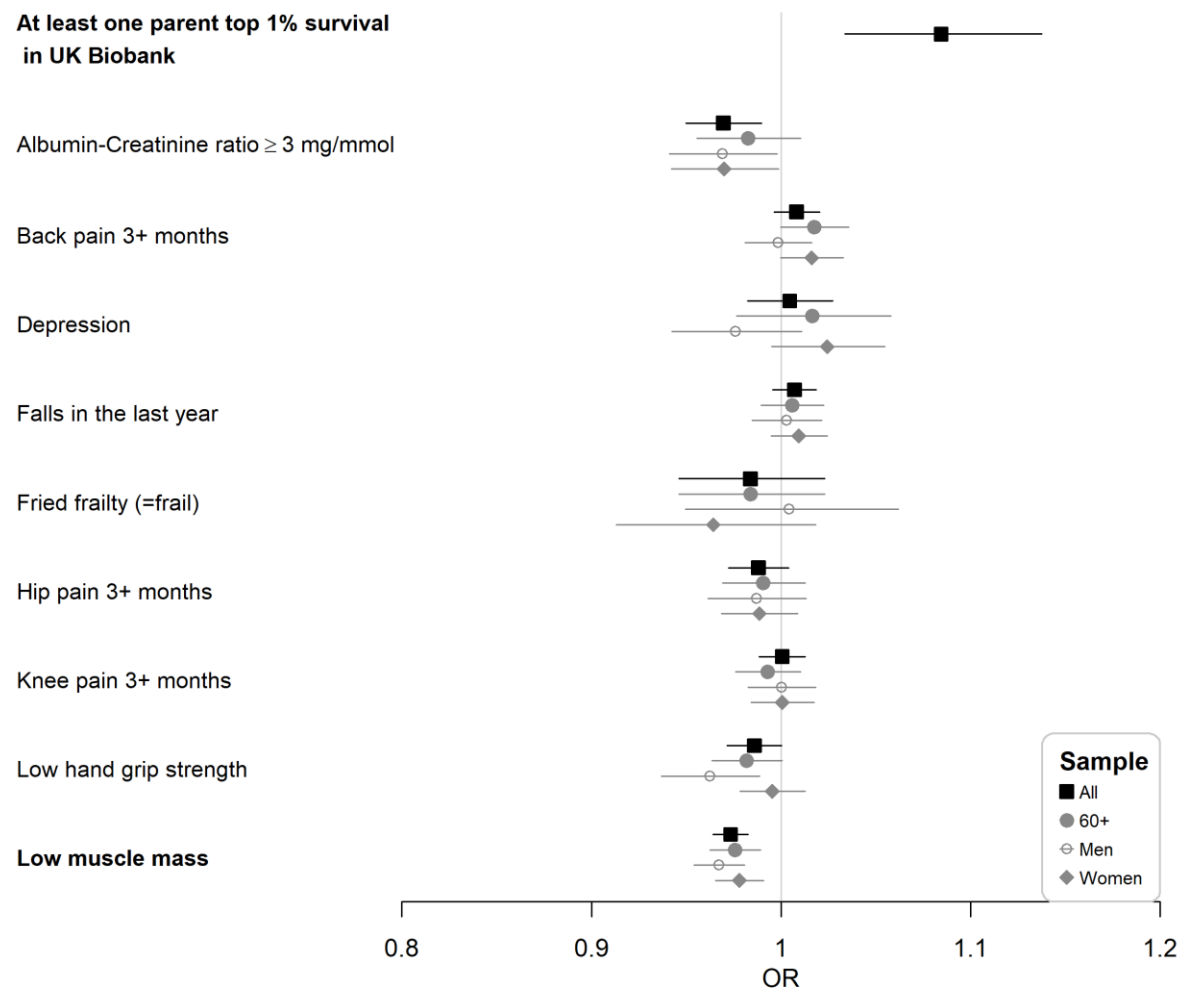
Figure 1. Odds ratio (OR) per C allele of rs3184504 and 95% confidence interval for parental extreme longevity or a binary baseline phenotype using all samples (All), 60 or older (60+), men only (Men), or women only (Women). Highlighted in bold if the p-value smaller than the Bonferroni-corrected level ($0.05/52 = 0.00096$).

Figure 2. Standard Deviation (SD) change per C allele of rs3184504 and 95% confidence interval for a continuous baseline phenotype or the 49-item multi-morbidity-based frailty index using all samples (All), 60 or older (60+), men only (Men), or women only (Women). Highlighted in bold if the p-value smaller than the Bonferroni-corrected level ($0.05/52 = 0.00096$). **Figure 3.** Odds ratio (OR) per C allele of rs3184504 and 95% confidence interval for being above or below the reference range of a hematological measure using all samples (All), 60 or older (60+), men only (Men), or women only (Women). Highlighted in bold if the p-value smaller than the Bonferroni-corrected level ($0.05/52 = 0.00096$).

Figure 4. Odds ratio (OR) per C allele of rs3184504 and 95% confidence interval for a disease outcome using all samples (All), 60 or older (60+), men only (Men), or women only (Women). Highlighted in bold if the p-value smaller than the Bonferroni-corrected level ($0.05/52 = 0.00096$). All women or women of 60 or older only for breast cancer and all men or men of 60 or older only for prostate cancer.

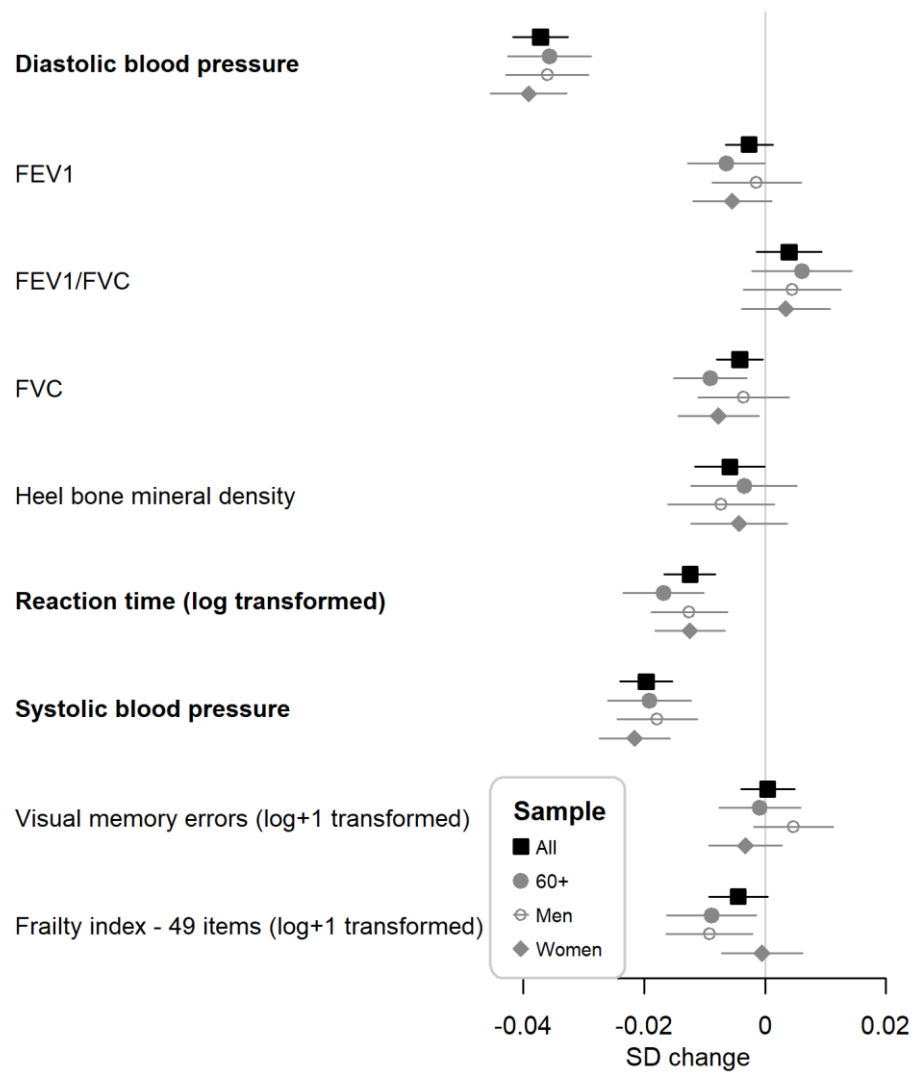
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Figure 1



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Figure 2



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Figure 3

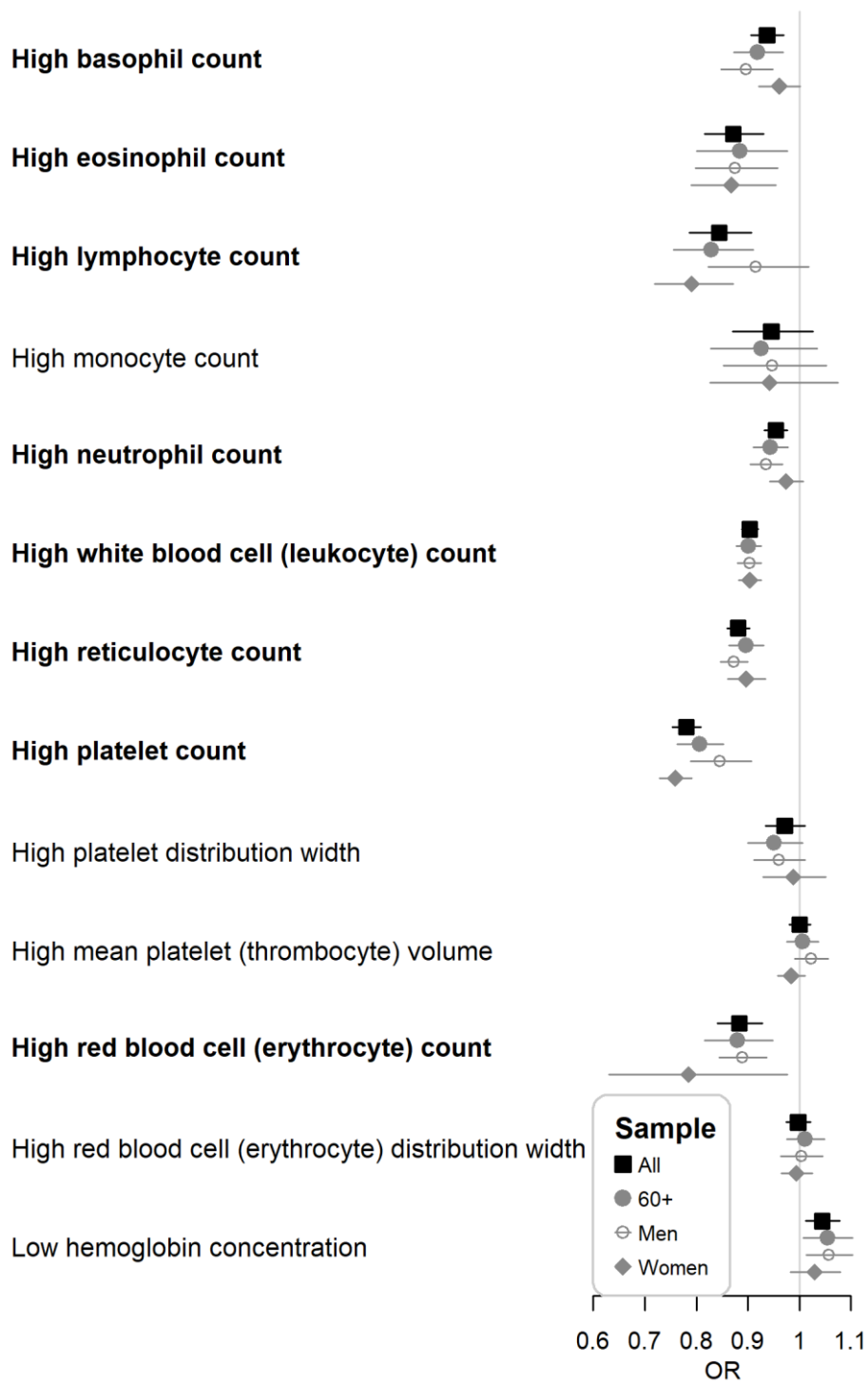
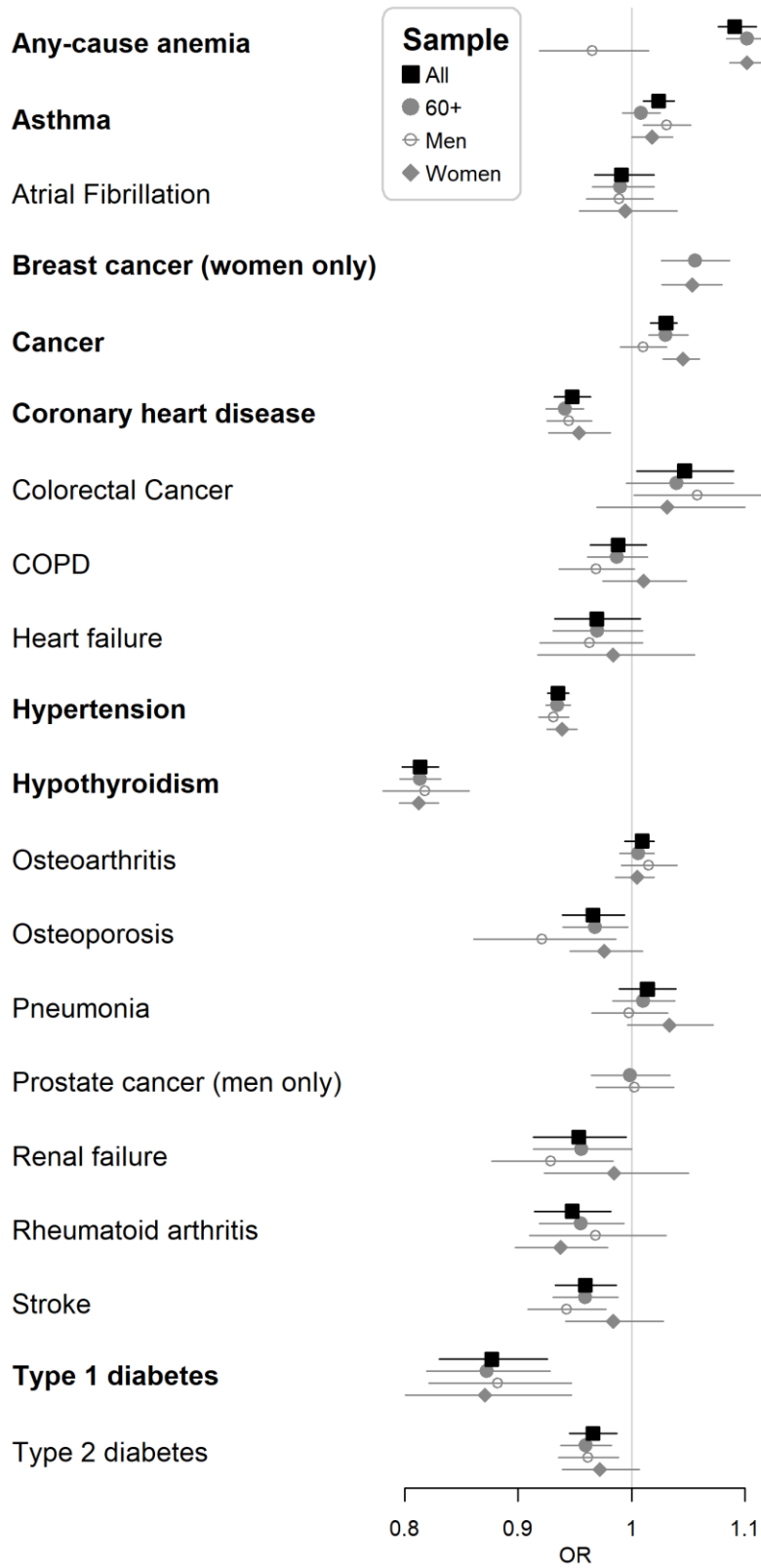


Figure 4



Script