Genome-wide autozygosity is associated with lower general cognitive ability

D. P. Howrigan
M. A. Simonson
G. Davies
S. E. Harris
A. Tenesa

See next page for additional authors

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Authors
D. P. Howrigan, M. A. Simonson, G. Davies, S. E. Harris, A. Tenesa, J. M. Starr, D. C. Liewald, D. I. Boomsma, P. DeRosse, M. C. Keller, and +37 additional authors
The impact of genome-wide autozygosity on general cognitive ability

Daniel P. Howrigan1,2, Matthew A. Simonson3, Gail Davies4, Sarah E. Harris5,6, Albert Tenesa7,8, John M. Starr9,5, David C Liewald5, Ian J. Deary4,5, Allan McRae10,11, Margaret J. Wright10, Grant W. Montgomery10, Narelle Hansell10, Nicholas G. Martin10, Antony Payton12, Michael Horan13, William E. Ollier12, Abdul Abdellaoui14,15, Dorret I. Boomsma14,15,16, Pamela DeRosse17,18,19, Emma E. M. Knowles20, David C. Glahn20, Srdjan Djurovic21,22, Ingrid Melle21,22,23, Ole A. Andreassen21,22,23, Andrea Christoforou24,25, Vidar M. Steen24,25, Stephanie Le Hellard24,25, Kjetil Sundet21,26, Ivar Reinvang26, Thomas Espeseth26,27, Astri J. Lundervold28,29,30, Ina Giegling31, Bettina Konte31, Annette M. Hartmann31, Dan Rujescu31, Panos Roussos32,33, Stella Giakoumaki34, Katherine E. Burdick32, Panos Bitsios35,36, Gary Donohoe37, Robin Corley38, Peter M. Visscher5,10,11,39, Neil Pendleton12, Anil K. Malhotra17,18,19, Benjamin M. Neale1,2, Todd Lencz17,18,19, and Matthew C. Keller38,40

1Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA 2Stanley Center for Psychiatric Genetics, Broad Institute of Harvard and MIT, Cambridge Center, Cambridge, MA, USA 3Division of Data Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA 4Department of Psychology, University of Edinburgh, Edinburgh, UK 5Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK 6Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK 7Institute of Genetics and Molecular Medicine, MRC Human Genetics Unit, Western General Hospital, University of Edinburgh, Edinburgh, UK 8The Roslin Institute, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Roslin, UK 9Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK 10Queensland Institute of Medical Research Berghofer, Brisbane, QLD, Australia 11Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia 12Centre for Integrated Genomic Medical Research, Institute of Population Health, University of Manchester, Manchester, UK 13Centre for Clinical and Cognitive Neurosciences, Institute of Brain Behaviour and Mental Health, University of Manchester, Salford Royal NHS Foundation Trust, Salford, UK 14Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands 15Neuroscience Campus Amsterdam, Amsterdam, The Netherlands 16EMGO+ Institute for Health and Care Research, Amsterdam, The Netherlands

Correspondence: Dr DP Howrigan, Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, 185 Cambridge St, CPZN 6818, Boston, MA 02114, USA or Dr MC Keller, Department of Psychology, University of Colorado at Boulder, Boulder, CO 80303, USA; Email: daniel.howrigan@gmail.com or Email: matthew.c.keller@gmail.com.

CONFLICT OF INTEREST STATEMENT
The authors declare that they have no competing financial interests.
Inbreeding depression refers to lower fitness among offspring of genetic relatives (1). This reduced fitness is caused by the inheritance of two identical chromosomal segments (autozygosity) across the genome, which may expose the effects of (partially) recessive deleterious mutations. Even among outbred populations, autozygosity can occur to varying degrees due to cryptic relatedness between parents (2). Using dense genome-wide SNP data, we examined the degree to which autozygosity associated with measured cognitive ability in an unselected sample of 4,854 participants of European ancestry. We used runs of homozygosity—multiple homozygous SNPs in a row—to estimate autozygous tracts across the genome. We found that increased levels of autozygosity predicted lower general cognitive ability, and estimate a drop of 0.6 standard deviations among the offspring of first cousins (p = 0.003 - 0.02 depending on the model). This effect came predominantly from long and rare autozygous tracts, which theory predicts as more likely to be deleterious than short and common tracts. Association mapping of autozygous tracts did not reveal any specific regions that were predictive beyond chance after correcting for multiple testing genome-wide. The observed effect size is consistent with studies of cognitive decline among offspring of known consanguineous relationships (3). These findings suggest a role for...
INTRODUCTION

General cognitive ability, traditionally measured through IQ-type psychometric tests, is a composite measure of cognition across multiple domains (4-6). It reliably predicts many life outcomes, such as health, longevity, social mobility, and occupational success (7-10). Decades of behavioral genetic research on general cognitive ability have shown moderate to high heritability estimates across development (11, 12), (13, 14). Results from GWAS and mixed linear models estimating variance components from SNPs suggest that the genetic variation underlying general cognitive ability is highly polygenic and mostly additive in nature (15-17). Furthermore, family studies have shown that offspring of consanguineous marriages have lower cognitive performance than the general population, supporting a role for inbreeding depression on general cognitive ability (3, 18-22).

The hypothesized cause of inbreeding depression, directional dominance of alleles that affect fitness, is thought to occur because selection acts more efficiently on additive effects than on recessive effects, which tends to bias deleterious effects toward a recessive mode of action (23). Inbreeding increases the probability that recessive/partially recessive deleterious mutations are homozygous by increasing the proportion of the genome that is autozygous (stretches of two homologous chromosomes in the same individual that are identical by descent). It is important to recognize that traits influenced by inbreeding depression are not predicted to have high levels of non-additive genetic variation; if inbreeding depression occurs because of the effects of rare, partially recessive deleterious mutations, most of the genetic variation will be additive (24, 25). While highly inbred individuals are autozygous for a substantial proportion of their genome (e.g. first cousin inbreeding leads to 6.25% average autozygosity genome-wide), autozygosity still occurs in outbred populations, albeit at lower levels, due to shared distant common ancestors between mates of no known relationship. Using high-density SNP arrays, the existence of autozygosity arising from distant inbreeding can be inferred using runs of homozygosity (ROH)—multiple homozygous SNPs in a row (2, 26, 27). To the degree that ROHs accurately measure autozygosity, ROHs capture not only homozygosity at measured SNPs, but also homozygosity at rare, unmeasured variants that exist within ROHs (28, 29). Thus, inbreeding estimates based on SNP-by-SNP excess homozygosity (F_snip) capture the effects of homozygosity at common variants, while inbreeding estimates based on the proportion of the genome in ROHs (F_roh) capture the effects of homozygosity at both common and rare variants.

To date, a number of studies have examined the effect of F_roh burden and individual ROH regions on case/control and quantitative phenotypes, with early studies showing mixed results (30), including a non-significant F_roh-cognitive ability relationship among individuals of European ancestry (N=2329) (31). Given the low variation in F_roh among outbred samples, it is likely that these studies were underpowered (29). Investigations with larger samples have been more successful, finding increased F_roh burden associated with...
schizophrenia (32), height (33), and personality (34). Here, we present an analysis of Froh on general cognitive ability for 4854 individuals of European ancestry from eight samples, including five samples from the COGENT consortium (35). Understanding the contribution of autozygosity to individual differences in general cognitive ability can help elucidate the genetic architecture underlying this important and highly polygenic trait.

MATERIALS AND METHODS

Genetic and Sample quality control

Quality control (QC) procedures focused on properties that would be appropriate across a range of genotyping platforms that differed in SNP density. The main goal—analyzing runs of homozygosity to infer autozygosity—differed from the usual goal of finding associations between individuals SNPs and a phenotype, and so the procedures adopted were more stringent than those typically used in genome-wide association studies. Moreover, because so many SNPs (70-75% depending on the sample) were removed due to linkage disequilibrium pruning during ROH detection (see below), we could afford to use more stringent QC procedures, because dropped SNPs were likely to be in strong linkage disequilibrium with other nearby SNPs that were retained.

Table 1 lists the specific genotyping platforms used, with an average LD-pruned SNP density of 229K SNPs (range: 174K – 277K). The specific QC procedures and numbers of individuals or SNPs dropped at each step can be found in Table S4. Most steps are self-explanatory, so only those needing clarification are discussed. Individuals whose self-reported sex was discrepant from their genotypic sex were dropped, as these individuals might represent sample mix-ups. Individuals who self-identified as non-European ancestry were dropped, as both homozygosity and phenotypic measures might differ between ethnicities or across different levels of genetic admixture. We also merged the genotype data with HapMap2 reference samples (36), and removed anyone clearly outside of the European ancestry cluster. Finally, we did not remove individuals with excess genome-wide homozygosity as such individuals are more likely to be inbred and therefore informative for investigating the current hypothesis.

Runs of Homozygosity (ROHs) calling procedures

ROH were called in PLINK using the --homozyg command (37), which has been found to outperform other programs in accurately identifying autozygous segments (38). The current analysis incorporated the ROH tuning parameters recommended in Howrigan et al. (38). In particular, each dataset was pruned for either moderate LD (removing any SNP with $R^2 > 0.5$ with other SNP in a 50 SNP window) or strong LD (removing any SNP with $R^2 > 0.9$ with other SNP in a 50 SNP window). For moderate LD-pruned SNPs, the minimum SNP length threshold was set to 35, 45, or 50 SNPs. For strong LD-pruned SNPs, the minimum SNP length threshold was set to 65 SNPs. We did not allow for heterozygote SNPs, used a window size equal to the minimum SNP threshold, and allowed for 5% of SNPs to be missing within the window (38). In addition, PLINK’s --homozyg-group and --homozyg-match commands were used to find allelically matching ROH that overlapped at least 95% of physical distance of the smaller ROH. We chose the 65 SNP minimum pruned for strong
LD, as this parameter setting has been used in previous analyses (32). Primary Froh burden results, however, were similar for all four tuning parameters used (Table S1).

**Froh genotype**

Genome-wide ROH burden, or Froh, represents the percent of the autosome in ROHs. Froh was derived by summing the total length of autosomal ROHs in an individual and dividing this by the total SNP-mappable autosomal distance ($2.77 \times 10^9$). The distribution of Froh in the sample is listed in Figure S1. Froh can be affected by population stratification (e.g., if background levels of homozygosity or autozygosity differ across ethnicities), low quality DNA leading to bad SNP calls, and heterozygosity levels that differ depending on, for example, genotype plate, DNA sources, SNP calling algorithm, or sample collection site. We controlled for covariates in two steps – within dataset and across the combined datasets. Within each dataset, we controlled for the first ten principal components generated from an identity-by-state matrix derived from a subset of SNPs (~50,000) within each dataset. We also controlled for age and age-squared within dataset when provided, as age information was not available in four of the eleven studies (Table 2). We used the linear model residuals from within each dataset as our Froh genotype moving forward. Across the combined samples, we controlled for gender, dataset, the percentage of missing calls - which has been shown to track the quality of SNP calls (39), and excess SNP-by-SNP homozygosity ($F_{snp}$, from PLINK's --het command) - which can be used to test the effects of homozygosity at common but not rare variants.

**General cognitive ability phenotype**

Table 2 lists the sample characteristics and various measures of general cognitive ability employed (additional description in Supplementary information). Measures of general cognitive ability were standardized within each dataset (Figure S2). We controlled for potential confounds in same manner as the Froh genotype, regressing out the first ten principal components, age, and age-squared within each dataset, and dataset, gender, SNP missingness, and $F_{snp}$ across the combined dataset.

**Froh burden analysis**

To test the effect of Froh burden on general cognitive ability, we examined both fixed-effects modeling (i.e. lm() in R) and mixed-effects modeling treating dataset as a random effect (i.e. lmer() from the lme4 package in R). Both analyses showed very consistent results, and we used fixed-effects modeling approach for all analyses hereafter. For our primary analysis, we tested the effects of Froh after controlling for $F_{snp}$ as we have done previously (32), not only because this analysis provides information on the importance of rare recessive variants in particular, which are thought to be the primary cause of inbreeding depression (23), but also because controlling for $F_{snp}$ can increase power to detect Froh relationships in the presence of genotyping errors (29). We also report the effects of Froh not controlling for $F_{snp}$. In follow up analyses, Froh burden was partitioned into short and long ROH as well as common and uncommon ROH according to median splits of both variables. Due to the variation in SNP density across dataset platforms (ranging from 300k to over 1 million SNPs), median splits for both length and frequency were calculated within each dataset (see
Table S2). Across all datasets, 34% of the total length of ROHs was composed of short ROHs and 66% was composed of long ROHs, whereas 38% of the total ROH length was composed of common and 62% was composed of uncommon ROHs.

**ROH mapping analysis**

To investigate whether specific genomic regions predicted general cognitive ability, we co-opted the rare CNV commands used in PLINK, whereby each ROH segment was tested at the two SNPs defining the start and end position. At each position, all individuals with ROH overlapping the tested SNP were included as ROH carriers. General cognitive ability residuals, after controlling for all covariates, were used as the dependent variable. We restricted ROH mapping to positions where five or more ROHs existed across the sample, and derived statistical significance at each position from one million permutations in PLINK.

To derive a genome-wide significance threshold for multiple testing, we estimated the family-wise error rate directly from permutation. To do so, we ran 1000 permutations on the general cognitive ability phenotype and obtained empirical $p$-values in the same manner as above. We then extracted the most significant $p$-value from each permutation, and used the $95^{th}$ percentile (or 50$^{th}$ most significant $p$-value among the set) as our genome-wide significance threshold ($p = 4e^{-6}$). Thus, under the null hypothesis, we had a 5% chance of observing a single genome-wide significant hit.

**RESULTS**

Figure 1 shows the parameter estimates of $F_{roh}$ predicting general cognitive ability within each dataset and combined across the full sample. In the combined sample, higher levels of $F_{roh}$ were associated, albeit modestly, with lower general cognitive ability ($\beta = -9.8$, $t(4852) = -2.31$, $p = 0.02$). This estimate suggests that every one percentage point increase in $F_{roh}$ corresponds to a ~0.1 standard deviation reduction in general cognitive ability, extrapolating to an expected ~0.6 standard deviation reduction among the offspring of first cousins. Our estimate was not driven by potential outliers in $F_{roh}$, as it increased when we removed the 33 individuals with no ROH calls and 5 individuals with > 6% $F_{roh}$ ($\beta = -12.8$, $t(4814) = -2.68$, $p = 0.007$), and was insensitive to ROH calling thresholds ≥ 50 consecutive homozygous SNPs (Figure S3). The relationship between $F_{roh}$ and general cognitive ability remained stable across models where covariates were removed in step-wise fashion or split by age groups or sex. In particular, the estimate for $F_{roh}$ on general cognitive ability was more significant when SNP-by-SNP homozygosity, $F_{snps}$, was removed as a covariate ($\beta = -9.9$, $t(4852) = -2.92$, $p = 0.003$), whereas $F_{snps}$ did not itself predict general cognitive ability ($\beta = -0.1$, $t(4852) = -0.04$, $p = 0.97$), and suggests that homozygosity at rare variants drove the observed $F_{roh}$ effect. Finally, contrary to a previous report (31), we found no evidence for increased assortative mating or inbreeding at the upper tail of the cognitive ability distribution.

Additional analyses found that $F_{roh}$ from long ROH ($\beta = -9.2$, $t(4852) = -2.15$, $p = 0.03$), and rare ROH ($\beta = -15.4$, $t(4852) = -2.56$, $p = 0.01$) remain significant, whereas $F_{roh}$ estimates from short or common ROH did not ($p > 0.30$ for both, see Supplementary
Information for full analysis). Both short autozygous haplotypes, which arise from more distant common ancestry, and common autozygous haplotypes, which arise from chance pairing of common haplotypes segregating in the population, have had more opportunities to be subject to natural selection when autozygous. This may bias them to be less deleterious when autozygous than long or rare haplotypes.

In addition to Froh burden, we mapped individual ROH along the autosome to assess whether specific regions associate with general cognitive ability. Using PLINK, we mapped and analyzed ROH segments at their respective ends (i.e. the first and last SNP in the ROH), counting all overlapping ROH incorporating that SNP as ROH carriers. We observed minimal test statistic inflation across the genome (\(\lambda_{GC} = 1.02\); QQ plot shown in Figure S5), suggesting that the integration of various sub-populations within the full sample were adequately controlled and did not inflate ROH mapping test statistics. Although we did not identify any specific ROH regions that surpassed strict genome-wide correction (Figure 2), we highlight sixteen regions with \(p < 0.001\) as potential areas of interest (Table S3). Our top association, located on chromosome 21q21.1 (\(p = 5.4 \times 10^{-5}\), Figure S6), predicts lower general cognitive ability and has a distinct peak over USP25, a ubiquitin specific peptidase gene expressed across a variety tissues types, including brain (40).

DISCUSSION

After stringent quality control and the application of preferred methods for detecting autozygosity, we observe a significant, albeit modest, trend of autozygosity burden (Froh) lowering cognitive ability among outbred populations of European ancestry. Inbreeding among first cousins leads to an average Froh burden of 6.25%, and corresponds to a predicted drop of 9.19 IQ points in the current study, an effect consistent with previously detected effects from pedigree-based consanguineous inbreeding (3). In addition, we find that long and rare ROH are driving Froh association to general cognitive ability, as the relationship of Froh to general cognitive ability disappear when restricting to either short or common ROH, but remain when considering either long or rare ROH. At the level of individual ROH, however, we do not identify any specific autozygous loci that significantly predicted general cognitive ability after genome-wide correction.

There were several limitations to the current study that were largely a consequence of combining multiple datasets together. First, the operational construct of general cognitive ability differed somewhat between datasets (see Table 2 and Supplementary Information), and statistical power can be lost as a function of the degree of phenotypic heterogeneity in measured cognitive ability across samples. Second, the autozygosity – cognitive ability relationship might be mediated differentially across sites/datasets. For example, analysis of the Netherlands Twin Registry found that increased religiosity was associated with both higher autozygosity and lower rates of major depression in the Netherlands, which if unaccounted for, would have obscured the true relationship between major depression and autozygosity (41). More recent evidence in the same dataset found that increased parental migration mediated the relationship of education attainment to autozygosity (42). Unfortunately, these potential confounds are often unmeasured and were unavailable in the current study. Third, despite following strict QC procedures, the use of different genotyping
platforms affects ROH calls across datasets. Although dataset was included as a covariate, such differences add noise and reduce statistical power, and it is impossible to rule out all biases that could arise from such differences between datasets. Finally, we did not measure copy number deletions in our dataset, and hemizygosity due to deletions could be included in the Froh estimates. Previous studies, however, using deletions called from intensity data found that fewer than 0.3% of the total lengths of ROHs in their samples were actually hemizygous, suggesting that deletions had a minimal effect on the present results (2, 32).

Autozygosity is the most direct measure of inbreeding at the genetic level. It can help elucidate the genetic architecture underlying heritable traits like general cognitive ability and provide clues to the evolutionary forces that acted on alleles affecting the trait. Our results suggest that alleles that decrease cognitive ability are more recessive than otherwise expected, and are consistent with the hypothesis that alleles that lead to lower cognitive ability have, on average, been under negative selection ancestrally.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**NCNG**

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Bibliography

8. Deary IJ, Weiss A, Batty GD. Intelligence and personality as predictors of illness and death: How researchers in differential psychology and chronic disease epidemiology are collaborating to understand and address health inequalities. Psychological Science in the Public Interest. 2010; 11:53–79. [PubMed: 26168413]

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Figure 1. Forest plot of slope estimates and 95% confidence intervals of *Froh* predicting general cognitive ability. Points represent slope estimates and bars represent 95% confidence intervals. Datasets are color coded by the genotyping platform used. The three GAIN datasets were combined for clarity.
Figure 2. ROH mapping manhattan plot predicting general cognitive ability

Top panel: $-\log_{10} p$-values for ROH breakpoint regions predicting general cognitive ability. Regions with $p$-values below 0.001 are flagged for predicting lower cognitive ability (red) and higher cognitive ability (blue). The red dotted line is the genome-wide correction estimate, set at $4e^{-6}$, which is the top 5% of minimum $p$-values observed across 1000 permutations. Bottom panel: ROH frequencies for each region across the autosome, with the highest frequency of ROH due to balancing selection in the MHC (chr6) and recent positive selection in lactase persistence gene region (chr2).
### Table 1

<table>
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<th>Dataset</th>
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<th>Platform</th>
<th>SNPs passing QC</th>
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<th>avg ROH length (kb)</th>
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*Froh is calculated as proportion of an individual's genome captured in ROH.*
### Table 2

Descriptive statistics of general cognitive ability, age, and sex across datasets

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<th>Dataset</th>
<th>N</th>
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<th>Cognitive ability measures</th>
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<th>Male (%)</th>
<th>Female (%)</th>
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<td>United Kingdom</td>
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<td>WAIS-III: 4 subtests (Ages 16+) WISC-III: 4 subtests (Ages 5-16)</td>
<td>9.40 (2.53)</td>
<td>62 (91%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>MANC</td>
<td>763</td>
<td>England</td>
<td>Cattell Culture Fair Test</td>
<td>64.9 (6.14)</td>
<td>226 (30%)</td>
<td>537 (70%)</td>
</tr>
<tr>
<td>NEWC</td>
<td>717</td>
<td>England</td>
<td>Cattell Culture Fair Test</td>
<td>65.71 (6.10)</td>
<td>206 (29%)</td>
<td>511 (71%)</td>
</tr>
<tr>
<td>LOGOS</td>
<td>776</td>
<td>Greece</td>
<td>Cambridge NTAB: 3 subtests N-Back task Wisconsin card sort Stroop Gambling task Wechsler memory scale</td>
<td>22.13 (18-29)</td>
<td>776 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>NCNG</td>
<td>623</td>
<td>Norway</td>
<td>California Verbal Learning Test-II D-KEFS Color Word interference WAIS-III Matrix Reasoning subscale Multiple choice reaction time task</td>
<td>NA</td>
<td>200 (32%)</td>
<td>423 (68%)</td>
</tr>
<tr>
<td>ZHH</td>
<td>175</td>
<td>New York, USA</td>
<td>MATRICS Consensus Cognitive Battery</td>
<td>NA</td>
<td>85 (49%)</td>
<td>90 (51%)</td>
</tr>
<tr>
<td>TOP</td>
<td>305</td>
<td>Norway</td>
<td>WASI: 4 subtests National Adult Reading Test</td>
<td>NA</td>
<td>165 (54%)</td>
<td>140 (46%)</td>
</tr>
<tr>
<td>RUJ</td>
<td>586</td>
<td>Germany</td>
<td>WAIS-R</td>
<td>NA</td>
<td>293 (50%)</td>
<td>293 (50%)</td>
</tr>
<tr>
<td>Total</td>
<td>4854</td>
<td>---</td>
<td>---</td>
<td>--- (---)</td>
<td>2715 (56%)</td>
<td>2139 (44%)</td>
</tr>
</tbody>
</table>

Datasets where age information was unavailable were not included in the regression model.