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Physical and cognitive fitness in young adulthood and risk of amyotrophic lateral sclerosis at early age

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Abstract

Background: There is a clinical impression that amyotrophic lateral sclerosis (ALS) patients have higher level of physical fitness and lower body mass index (BMI) than average. In contrast, there is a lack of literature examining the relationship between cognitive fitness and ALS risk.

Methods: Data on physical fitness, BMI, intelligence quotient (IQ), and stress resilience were collected from 1,838,376 Swedish men aged 17-20 at conscription during 1968-2010. Their subsequent ALS diagnoses were identified through the Swedish Patient Register. Hazard ratios (HRs) and 95% confidence intervals from flexible parametric models were used to assess age-specific associations of physical fitness, BMI, IQ, and stress resilience with ALS.

Results: We identified 439 incident ALS cases during follow-up (mean age at diagnosis: 48 years). Individuals with physical fitness above the highest tertile tended to have a higher risk of ALS before age 45 (range of HRs: 1.42-1.75; statistically significant associations at age 41-43), compared to others. Individuals with BMI \geq 25 tended to have a lower risk of ALS at all ages (range of HRs: 0.42-0.80; statistically significant associations at age 42-48), compared to those with BMI $<$ 25. Individuals with IQ above the highest tertile had a statistically significantly increased risk of ALS at age 56 onward (range of HRs: 1.33-1.81), whereas individuals with stress resilience above the highest tertile had a lower risk of ALS at age 55 and younger (range of HRs: 0.47-0.73).

Conclusions: Physical fitness, BMI, IQ, and stress resilience in young adulthood might be associated with the development of early age ALS.

Background

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease characterized by progressive degeneration of the upper and lower motor neurons [1]. About 5-10% of ALS patients have a family history, whereas the aetiology for others is uncertain [1]. Non-genetic risk factors for ALS may include smoking, antioxidants intake, body mass index (BMI), physical exercise, and exposure to heavy metals and chemicals [2].

There is a clinical impression that ALS patients have high levels of physical fitness and low BMI [3]. However, limited evidence exists to date to support that premorbid physical fitness is associated with increased risk of ALS [4]. Mattsson et al. conducted a case-control study among young Swedish male conscripts and found that general physical fitness at age 18 was a risk factor for death due to ALS [5]. Lower premorbid BMI has also been associated with a higher risk of ALS [6]. However, no association was confirmed for BMI at the age of 18/21 [7].

There is a lack of literature examining the relationship between cognitive fitness and ALS risk. Higher intelligence quotient (IQ) is a protective factor against all-cause mortality [8], whereas its influence on ALS risk is unknown. Psychological stress has been proposed as a contributing factor for different neuro-pathologies [9], but its role in ALS has rarely been investigated.

Our aim was to explore the associations of physical fitness and BMI in young adulthood with future risk of ALS. Additionally, we aimed to investigate if early adulthood cognitive fitness, in terms of IQ and stress resilience, influences ALS risk.

Material and Methods

The Swedish Conscript Register collects data about all males that underwent conscription examination from 1968 onward. Military conscription examination was mandatory in Sweden until 2010; all Swedish boys aged 18 years were required to attend, except in cases of severe diseases. At the examination, data on physical fitness, BMI, IQ, and stress resilience were obtained.

Physical fitness was measured as the maximum working capacity in Watts (WMAX) on an electric bicycle and we used only WMAX that were adjusted for weight as previously suggested [5]. BMI was computed from measured weight and height at the examination (underweight <18.5 kg/m², normal 18.5-24.99 kg/m², and overweight or obese ≥ 25 kg/m²).

IQ was assessed by written tests with progressive difficulty; a total score was obtained by summing verbal IQ, visuospatial ability, general knowledge, and mechanical ability [10].

Psychological functioning, a proxy for stress resilience, was evaluated by a clinical psychologist during a 20-25 minutes semi-structured interview [11]. IQ and stress resilience values were transformed into a standard nine-level scale and categorized into high (7-9), medium (4-6), and low (1-3).

We included all male conscripts without ALS at the age of 17-20 who were examined during 1968-2010 (N= 1,901,807).

Follow-up

Individual follow-up of the conscripts was accomplished through cross-linkages with the Swedish Patient Register, Cause of Death Register, and Migration Register, using unique personal identification numbers.

The Swedish Patient Register was established in 1964/1965 and since 1987 it includes all somatic hospital discharges in Sweden [12]. From 2001 it includes hospital-based out-patient care. An ALS diagnosis was identified if a diagnosis, main or secondary, had International Classification of Disease (ICD)-9 code 335C between 1987-1996 or ICD-10 code G12.2 since 1997. The first date of hospital contact for ALS was defined as the date of diagnosis. The Swedish Patient Register has a high accuracy for chronic diseases [12] and hospital discharge records have been shown as valid ascertainment for ALS [13].

Date of death and date of emigration were collected from the nationwide Cause of Death Register and the Migration Register, respectively.

The entire cohort was followed from January 1st 1987 or date of conscription examination, whichever occurred later, to ALS diagnosis, death, emigration out of Sweden, or end of study (December 31, 2013), whichever occurred first. The conscripts who died (N=6,531) or emigrated from Sweden (N=10,634) before the beginning of follow-up were excluded, leaving 1,884,642 (99.1%) participants in the analyses.

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Statistical analyses

We described the distribution of weight-adjusted physical fitness (WMAX/kg), BMI, IQ and stress reliance in the entire cohort. Spearman correlation coefficient (ρ) was used to test the correlations between these variables.

To investigate the age-specific impact of high levels of WMAX/kg (≥ 4.25 W/kg), BMI (≥ 25), IQ (7-9), and stress resilience (7-9) in comparison to lower levels on ALS risk, we fitted flexible parametric models with attained age as the time scale to derive hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). A simple model was used to estimate HRs after taking into account attained age. A fuller model was used to estimate HRs mutually adjusted for WMAX/kg and BMI, or IQ and stress resilience. Since pulse has been suggested as one prognostic indicator of ALS [14] and correlates with physical fitness [15], we included resting heart rate (RHR) as an additional variable in the multivariable model for physical fitness. Since the assessment of IQ changed in 1994 in the Conscript Register [8] we considered calendar period of examination (1968-1980, 1981-1993, and 1994-2010) as an additional variable in all the models. To assess the potential influence of socioeconomic status (SES), we adjusted for parental SES (blue collar, white collar, farmers, self-employed, and other) in all analyses. We linked the conscripts to the Swedish Multi-Generation Register [16] and identified their parents. The parents were subsequently linked to the Swedish Population and Housing Censuses that were conducted every five years by Statistics Sweden to identify information on SES.

To assess the impact of physical and cognitive fitness on ALS independently of each other, in an additional analysis, we mutually adjusted for WMAX/kg, BMI, IQ, and stress resilience.

A total of 46,266 conscripts with incomplete information on physical fitness, BMI, RHR, IQ, and stress resilience were excluded, leaving 1,838,376 (97.5%) in the final analyses.

Five and three degrees of freedom were used in the flexible parametric models for modelling the baseline hazard and the time-dependent effect, respectively [17]. Associations with two-sided p-values <0.05 were considered statistically significant. The statistical analysis was performed using Stata ver. 13.1 (StataCorp, Texas, USA).

Results

Baseline characteristics of the study participants are presented in Table 1. WMAX/kg and BMI were negatively correlated ($\rho=-0.23$; $p < 0.001$) whereas IQ and stress resilience were positively correlated ($\rho=0.37$; $p < 0.001$; Supplementary Figure 1).

During follow-up, we identified 439 incident ALS cases. Mean age at ALS diagnosis was 48 years (range 21-62 years, standard deviation=8.74).

Age-specific HRs of ALS for physical and cognitive fitness are presented in Figures 1 and 2. Compared to lower WMAX/kg, high WMAX/kg (≥ 4.25 W/kg) tended to be associated with higher risk of ALS before 45 years of age (range of HRs: 1.42-1.75), after further adjustment for BMI and RHR. The association was only statistically significant for the age of 41-43 years. Overweight or obese, compared to normal weight and underweight, tended to be associated with a lower risk of ALS in both models. A statistically significant association was noted between age 42 and 48 after adjustment for WMAX/kg (range of HRs: 0.42-0.50).

High IQ, compared to lower IQ, was associated with a statistically significantly higher ALS risk from age 56 onward after further adjustment for stress resilience (range of HRs: 1.33-

1.81). High stress resilience, compared to lower stress resilience, was associated with a lower risk of ALS at age 55 or younger, both in the simpler model and after adjusting for IQ (range of HRs: 0.47-0.73 in fuller model).

Mutual adjustment for physical and cognitive fitness yielded similar results (Supplementary Figure 2).

Discussion

Based on a large prospective cohort of Swedish male conscripts, we found that physical and cognitive fitness in early adulthood might be associated with the subsequent risk of early age ALS.

Our cohort addressed a young sample of ALS patients. The mean age at diagnosis (48 years) was about 17 years younger than the mean age at ALS diagnosis reported in population-based studies across Europe [18]. Early onset ALS patients, commonly demonstrating a relatively longer survival and special pathological features, might be of special interest both regarding aetiology and disease natural history [19]. The underlying reasons for early onset ALS include potentially both a high genetic burden [19] and intensive exposure to other non-genetic risk factors during early life.

It is therefore interesting that the association of high WMAX/kg with higher risk of ALS existed only before middle age (45 years) and not thereafter. This finding confirms the results of Mattsson et al. [5], who showed a higher risk of ALS death before age 44 years among conscripts with a high WMAX/kg. In addition, our finding showed that this association diminished and became null toward later ages.

In line with previous findings of an inverse association between premorbid BMI and ALS [6], we found that ALS patients had a lower BMI already at the age of 17-20 years compared to people without ALS. After adjustment for WMAX/kg, the impact of BMI appeared to diminish slightly, stressing the robustness of the association of premorbid BMI with later risk of ALS.

It has been reported that higher educational level is associated with higher risk of ALS [20]. However, to our knowledge, this is the first study to show that high IQ in early adulthood, before further education might be obtained, is already associated with higher risk of ALS. This finding suggests that high IQ might be one of the underlying reasons linking high educational level to an increased ALS risk.

Our study is the first to report that ALS patients tended to have lower stress resilience in early adulthood. An association between high self-reported stress and increased ALS risk has been reported previously [21] and a possible role of psychological stress in initiating motor neuron degeneration has been discussed [22]. Whether or not ALS patients have also lower stress resilience closer in time to diagnosis, compared to ALS-free individuals, needs to be investigated.

Although we mutually adjusted for IQ and stress resilience, it remains an interesting question why the impact of IQ and stress resilience was restricted to different ages.

The associations of early life physical and cognitive fitness with ALS might be specific for ALS relative to other neurodegenerative diseases. Using the same study materials, one study found no association of BMI, stress resilience, and IQ at conscription time with the risk of

multiple sclerosis (MS), whereas an inverse association of physical fitness with MS [23]. Two studies found lower physical fitness and lower IQ to be associated with an increased risk of early-onset dementia [24] [25].

The main strength of our study lies in the sample size, the population-based prospective cohort design, and the complete and long-term follow-up. Data on the exposure variables are believed to have high validity, since they were measured by health professionals at conscription, and were independently collected from the later ALS development.

The small numbers of ALS outcomes resulted in low statistical power for detecting associations in the age-specific analyses. The results on the specific age groups with statistically significant associations should therefore be interpreted with caution. Given the register-based nature of our study, we had no information on the genetic characteristics of the ALS patients identified and were not able to assess whether the studied associations could be modified by common ALS mutations. For example, *SOD1* mutations are known to be common in Northern Sweden [26]. Excluding all ALS patients that were residing in the northern part of Sweden (N=96; 21.9%) did however not change the results (data not shown). To assess the potential influence of *C9orf72* mutations on the study results, we excluded six ALS patients that had a diagnosis of frontotemporal dementia in the Swedish Patient Register (ICD-9 code 331B [1987-1996] and ICD-10 code G31.0 or F02.0 [1997- 2010]). These additional analyses lead also to largely unchanged results (data not shown).

We had no information on other potential ALS risk factors including occupation, smoking, diet, and lifestyle factors, which might serve both as confounders and mediators of the studied associations. Further studies with detailed information on early life physical and cognitive

fitness as well as lifestyle factors both during early life and thereafter might shed further light on the specific pathways underlying our findings. Given the historical nature and nationwide design of the study, we were not able to conduct medical records review for all the ALS patients identified. However, in a recent validation study of all ALS patients from the greater Stockholm area we found a positive predictive value of 91% for the Patient Register-based ALS diagnosis (unpublished data). Because the present study included only male patients that were on average 48 years, concerns of under-diagnosis of ALS might be minor. Finally, since our analysis was restricted to males, whether or not these findings are generalizable to females is not known.

In summary, physical fitness, BMI, IQ, and stress resilience in early life might be associated with the later development of early onset ALS.

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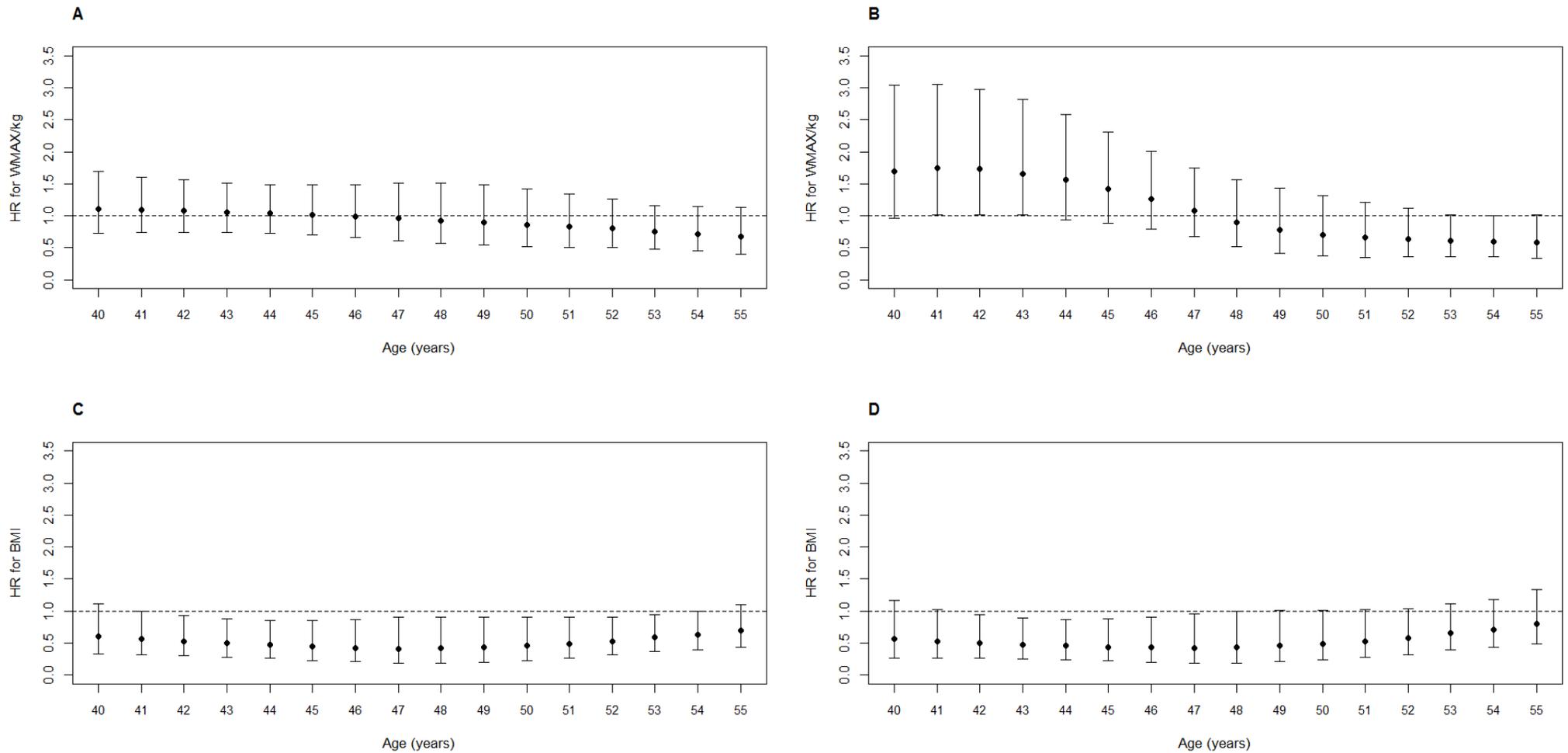
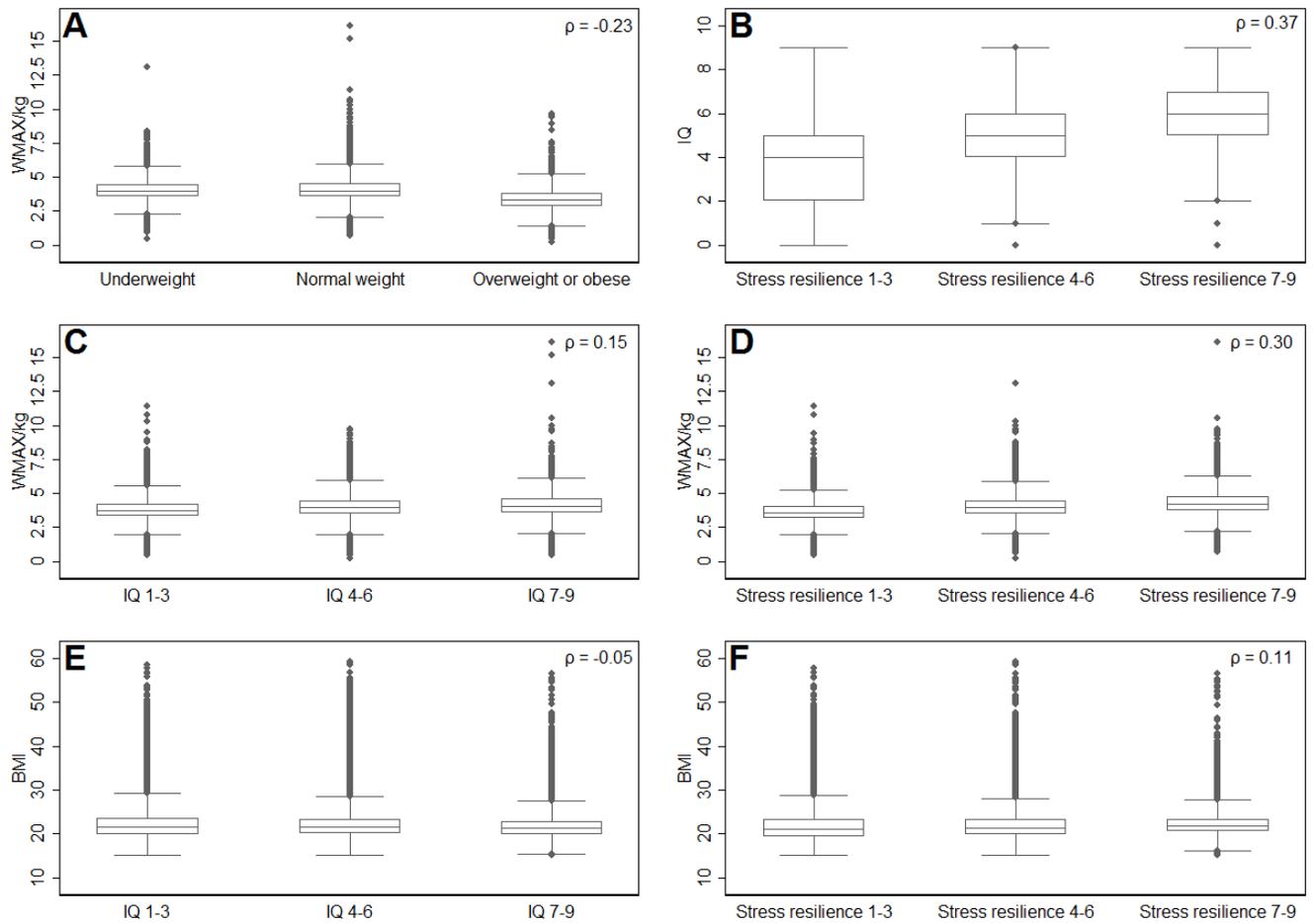


Figure 1.

Age-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of amyotrophic lateral sclerosis, comparing conscripts with high physical fitness (WMAX/kg; ≥ 4.25 W/kg; panels A and B) or high body mass index (BMI; ≥ 25 ; panels C and D) to conscripts with lower physical fitness and lower BMI. Models adjusted for: calendar period of conscription and parental socioeconomic status (SES) (panels A and C); calendar period of conscription, parental SES, BMI, and resting heart rate (panel B); calendar period of conscription, parental SES, and WMAX/kg (panel D).



Supplementary Figure 1

Box plots for physical fitness (WMAX/kg) by body mass index (BMI) (a), intelligent quotient (IQ) by stress resilience (b), WMAX/kg by IQ (c), WMAX/kg by stress resilience (d), BMI by IQ (e), and BMI by stress resilience (f), with corresponding Spearman correlation coefficients (ρ).

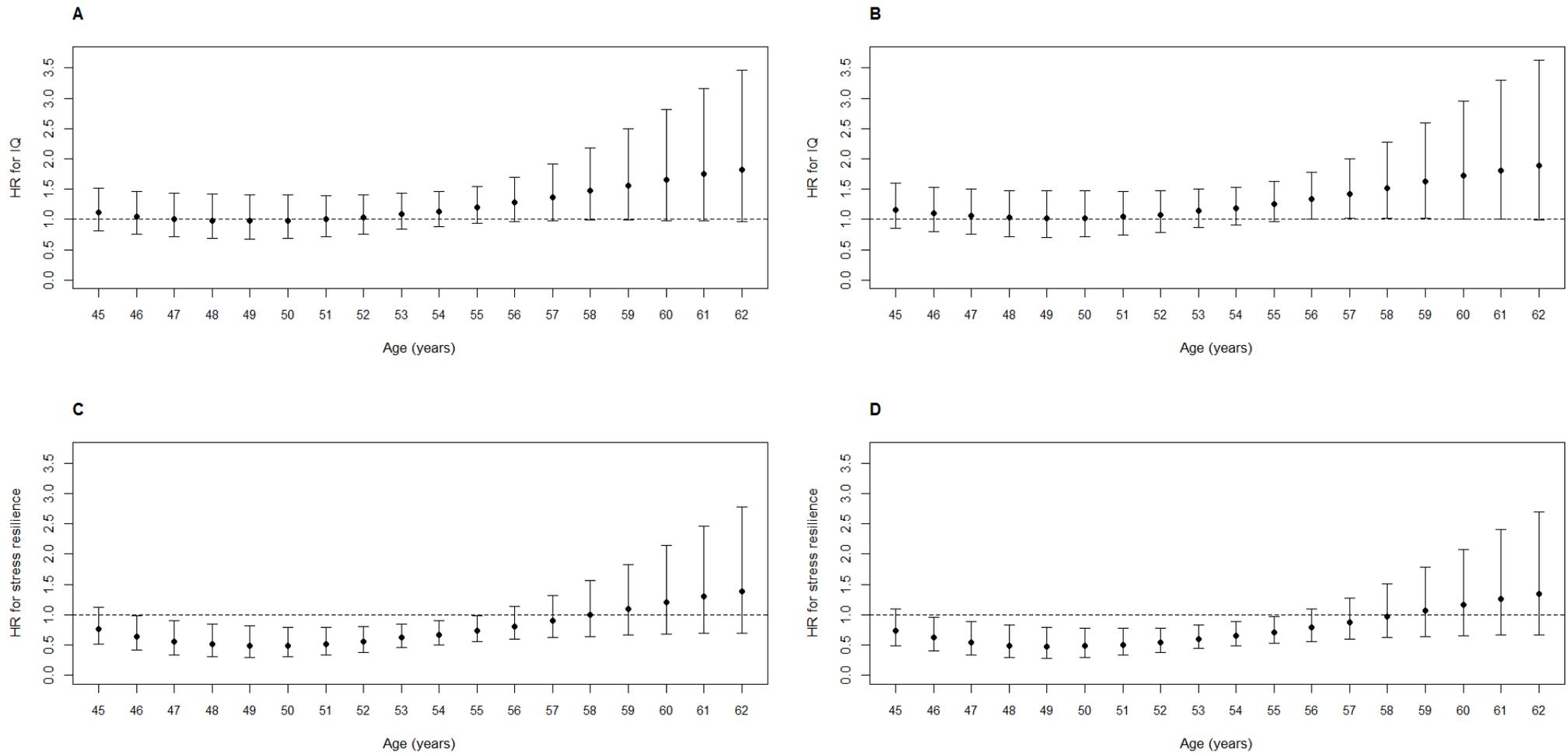
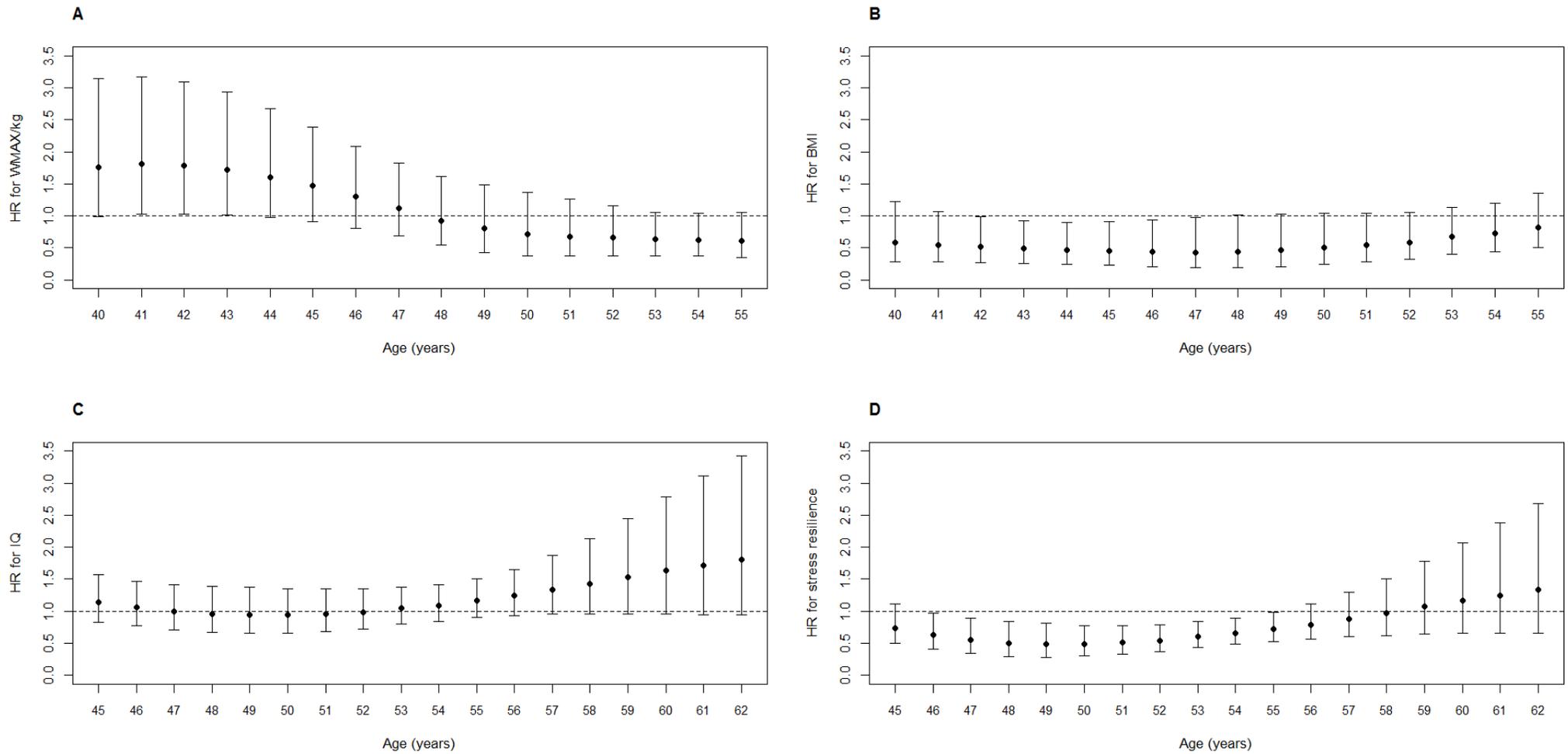


Figure 2.

Age-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of amyotrophic lateral sclerosis, comparing conscripts with intelligence quotient (IQ; panels A and B) or stress resilience (panels C and D) above the highest tertile to conscripts with lower IQ and lower stress resilience. Models adjusted for: calendar period of conscription and parental socioeconomic status (SES) (panels A and C); calendar period of conscription, parental SES, and mutually adjusted for IQ and stress resilience (panels B and D).



Supplementary Figure 2.

Age-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) of amyotrophic lateral sclerosis, for (a) physical fitness (WMAX/kg; ≥ 4.25 W/kg versus < 4.25 W/kg), (b) body mass index (BMI ≥ 25 versus BMI < 25), (c) intelligence quotient (IQ; highest tertile versus lower IQ), and (d) stress resilience (highest tertile versus lower stress resilience). All models are adjusted for calendar period of conscription examination, parental socioeconomic status, and mutually adjusted for WMAX/kg, BMI, IQ, and stress resilience.

Table 1. Baseline characteristics of the study participants

	N ¹	%
Age at conscript examination		
17 years	505,009	27.47
18 years	1,202,283	65.40
19 years	112,074	6.10
20 years	19,010	1.03
Calendar period of conscript examination		
1968-1980	532,102	28.94
1981-1993	686,028	37.32
1994-2010	620,246	33.74
Weight-adjusted physical fitness		
≤ 3.61 W/kg	483,218	32.59
3.62 - 4.24 W/kg	493,225	33.27
≥ 4.25 W/kg	506,101	34.14
Body Mass Index		
Underweight (<18.5 kg/m ²)	136,816	7.44
Normal (18.5 - 24.99 kg/m ²)	1,365,247	74.26
Overweight or Obese (≥25 kg/m ²)	336,313	18.29
Intelligent Quotient (stanine)		
1-3	391,406	21.60
4-6	982,335	54.20
7-9	438,576	24.20
Stress resilience (stanine)		
1-3	356,800	20.96
4-6	983,495	57.77
7-9	362,195	21.27

¹Missing information on 355,832, 26,059, and 135,886 participants for weight-adjusted physical fitness, intelligent quotient, and stress resilience respectively.