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Associations between Neighborhood-Level Factors and DNA Methylation in Breast Tumor Tissue: Using Social Epigenomics to Explore Cancer Disparities

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By

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B.A., Northwestern University, 2018

Faculty Thesis Advisor: Lauren E. McCullough, PhD, MSPH

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Abstract

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Background: Social exposures may play an influential role in epigenetic alterations that disproportionately affect racial disparities in breast cancer outcomes. This study examined the possible association between neighborhood-level factors and DNA methylation in non-Hispanic Black and White women diagnosed with breast cancer.

Methods: Genome-wide DNA methylation was measured using the EPIC array in breast cancer tumor tissue of 96 women. Linear regression models were used to examine the association between neighborhood-level factors and tumor tissue methylation, regressing methylation β values for each cytosine and guanine dinucleotide (CpG) site on neighborhood-level factors while adjusting for covariates. Neighborhood-level data were obtained from the Opportunity Atlas. Statistical significance was set at a false detection rate (FDR) < 0.05. For statistically significant CpG sites, we explored interactions with race. We used multivariable Cox-proportional hazard models to estimate whether methylation in these sites were associated with all-cause mortality.

Results: 26 of the CpG sites were FDR significant at the 0.05 threshold. We observed interactions between population density and race at four CpG sites. We observed an association between methylation and all-cause mortality at 11 CpG sites.

Conclusions: We identified novel associations between neighborhood-level factors and DNA methylation, and interactions with race. Our data suggest that dysregulation in the 11 CpG sites may be associated with all-cause mortality.

Impact: Neighborhood-level factors may contribute to differential tumor methylation in genes related to tumor progression and metastasis. This contributes to the field of social epigenomics, examining the potentially instrumental role social exposures play in understanding cancer disparities.

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Associations between Neighborhood-Level Factors and DNA Methylation in Breast Tumor Tissue: Using Social Epigenomics to Explore Cancer Disparities.

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Abstract

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Introduction

Breast cancer is the most common cancer in American women and one of the leading causes of cancer death (1), however substantial disparities exist in mortality by race, socioeconomic status, and neighborhood-level characteristics (2, 3). While emerging research supports the role of individual and area-level social determinants in breast cancer outcomes, little information is known regarding potential biological mechanisms underlying these associations. Social epigenomics is the growing field that examines how social and environmental experiences may impact the epigenome through histone modification, telomere shortening, and DNA methylation (4). These studies reveal how social environments may disproportionately affect minority health and how minority populations are more exposed to adverse environments, thus resulting in health disparities (4). Previous studies have found an association between individual-level SES and DNA methylation among children, young adults, and adults (5 -11) and how methylation may differ by race (12). While this suggests that individual social factors may influence one's epigenome, it does not reveal the potential role one's social environment may play in DNA methylation. The role that one's neighborhood plays in affecting health is a unique one, as it affects health multidimensionally. Even after accounting for individual-level socioeconomic factors, living in a disadvantaged neighborhood is associated with poor health outcomes (12). Additionally, chronic stress due to unfavorable neighborhood conditions can result in dysregulation of inflammatory and stress reactivity pathways, which can be driven by epigenetic modifications such as DNA methylation (13).

Epigenetic modifications are genomic alterations that do not involve changes to the underlying DNA sequence. These mechanisms have become a reliable biomarker that can comprehensively capture both genetic and environmental influences on as potential drivers of disease. DNA methylation has become a leading epigenetic mechanism to study due to its influence on gene expression and its malleability to lifestyle and environmental exposures (14). Aberrant DNA methylation can result in the increased expression of oncogenes and silencing of tumor suppressor genes; a common occurrence in breast carcinogenesis (14, 15). Exploring the role of area-level sociodemographic characteristics on methylation may give mechanistic insights to the role that social stress plays in breast cancer progression and potential race disparities.

No study to date has used a genome-wide approach to assess neighborhood factor-associated methylation and breast cancer prognosis. Ultimately, the purpose of this study was to conduct an epigenome-wide association study (EWAS) of breast tumor tissue to identify CpG sites associated with several neighborhood-level factors. Additionally, we explored interaction by race and downstream associations with breast cancer prognosis.

Methods

Study Population

Study protocol follows the methodology done in Leet et al. (16). Fresh tumor specimen and Clinical data were collected from patients receiving surgery at three metro-Atlanta area hospitals (Emory University Hospital, Emory University Hospital Midtown, and Grady Memorial Hospital) by the Glenn Family Breast Satellite Tissue Bank at the Winship Cancer Institute of Emory University. Stratified sampling was implemented to identify 99 non-Hispanic White (NHW) and non-Hispanic Black (NHB) women diagnosed with breast cancer between 2008 and 2017. Women were eligible for inclusion in this study if they were at least 21 years of age, self-reported NHW or NHB, diagnosed with a first-primary stage I, II, or III breast cancer, and received surgery at one of the aforementioned hospitals. Women who were previously diagnosed with breast cancer or did not have a fresh tissue specimen were excluded from this study.

Data Collection

Clinical records of women who underwent surgery provided covariate data, including age at diagnosis, race, self-reported smoking status, educational attainment, and family history of breast cancer. Patient zip codes were collected from the Georgia Cancer Registry. Clinical characteristics were also obtained from records, including ER status, human epidermal growth factor 2 (HER2) status, and progesterone receptor (PR) status; tumor grade; receipt of endocrine therapy, radiation, and chemotherapy; comorbidities; breast cancer mortality; and all-cause mortality. All-cause mortality, including breast cancer-specific mortality, was considered a poor prognosis. We anticipate that any mortality in this sample would be at least partially driven by breast cancer due to a short follow-up period of 10 years (17).

Neighborhood level factors were collected from the *Opportunity Atlas*, a publicly available atlas of anonymized longitudinal data for nearly every neighborhood and census tract in the United States (18). The *Opportunity Atlas* compiles data from publicly available Exposures that were collected from the *Opportunity Atlas* include median rent (2012 - 2016), job growth rate (2004-2013), median household income (2012-2016), poverty rate (2012-2016), fraction college graduates (2012 -2016), fraction non-white (2010), fraction single parents (2012-2016), population density (2010), and job density (2013). The target sample population consists of all children in the 1978-1983 birth cohort who, along with their parents, were either born in the US or are authorized immigrants. Individual-level data were collected from three Census Bureau data sources: the Census 2000 and 2010 short forms; federal income tax returns in 1989, 1994, 1995, and 1998-2015; and the Census 2000 long form and the 2005-2015 American Community Surveys (ACS). The use of the *Opportunity Atlas* is analogous to obtaining neighborhood characteristics data from the aforementioned sources and are reflective of the years during which data were collected.

Methylation Data

DNA methylation was measured in 99 breast tumor tissue samples using the Illumina Infinium MethylationEPIC Beadchip (Illumina, San Diego, CA, USA). Methylation assays were performed in accordance with the Infinium HD Methylation Assay protocol. The protocol uses bisulfite treatment of DNA to convert unmethylated cytosines to uracil, allowing identification of methylated versus unmethylated loci. Two site-specific probes then bind to loci-flanking methylated or unmethylated sequences. The fluorescent signal from the methylated probe (M) relative to the total signal of methylated (M) and unmethylated (U) probes combined is the proportion of DNA strands that are methylated for that CpG site (19). The β-value represents this: $\beta = [M/(M+U)]$. The β-value ranges from 0 to 1, where 1 represents 100% of the cells being methylated at a CpG site. Three samples were removed during pre-processing due to poor performance.

Quality control (QC) was conducted on the data using the *CpGassoc* package in R. Data points with detection p-values > 0.001 or with low signal were set to missing, and CpG sites with missing values (2,869) in over 10% of the samples were removed from the dataset. A stricter probe filtering, as suggested by Zhou et al. (doi: 10.1093/nar/gkw967) was employed by filtering out MASK_general CpG sites. The final sample set had non-missing data for at least 95% of CpG sites. After QC, 758,942 CpG sites remained for evaluation with neighborhood level factors.

Statistical Analysis

Analyses were carried out using R (www.r-project.org/). Demographic characteristics were reported as means or frequencies. DNA Methylation at each CpG site across the entire genome was examined using EWAS. Linear regression models assessed whether individual mean β-values differed due to neighborhood level factors measured, race, or poor prognosis, adjusting for model-specific covariates based on a-priori knowledge of the literature (20, 21).

For the EWAS, the CpGassoc package was used to fit a linear regression model for each CpG site. Every regression modeled methylation and one of the neighborhood level factors as the primary predictor, adjusting for age, race, smoking status, and chip position. These regressions were repeated for all eleven of the neighborhood level factors collected in this analysis. A fixed effect for each BeadChip was included in every model to account for any potential chip-to-chip differences in measurement and to adjust for batch effects as well. Significance was defined as a false discovery rate (FDR) q-value < 0.05. Outliers in EWAS were excluded in a *post-hoc* sensitivity analysis, which seems to have been driven by only one patient. Gene annotation for each probe was determined using the Illumina annotation file. The UCSC_RefGene_Name column provided information of site associated with multiple transcripts of the same gene or multiple genes.

In order to assess whether the relationship between each of the neighborhood level factors and tumor methylation was modified by race, the top differentially methylated CpG sites identified in the primary EWAS were tested for interaction. For each of the CpG sites, the β-values were regressed on the neighborhood-level factors with an interaction between the neighborhood-level factors and race. All interaction analyses were adjusted for age, race, and chip position, and the statistical significance was set at $p < 0.05$.

In order to determine whether neighborhood-level factor-associated methylation was associated with mortality, multivariable Cox proportional-hazard ratios (HR) were used to examine associations between the top CpG sites and all-cause mortality. Treatment characteristics, ER status was considered as a potential covariate in the model, however it was excluded due to causal graphical analyses indicating that it was a likely mediator of the exposure-outcome relationship. In the final models, we examined models adjusting for (1) age, (2) age and race, and (3) age, race, cancer stage, and cancer subtype.

Results

Demographic information is presented in **Table 1**. NHB women in our study sample, on average were older and had a higher BMI compared to NHW women (mean age = 58 vs 50 years, respectively, mean BMI = 34.64 vs 29.84 kg/m^2, respectively). No significant differences between NHB and NHW women with regards to ER status and chemotherapy status. Information on neighborhood-level factors are presented in **Table 2**. NHB women in our study tended to reside in neighborhoods that had lower rent prices, higher poverty rates, and lower median household incomes compared to NHW women. Additionally, the neighborhoods that NHB women resided in had a greater non-white and single parent population proportion while having a lower college-educated population proportion compared to neighborhoods that NHW women lived in. NHB women also lived in neighborhoods that had a substantially lower job density compared to NHW women (1,327 persons/mi^2 vs 2,784 persons/mi^2).

In the primary analysis assessing epigenome-wide association of DNA methylation with the 9 neighborhood-level factors and after removing outliers, 26 CpG sites passed the FDR threshold of 0.05 for significance. Of these 26 sites, 5 were significantly associated with neighborhood college graduation rates, and 21 with neighborhood job density. We further examined these sites for potential interaction with race and in association with all-cause mortality. These sites are listed in **Supplementary Table 1**.

We performed interaction analyses, post-sensitivity analysis, to examine whether differences exist in the relationship between each of the neighborhood-level factors and DNA methylation in NHB vs NHW women. There was 1 CpG site, cg22544350, where the relationship between college graduation rates and DNA methylation varied significantly by race in the *KDM5A* and *CCDC77* genes. There were 3 CpG sites where the relationship between job density and DNA methylation differed substantially by race, in the *TNRC18*, *ZNF282*, and *SPTLC2* genes. After adjusting for multiple comparisons, however, none of these four sites were no longer significantly interactive with race.

We found eleven sites that was associated all-cause mortality, post-sensitivity analysis (**Table 3**). Nine CpG sites in the *ZNF282, TLDC2, IFT140, TMEM204, AFAP1,* and *GNAI2* genes were associated with a better prognosis. Two CpG sites in the *LOC100129716, ARRDC3,* and *ST3GAL4* genes were associated with a poor prognosis, but only after fully adjusting models for age, race, stage, and subtype. After adjusting for multiple comparisons, however, only one CpG site, cg08214329, was shown to be associated with a better prognosis. This association was no longer significant in the fully adjusted model.

Discussion

This study is the first untargeted analysis to examine neighborhood-level factor-associated methylation in breast tumor tissue using the EPIC array. While a larger sample size is necessary to detect more robust associations between neighborhood-level factors and DNA methylation, we found unique interactions between the 14 FDR-significant CpG sites and race and all-cause mortality. Sites in the *KDM5A, CCDC77*, *TNRC18*, *ZNF282*, and *SPTLC2* genes exhibited differential associations by race. Additionally, sites in the *ZNF282, TLDC2, IFT140, TMEM204, AFAP1, GNAI2, LOC100129716, ARRDC3,* and *ST3GAL4* genes were associated with all-cause mortality.

Several of these genes have been implicated to be associated with cancer prognosis in previous studies. Draheim et al. found that *ARRDC3* has plays a role in suppressing breast cancer progression through downregulation of integrin b4 (22). *ARRDC3* overexpression has shown a decrease in cancer cell proliferation *in vivo*, which is contrary to the results found in our study, where decreased methylation of *ARRDC3* is associated with a worse prognosis. Yang et al. found that an inhibition of *KDM5A*, a histone demethylase, can be a therapeutic mechanism for breast cancers that overexpress KDM5A (23). *ZNF282*, which transcribes for Zinc finger protein 282 (ZFP282) , has been found to promote carcinoma and tumorigenesis in esophageal and breast tissue (24, 25). Yu et al. elucidated the small ubiquitin-like modifying (SUMO) role that ZFP282 plays in estrogen signaling and breast tumorigenesis in mouse models. While the SUMO pathway is hyperactivated in breast cancer, it is unclear whether ZFP282 always operates through the SUMO pathway, particularly in humans, as our results show ZNF282 playing a protective role when methylation decreases. Sialytransferases, particularly *ST3GAL4*, have shown to play a protective role in gastric and cervical cancers, however their role in breast cancer is unclear (26, 27). Jun et al. have found that an overexpression of ST3Gal IV may contribute to α 2,3-linked sialic acid residues expression, which are associated with the malignant activity of gastric cancer cells (26). Additionally, Roa-de La Cruz et al. found that the Variant 1 mRNA transcript of *ST3GAL4* demonstrated decreased expression in malignant cervical tissue, and that deregulation of the *ST3GAL4* gene may contribute to premalignant and malignant behavior of cervical tissue (27). Dianatpour et al. found an upregulation of AFAP1 antisense RNA1 (APAF1-AS1) in breast tumor samples, however there was no significant expression differences in *APAF1* between breast tumor tissue and adjacent non-cancerous tissues (28). *GNAI2* has been studied in ovarian cancer by Raymond et al, shown to have a decreased message in patients with ovarian cancer (29).

Neighborhood-level factors and differential DNA methylation has previously been studied in only a few studies, suggesting the novel nature of studying social epigenomics. Previous studies have found that neighborhood-level factors and DNA methylation have been associated with adverse health outcomes such as cardiovascular disease, depression, and increased epigenetic aging (30-33). Additionally, there may be generational epigenetic impacts that have been linked to methylation of cancer related genes in offspring of mothers who reside in disadvantageous neighborhoods (34). While they have not been reproduced in other studies, the results found in this study pave the way for future work to be done in this field. This work has implications for the role of social epigenomics in the future of research pursuits. While one’s genetics cannot be alter throughout one’s life course, their epigenome is malleable and subject to changes due to environmental and external factors. Epigenetic changes modulate gene transcription, ultimately resulting in downstream phenotypes of chronic conditions and disease. The role one’s environment, physically and socially, plays in epigenetic processes may be substantial. DNA methylation can be induced by stress, which can be caused by adverse neighborhood and environment factors.

In this study, we saw that mortality is not differential by race; all-cause and breast cancer mortality was similar between NHB and NHW women. The disparities in mortality here are driven by where people live—a social factor which we can change. Neighborhood job density, generally, was associated with a better prognosis in survival, meaning those who live in neighborhoods with a greater number of jobs for a given area are more likely to survive longer compared to those residing in lower job density neighborhoods. Why this may be is unclear, however job density may be associated with residential development, making these neighborhoods socially desirable in other factors that may be beneficial to stress and health. Neighborhoods that offer socially positive externalities may, in turn, reduce one’s stress, preventing any stress-induced DNA methylation of certain genes. This research aims to merge the roles that social environments and epigenetic mechanisms play in cancer and other chronic disease, suggesting the mediating role DNA methylation may play in the relationship between social determinants of health and health disparities.

Our study is not without limitations. While we were able to detect a handful of effects between CpG site methylation and neighborhood-level factors even after correcting for multiple comparisons, our study was underpowered due to a limited sample size. Additionally, there is no clarity regarding the degree to which each individual neighborhood-level factor contributes to stress-induced DNA methylation. While we did not account for several known risk factors in our study, including but not limited to breastfeeding, hormone therapy use, and nulliparity, it is unlikely these covariates affect breast tumor methylation from the social-stress pathway we believe neighborhood-level factors operate through. Lastly, this work solely focuses on DNA methylation, very much upstream from the breast cancer phenotype. We examined one layer of information and did not go back to do any deep sequencing or gene expression as this was simply a first pass.

Sensitivity analyses that excluded one or two individuals resulted in several more insignificant results than we began with in our limited sample population. However, our preliminary results reveal potential epigenetic pathways that drive the association between neighborhood-level factors and breast cancer prognosis. Despite our limitations, this study took an untargeted approach to examine potential epigenetic mechanisms association neighborhood-level factors with breast cancer prognosis in a diverse population of women that underwent breast cancer surgery. Future research efforts with a larger, equally diverse patient population are necessary to validate these preliminary results and further explore the epigenetic mechanisms identified in this study.

Data Availability

All data can be made available upon reasonable request to study PI (lauren.mccullough@emory.edu).

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Author Contributions

LM conceived the research and designed the study. LM, SGM, and KG secured funding for the research. OD, MT, and LM, curated clinical data for the research. UK and LM obtained and processed specimens. LM, WD, JG, and KC drafted the analytic plan and supervised all the work.

JG performed the statistical analysis. JMK aided in data interpretation. LM, JG, and JMK drafted the manuscript. All authors contributed to the development of the manuscript.

Conflict of Interests

No conflict of interests to disclose.

Contribution to the Field

Breast cancer racial disparities have been well studied and established, as African American women are more likely to develop more aggressive tumor types, have a higher rate of mortality post-diagnosis, and experience poorer responses to therapy. One potential contributor to this trend is the high rate of African American women who live in worse neighborhoods, and the associated stress that comes with living in these areas. Stress has been shown to influence DNA methylation, and DNA methylation has been shown to affect the expression of tumor suppressor genes and oncogenes. We examined the association between various neighborhood-level factors and the epigenetic profile in breast tumor tissue to identify significantly associated CpG sites. Additionally, we examined whether these CpG were differentially methylated by race and if they were potentially impacting all-cause mortality. We identified several differentially methylated sites associated with certain neighborhood-level factors, with certain sites differentially methylated by race or associated with all-cause mortality. These findings may suggest a stress-related biological mechanism underlying the epidemiological association between neighborhood-level factors and breast cancer that contribute to racial disparities in breast cancer. Identifying biological mechanisms that connect social determinants of health and breast cancer may reveal potential intervention pathways at various socio-ecological levels.

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Tables and Figures

Table 1. Counts and means (standard deviation) are presented for categorical and continuous variables pertaining to patient characteristics, respectively.

	Total	**African**	**Caucasian**
n	96	70	26
BMI mean (SD)	33.23	34.64 (9.86)	29.84 (6.40)
Smoking Status			
Smoker	41	34	7
Non-smoker	54	35	19
Age mean (SD)	56.28	58.65 (12.41)	50.1 (11.78)
Age			
≤49	27	15	12
50-59	34	26	8
≥60	34	29	5
Breast Cancer Subtype			
Luminal A	63	47	16
Luminal B	9	7	2
Her2+	4	3	1
TNBC	20	13	7
All-Cause Mortality			
Yes	25	19	6
No	71	51	20
Breast Cancer Mortality			
Yes	16	11	5
No	80	59	21
Chemo			
None	43	32	11
Adjuvant	31	24	7
Neo-Adjuvant	1	0	1
Both	21	14	7

Table 2. Means (standard deviation) are presented for neighborhood-level factors of the neighborhoods of residence, stratified by race.

	Data Source	**Total**	**African**	**Caucasian**
n		96	68	26
Median Rent, 2006-2010 ($)	American Community Survey	958.73 (236.06)	922.73 (219.00)	1050.12 (256.98)
Poverty Rate, 2006-2010 (%)	American Community Survey	26.21 (12.40)	28.96 (16.53)	18.94 (12.40)
Median Household Income, 2012-2016 ($)	American Community Survey	44,210.53 (20,659.81)	40,956.52 (20,512.14)	52,846.15 (18,805.75)
Fraction Non-White, 2010 (%)	2010 Decennial Census	66.71 (27.50)	72.92 (26.02)	50.93 (25.15)
Fraction Single Parents, 2006-2010 (%)	American Community Survey	53.47 (23.53)	60.11 (22.14)	36.60 (18.14)
Population Density, 2010 (persons/mi^2)	2010 Decennial Census	3,169.84 (2,605.28)	3,270.02 (2,268.96)	2,915.56 (2,605.28)
Job Growth Rate, 2004-2013 (%)	Longitudinal Employer-Household Dynamics and Local Area Unemployment Statistics	1.36 (8.45)	2.21 (9.29)	-0.75 (5.49)
Job Density, 2013 (jobs/mi^2)	Longitudinal Employer-Household Dynamics and Local Area Unemployment Statistics	1,738.45 (2,383.05)	1,326.68 (1,163.75)	2,783.70 (3,945.40)
Fraction College Graduates, 2006-2010 (%)	American Community Survey	41.78 (9.25)	42.73 (9.25)	39.23 (8.93)

Table 3. Hazard ratios models of the 26 FDR-significant neighborhood-level factor-associated CpG sites adjusted for (1) age, (2) age and BMI, (3) age, ER status and clinical stage, and (4) restricted to neo-adjuvant therapy.

CpG Label	**Adjusted for age HR (95% CI)**	**Adjusted for age and Race HR (95% CI)**	**Adjusted for age, race, clinical stage, and subtype (95% CI)**
cg00730549	0.94 (0.88, 1.01)	0.94 (0.87, 1.01)	0.94 (0.86, 1.03)
cg00851060	0.96 (0.92, 1.00)	0.96 (0.92, 1.00)	0.98 (0.93, 1.03)
cg00950813	0.96 (0.93, 0.99)	0.95 (0.92, 0.99)	0.95 (0.91, 1.00)
cg02449575	0.96 (0.90, 1.04)	0.97 (0.90, 1.04)	0.95 (0.87, 1.04)
cg03115690	0.93 (0.88, 0.99)	0.93 (0.87, 0.99)	0.97 (0.90, 1.05)
cg04734977	0.95 (0.66, 1.39)	0.95 (0.65, 1.40)	0.84 (0.52, 1.36)
cg06520003	1.02 (0.97, 1.11)	1.02 (0.94, 1.11)	0.98 (0.90, 1.07)
cg07141484	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)	0.91 (0.84, 0.99)
cg07422416	1.00 (0.97. 1.04)	1.00 (0.97, 1.04)	1.00 (0.95, 1.05)
cg07994487	0.94 (0.91, 0.98)	0.94 (0.91, 0.98)	0.95 (0.91, 1.00)
cg08214329	0.92 (0.88, 0.97)	0.92 (0.88, 0.97)	0.93 (0.87, 0.98)
cg09178970	0.96 (0.75, 1.24)	0.97 (0.75, 1.25)	1.10 (0.81, 1.49)
cg09254001	0.97 (0.55, 1.71)	0.96 (0.55, 1.70)	0.79 (0.38, 1.66)
cg09866303	0.97 (0.93, 1.02)	0.97 (0.93, 1.02)	0.97 (0.92, 1.02)
cg14838356	0.98 (0.94, 1.01)	0.97 (0.94, 1.01)	0.97 (0.92, 1.02)
cg15196042	1.58 (0.96, 2.58)	1.58 (0.97, 2.60)	1.97 (1.00, 3.87)
cg15375883	1.20 (0.99, 1.44)	1.19 (0.99, 1.44)	1.27 (1.04, 1.56)
cg16088676	0.93 (0.89, 0.98)	0.93 (0.89, 0.97)	0.94 (0.89, 1.00)

cg16609534	0.89 (0.80, 0.99)	0.89 (0.80, 0.99)	0.88 (0.79, 0.99)
cg17606115	0.88 (0.80, 0.98)	0.88 (0.80, 0.98)	0.89 (0.79, 1.00)
cg18658674	0.97 (0.93, 1.00)	0.97 (0.93, 1.00)	0.98 (0.94, 1.03)
cg20226051	1.08 (0.71, 1.65)	1.07 (0.70, 1.64)	1.12 (0.63, 2.00)
cg20576936	0.98 (0.93, 1.04)	0.98 (0.93, 1.04)	0.96 (0.90, 1.03)
cg21900997	0.91 (0.82, 1.00)	0.91 (0.81, 1.02)	0.90 (0.78, 1.02)
cg22544350	0.97 (0.90, 1.03)	0.96 (0.90, 1.03)	0.92 (0.84, 1.01)
cg25994418	1.00 (0.96, 1.05)	1.00 (0.95, 1.05)	0.98 (0.93, 1.03)

Supplemental Table 1

CpG Label	Exposure Associated	T.statistic	FDR	effect.size	std.error	Reference Genes	Chromosome
cg00730549	College	-5.77	0.0376	-0.000486	8.423E-05	ZNF680	7
cg00851060	College	-5.72	0.0376	-0.000364	6.367E-05	IKBIP, APAF1	12
cg00950813	College	-5.68	0.0376	-0.0004176	7.35E-05	LOC100129716, ARRDC3	5
cg02449575	College	-5.69	0.0376	-0.0003688	6.478E-05	MTF1	1
cg03115690	College	-5.87	0.0376	-0.0049286	0.0008394	KDM5A, CCDC77	12
cg04734977	Job Density	-4.99	0.0306	1.743E-07	2.729E-06	TNRC18	7
cg06520003	Job Density	-4.86	0.039	1.034E-05	8.083E-06		
cg07141484	Job Density	-5.20	0.0193	2.088E-06	5.454E-06	ZNF282	7
cg07422416	Job Density	-5.34	0.0134	4.618E-07	9.738E-07	SPTLC2	14
cg07994487	Job Density	-5.07	0.027	5.072E-07	4.565E-06		
cg08214329	Job Density	5.00	0.0306	-3.505E-07	9.032E-07	ACSF2	17
cg09178970	Job Density	-4.90	0.0362	9.016E-07	3.106E-06	TLDC2	20
cg09254001	Job Density	4.82	0.0429	-3.209E-06	4.291E-06	MFHAS1	8
cg09866303	Job Density	-5.05	0.0277	5.235E-06	3.587E-06	IFT140, TMEM204	16
cg14838356	Job Density	-5.05	0.0274	4.472E-06	4.218E-06	IFT140, TMEM204	16
cg15196042	Job Density	-4.88	0.0378	-1.941E-06	4.072E-06	VPS37B	12
cg15375883	Job Density	-5.07	0.027	7.246E-07	1.868E-06	RREB1	6
cg16088676	Job Density	-5.42	0.0108	-8.453E-07	6.196E-06	AGO2	8
cg16609534	Job Density	5.57	0.0075	-3.562E-07	6.58E-06	ST3GAL4	11
cg17606115	Job Density	-4.96	0.0314	-2.876E-06	4.426E-06		
cg18658674	Job Density	-4.95	0.0314	-5.582E-07	3.719E-07	AFAP1	4
cg20226051	Job Density	-5.22	0.0185	-5.707E-06	5.823E-06	GNAI2	3
cg20576936	Job Density	-4.83	0.0427	-4.688E-07	5.177E-07		
cg21900997	Job Density	-4.98	0.0311	-1.712E-07	4.066E-07	ZNF627	19
cg22544350	Job Density	-5.29	0.0155	2.176E-08	1.063E-07	SCMH1	1
cg25994418	Job Density	-4.98	0.0311	1.062E-06	5.998E-06	PLCG1	20

Supplemental Table 1 The 26 FDR-significant CpG sites associated with a neighborhood-level factor in breast tumor tissue. T-statistics, p-value and false discovery rate p-value have been provided. Reference gene and chromosome number obtained from the Illumina annotation file.

Chapter II: Extended Results

Literature Review

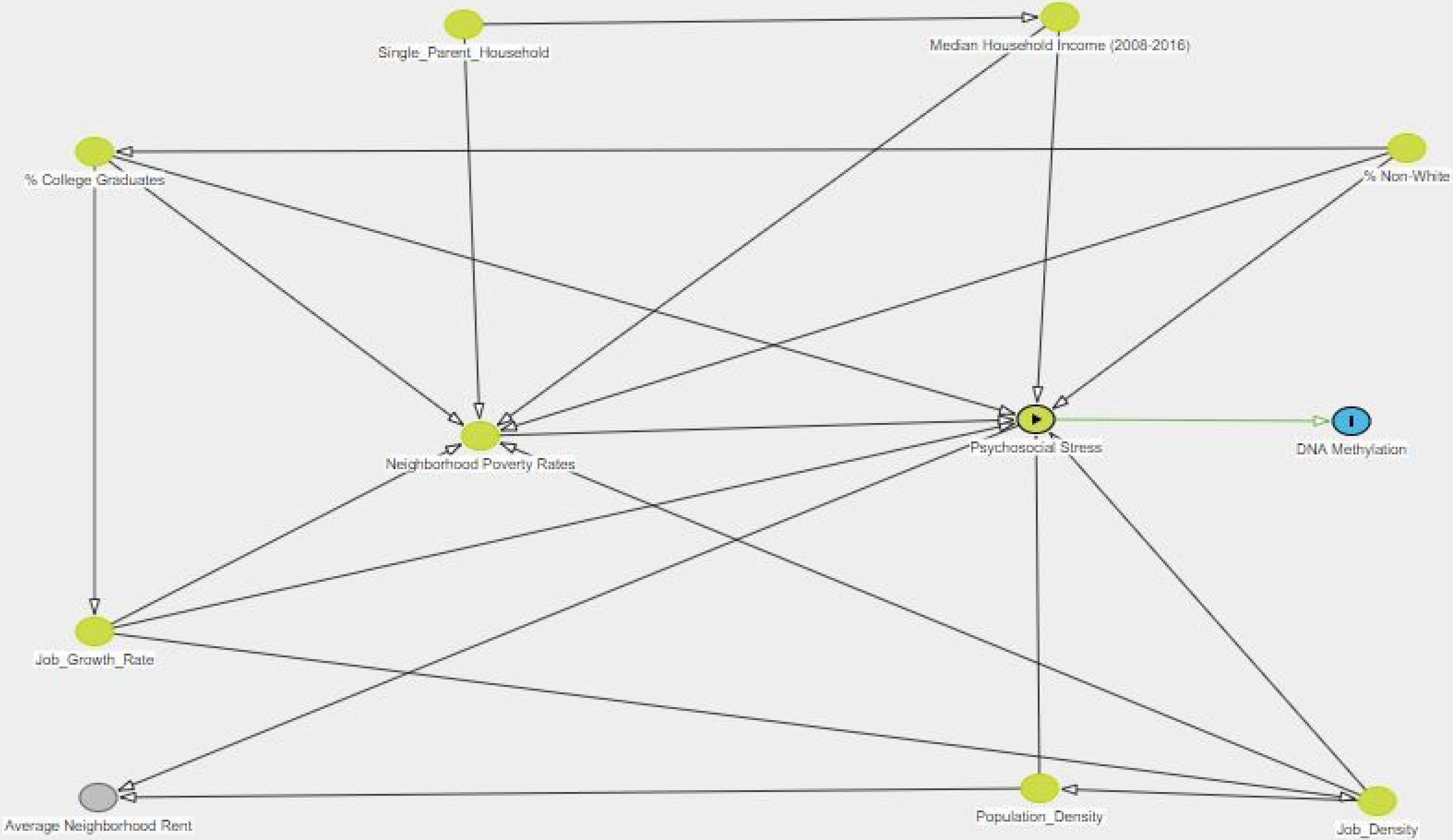
Title	Author, Year	PMID	Population			Specific Research Question	Variable assessment			
			N	race/ ethnicity	Years		Exposure assessment (Financial marker used and level -- e.g. indivivual/community)	Tissue used for Analysis	Outcome assessment	What Outcome Approach Did They Use?
Neighborhood Characteristics Influence DNA Methylation of Genes Involved in Stress Response and Inflammation: The Multi-Ethnic Study of Atherosclerosis	**Smith, Jennifer, 2017**	**28678593**	1,226	NHW, AA, Hispanic	2000-2002	Is there an association between Neighborhood Socioeconomic Disadvantage and DNA Methylation? Is there an association between Neighborhood Social Environment and DNA Methylation?	Neighborhood Socioeconomic Disadvantage: Created based on a principal components analysis of 16 census-tract level variables from the 2000 US Census. Neighborhood Social Environment: sum of standardized conditional empirical Bayes estimate scales for aesthetic quality, safety, and social cohesion.	Blood	DNA Methylation	Illumina HumanMethylation450 BeadChip, Candidate Gene (n = 18)
Factors Underlying Variable DNAm in a Human Community Cohort	**Lam, Lucia, 2012**	**23045638**	92	Caucasian, Non-Caucasian	NA	What are factors that affect the human epigenome, and is there a functional relation to gene expression?	Blood composition, demographic factors (sex, racial/ethnic background), early life SES, current SES, cortisol levels, perceived stress, principal components.	Peripheral blood mononuclear cells (PMBCs)	DNA Methylation	Illumina HumanMethylation27 array
Genome-Wide Analysis of DNA Methylation in Relation to Socioeconomic Status during Development and Early Adulthood	**McDade, Thomas, 2019**	**30771258**	489	Filipino	1983-2005	Are profiles of DNA methylation in young adulthood predicted by SES early in development, and in early adulthood, in the Phillippines?	SES (constructed using weekly household income, household assets, and maternal and paternal education.)	Leukocytes	DNA Methylation	Illumina HumanMethylation450 BeadChip
Life Course Socioeconomic Status and DNA Methylation in Genes Related to Stress Reactivity and Inflammation: The Multi-Ethnic Study of Atherosclerosis	**Needham, Belinda, 2015**	**26295359**	1,231	NHW, AA, Hispanic, Chinese-American	2010-2012	In there an association between SES and gene-specific DNAm in a large, population-based sample of US adults in the MESA study?	Maternal Education an indicator of childhood SES, Self-reported education an indicator of adult SES, both indicators used to measure SES trajectories (persistent low SES, upward social mobility, downward social mobility, persistent high SES)	Blood	DNA Methylation	Illumina HumanMethylation450 BeadChip, Candidate Gene (n = 18)
The Biological Embedding of Early-Life Socioeconomic Status and Family Adversity in Children's Genome-Wide DNA Methylation	**Bush, Rachel, 2018**	**30351206**	178	AA, Asian, Caucasian, Latino, Multiethnic, Other	2003-2005	Is there an association between early-life socioeconomic status, family adversity and DNA methylation in children	Household income, Highest level of parental education, Family adversity composited into one adversity index (financial stress, parenting overload, marital conflict, depression, negative/anger expressiveness, harsh/restrictive parenting)	Saliva	DNA Methylation	Illumina HumanMethylation450 BeadChip
DNA Methylation and Socioeconomic Status in a Mexican-American Birth Cohort	**Coker, Eric, 2018**	**NA**	241	Mexican-American	1999-2000	Does maternal SES at the individual, household, and neighborhood level influence the newborn epigenome in terms of DNAm of LINE-1 and Alu repeat elements? Does diet quality during pregnancy affect this association?	Maternal education, household income, household poverty income ratio, % of homes below poverty line, median household income, % of high school educated within census tracts, diet during pregnancy measured by FFQ	Cord Blood	DNA Methylation	Pyromark Q96MD System, Candidate Gene (n = 2)
Social Adversity and Epigenetic Aging: A Multi-Cohort Study on Socioeconomic Differences in Peripheral Blood DNA Methylation	**Fiorito, Giovanni, 2017**	**29176660**	5,111	Italian, Irish, Australian	NA	Is there an association between SES and intrinsic epigenetic age acceleration	Highest level of educational attainment as a proxy for SES	Blood	DNA Methylation	Illumina 850k methylation BeadChip

Title	Author, Year	PMID	Population			Specific Research Question	Variable assessment			
			N	race/ ethnicity	Years		Exposure assessment (Financial marker used and level -- e.g. indivivual/community)	Tissue used for Analysis	Outcome assessment	What Outcome Approach Did They Use?
Life Course Socioeconomic Status and DNA Methylation of Genes Regulation Inflammation	**Stringhini, Silvia, 2015**	**25889032**	857	Italian	NA	Is there an association between life-course SES and DNA methylation of candidate genes selected on the basis of their involvement in SES-related inflammation?	Life course SES (Household's highest occupational position and father' occupational position combined to create an indicator of life-course SE trajectories)	Blood	DNA Methylation	Illumina HumanMethylation450 BeadChip
Neighborhood Environment and DNA Methylation: Implications for Cardiovascular Disease Risk	**Giurgescu, Carmen, 2019**	**30635842**	NA	NA	NA	Literature review assessing the association between neighborhood environment and DNAm in relation to CVD risk	NA	Blood	DNA Methylation	NA
Neighborhood Crime and Depressive Symptoms among African American Women: Genetic Moderation and Epigenetic Mediation of Effects	**Lei, Man-Kit, 2015**	**26513121**	99	African American	1997-2008	Is there an association between living in a disordered/high crime neighborhood and risk for depression?	Neighborhood crime (11-item scale)	Blood	DNA Methylation	Illumina HumanMethylation450 BeadChip
Neighborhood Disadvantage and Biological Aging: Using Marginal Structural Models to Assess the Link Between Neighborhood Census Variables and Epigenetic Aging	**Lei, Man-Kit, 2019**	**28329838**	100	African American	NA	Is there an association between neighborhood disadvantage and epigenetic aging?	Neighborhood census variables	Need to purchase article for information	DNA Methylation	Need to purchase article for information
Differential DNA Methylation Between African Americans and European Americans: the Role of Childhood Socioeconomic Status and Relations to Health Disparity	**Pan, Yue, 2019**	**NA**	468	African American, European Americans	NA	Are there ethnicity-related methylation patterns, and do these methylation patterns have a relationship with health disparities? Does ethnicity serve as an effect modifier in studying the difference in childhood SES between AAs and EAs?	Childhood SES assessed using parental Hollingshead score	Leukocytes	DNA Methylation	Illumina HumanMethylation450 BeadChip
An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents	**Swartz, Johnna, 2017**	**27217150**	132	Caucasian, Non-Caucasian	NA	Are changes in gene methylation associated with lower SES good predictors of risk-related brain function?	Emotional neglect, SES (parental education levels, individual income), stressful life events	Peripheral Tissues	DNA Methylation	Need to purchase article for information
Neighborhood and Family Enivironment of Expectant Mothers May Influence Prenatal Programming of Adult Cancer Risk: Discussion and an Illustratic Biomarker Example	**King, Katherine, 2016**	**27050035**	489	White, Black, Asian, Other, Hispanic	NA	Does maternal stress due to neighborhood environment result in DNAm in cancer-linked genes in offspring during gametogenesis.	Neighborhood Disadvantage (using census data of 6 measures of census tract social composition: % NHB, % poverty, % households on public assistance, % households with unmarried female head, % population under age 18, % civilian labor force over 16 unemployed.	Cord Blood	DNA Methylation	Bisulfite pyrosequencing

Author	**Variable assessment**	**Statistical approach**	**Results (report main effect estimates only)**	**Overarching conclusions**	**Notes**
	Other important variables	**Specify model used**			
Smith, Jennifer, 2017	Sex, Race/Ethnicity, Age, Childhood SES, Adult SES, Residual Sample Contamination with Non-Monocytes	Linear Multivariate Regression Models	Neighborhood Socioeconomic Disadvantage associated with 2 stress-related genes (CRF, SLC6A4) and 2 inflammation-related genes (F8, TLR1) at FDR = 0.10. Neighborhood Social Environment associated with DNAm in 4 stress related genes (AVP, BDNF, FKBP5, SLC6A4) and 7 inflammation related genes (CCL1, CD1D, F8, KLRG1, NLRP12, SLAMF7, TLR1)	This study confirms what the growing field of social epigenomics argues, which is that social context can influence DNAm over the life course. This study shows that neighbhorhood-level context can impact the epigenome even after accounting for individual-level SES. Stress and inflammatory pathways may be responsive to both neighborhood-level interventions. Both neighborhood-level socioeconomic disadvantage and social environment were associated with an increase in methylation in genes that were related to stress and inflammation.	This study is probably the closest thing to what our research question focuses on. This study uses census-tract level variables from the 2000 Census to construct scores for Neighborhood Socioeconomic Disadvantage and Neighbhood Social Environment. This is also the only study that really focuses on overall neighborhood quality in relation to DNA methylation, however this study, like the others, do not focus on cancer.
Lam, Lucia, 2012	Sex, Age, Race/Ethnicity, Early-life Poverty, Adult Psychosocial Stress,	Multiple Regression	264 CpG sites associated with lymphocyte percentage, 248 CpG sites associated with monocyte percentage at FDR of 0.05. 123 CpG loci associated with sex, 299 CpG sites associated with ethnicity (FDR = 0.25), 2 CpG sites associated with aging, 3 loci associated with early life SES (FDR = 0.25), 5 associated with total cortisol (FDR = 0.25).	Blood composition, demographic factors, early-life SES, preceived stress were associated with DNAm in this exploratory analysis.	Very early study in social epigenomics, nothing very conclusive as this is very exploratory. Contributes to the notion that social factors may impact the epigenome.
McDade, Thomas, 2019	Sex, Smoking, Population Stratification	Linear Regression Models, Parametric Empirical Bayes Smoothing Formula, Functional Enrichment Analysis	2,546 CpG sites differented significantly (FDR < 0.05) between those who had low SES in both early life and early adulthood and those who had high SES in early life and early adulthood.	SES, one of the most powerful determinants of health, can drive underlying biological mechanisms through DNAm when comparing those who have been of persistently low SES compared to those of persistently high SES.	High sample size here is impressive, and comparison to other studies that are in this same literature review shows consistency in results in terms of CpGs in 18 inflammation and stress related genes. Functional significance of these findings, however, are not clear.
Needham, Belinda, 2015	Age, Sex, Race/Ethnicity, and Enrichment scores for neutrophils, B cells, T cells, and NK cells	2-level multi-level models	Statistically significant main effect of low childhood SES and/or interaction between childhood SES and site type (Promotor or Shore/Shelf) in 4 stress related genes (AVP, BDNF, FKBP5, and OXTR) and 3 inflammation related genes (CCL1, CD1D, F8)	This study found that SES was associated with DNAm in 10 of the 18 candidate genes that were associated with either stress or inflammation. Childhood SES was approximately associated with the same number of stress and inflammation related genes, whereas adult SES was primarily associated with inflammation related genes, implicating that childhood and adulthood low SES may operate through different biological pathways.	This study was the precursor to the Smith et al. study that looks at neighborhood characteristics rather than SES. Both of these are candidate gene studies as opposed to the exploratory study that we are doing, however the sample size in these studies are quite large which is impressive.
Bush, Rachel, 2018	Age, Genetic Ancestry	Linear mixed effects modeling	488 CpG sites were significantly differentially methylated in association with income-per dependent, 354 with highest household education, and 102 with family adverstiy, after corrections for genetic ancestry and self-reported ethnicity.	Family income, parental education, and family psychosocial adversity associated with increased/decreased DNAm, gene ontology pointed to genes serving immune/developmental regulation functions.	Interesting to use saliva and not blood in this study.
Coker, Eric, 2018	Maternal age at delivery, maternal smoking, # of years living in the US, maternal diet quality during pregnancy, maternal urinary phtalate concentration of MBzP during pregnancy.	Linear mixed effects modeling	After adjustment, the 2nd household income quartile and 2nd poverty income ratio quartile were marginally associated with higher methylation compared to the highest SES quartile categories.	Very modest association between prenatal socioeconomic environment and DNA methylation of LINE-1 repeat elements in infant cord blood. Neighborhood poverty was significantly associated with hypermethylation.	Results seem modest. Hard to see what is the degree of impact here biologically in this study. Interesting to see a very candidate gene driven approach that had modest results be published.
Fiorito, Giovanni, 2017	Age, Sex, Smoking Status, BMI, Alcohol, Mediterranean Diet Score, Physical Activity.	Meta analysis	Epigenetic age increased by 0.75 and 0.99 years for those of medium and low SES compared to those of high SES, respectively. None of the covariates were associated with a statistically significant reduction in the effect size for the SES-AA association.	This meta-analysis shows an association between SES and epigenetic aging in three large cohort studies, as lower SES was associated with accelerated epigenetic aging, and confirm that SES may play a biological role in health.	Edu as a proxy for SES seems, for the most part, okay but I still have my concerns. Populations of individual cohorts also has some limitations that are important to address, in terms of the the cohort composition.

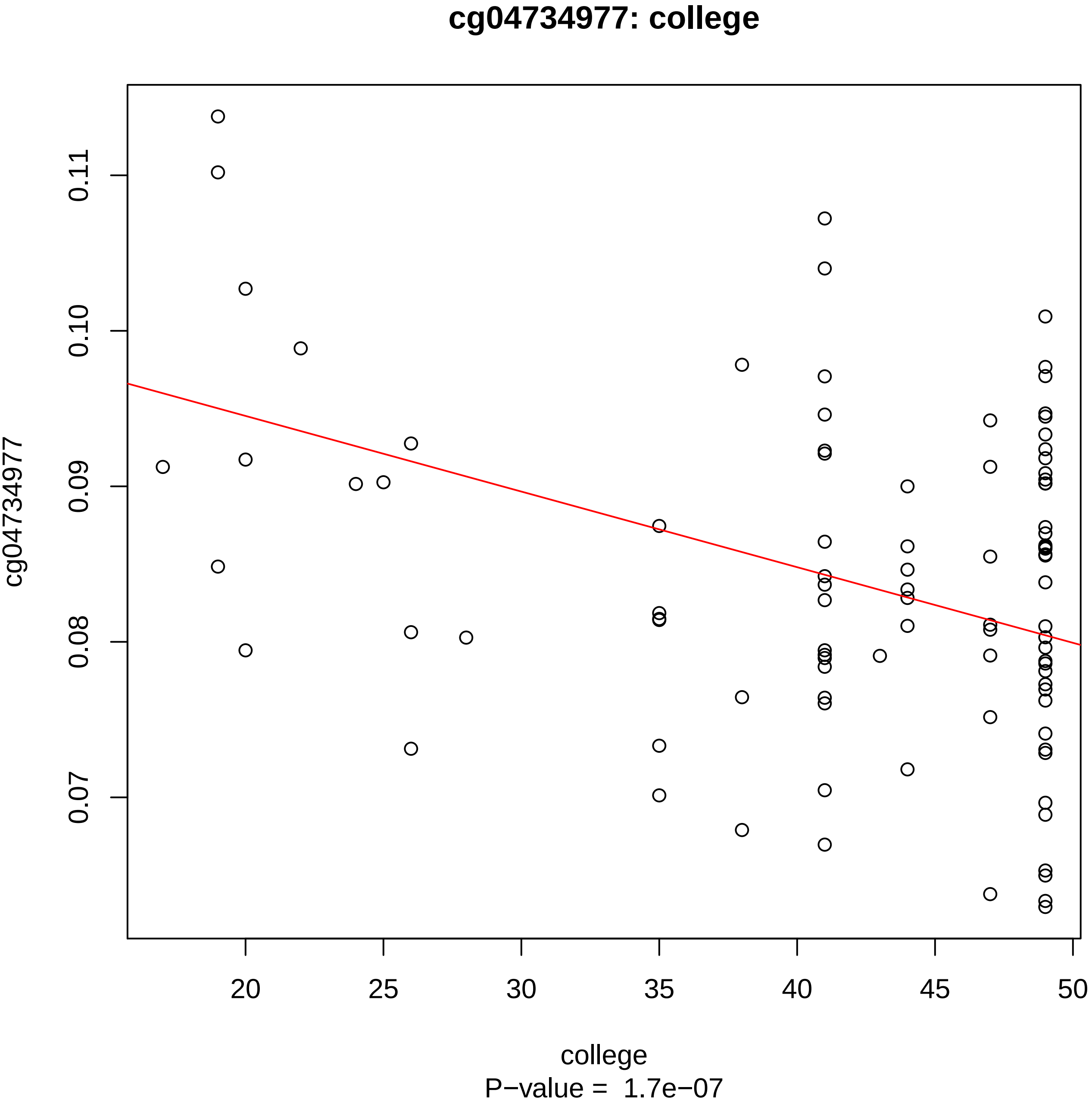
Author	Variable assessment	Statistical	Results (report main effect estimates only)	Overarching conclusions	Notes
	Other important variables	Specify model used			
Stringhini, Silvia, 2015	Smoking status, Physical Activity, Alcohol Intake, Mediterranean Diet Score, Height, Weight, BMI, Age, Sex, Season of Blood Collection, Disease status (Colon cancer case, Breast cancer case/control)	Adjusted linear regression models	After the FDR threshold was applied, there were no significant associations between father's occupational position and DNAm, there were 41 significant associations between household's occupation position and DNAm, and there were 12 significant associations between SES trajectory and DNAm	SES was associated with decreased DNAm in several regions in pro-inflammatory genes, specifically with the NFATC1 gene. This gene was strongly associated with social rank in macaques, and is involved in the expression of cytokine genes in T cells.	Like all of the studies, it is hard to tell the extent to which DNAm variations affect gene expression levels. Interesting proxies for SES.
Giurgescu, Carmen, 2019	NA	NA	Coker et al found that higher cord blood LINE-1 methlation among those living in neighborhoods with greater poverty. King et al found that prenatal neighborhood disadvantage was associated with higher MEG3 methylation in newborn cord blood. Lei et al did not find differences in self-reported neighborhood crim and 5-HTT methylation. Smith et al found an association between neighborhood SE disadvantage/social environment and DNAm in stress and inflammation related genes. Janusek et al. found that greater indirect exposure to neighborhood violence was associated with a steeper rise and slower decline of salivary IL-6 levels but was not related to DNAm	Really good article summarizing the findings of the only 5 neighborhood and DNAm papers as of 2019.	Figure 1 in this paper would actually be something worth reproducing for my paper.
Lei, Man-Kit, 2015	Age, Relationship Status, Education, Household Income, Residential Hisotry, Neighborhood Disadvantage, Cigarette Consumption	Poisson Regression, Candidate Gene (n = 1)	5-HIT methylation was not impacted by 5-HITLPR genotype or neighborhood crime alone, but was impacted by the interaction between genotype and neighborhood crime, as methylation was significantly steeper for those with at least 1 short allele at the gene.	Argument for gene*environment interaction that may impact DNA methylation, and how that can result in differential depressive symptoms in this AA population	Issue of causality here maybe? How does gene impact DNA methylation?
Lei, Man-Kit, 2019	Need to purchase article for information	Need to purchase article for information	Neighborhood disadvantage was associated with accelerated biological aging.	Neighborhood context can be a determinant of healthy aging, which can downstream impact disease status.	Need full article
Pan, Yue, 2019	Need to purchase article for information	Need to purchase article for information	1671 DMCs identified, gene ontology analysis showed that these CpG sites were associated with genes involved in chemical dependencies, tobacco use, CVD, metabolic disorders, developmental disorders, body weight.	Ethnicity may play a role in differential DNA methylation, and can be an effect modifier between SES and methylation.	Need full article
Swartz, Johnna, 2017	Age, Gender, Anxiety Diagnosis	MLE, multi-group analyses, candidate gene (n = 1)	Lower SES at younger age predicts greater increase in SLC6A4 methylation at older age.	Earlier life SES may impact DNAm at later ages	Limited covariates used in this study, intersting consider diet and smoking were not considered.
King, Katherine, 2016	Maternal relationship, mother coresidence, individual SES, newborn gender, antibiotic use, smoking, BMI	ANOVA, candidate gene (n = 1)	Neighborhood disadvantage was associated with significantly higher methylation of MEG3 gene. Children of hispanic and NHB mothers had highest methylation.	Socioeconomically disadvantaged neighborhoods can impact DNA methylation in newborns. Race differences are social in origin rather than linked to genetic ancestry.	MEG3 associated with cancer outcomes, may be linkable to the study we are doing in certain aspects. Does not provide insight, however, on how this methylation may persist or change over time.

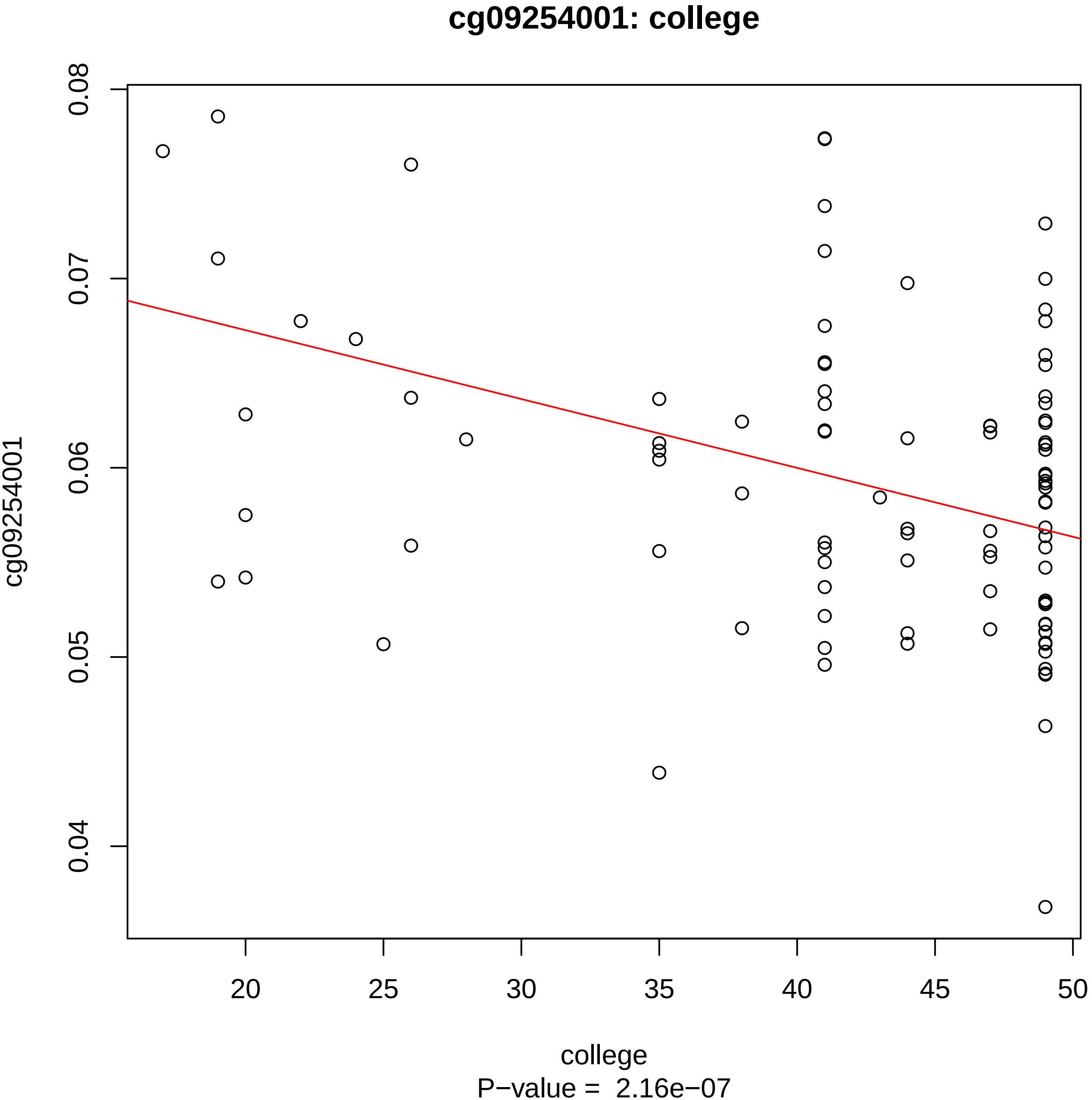
Directed Acyclic Graph

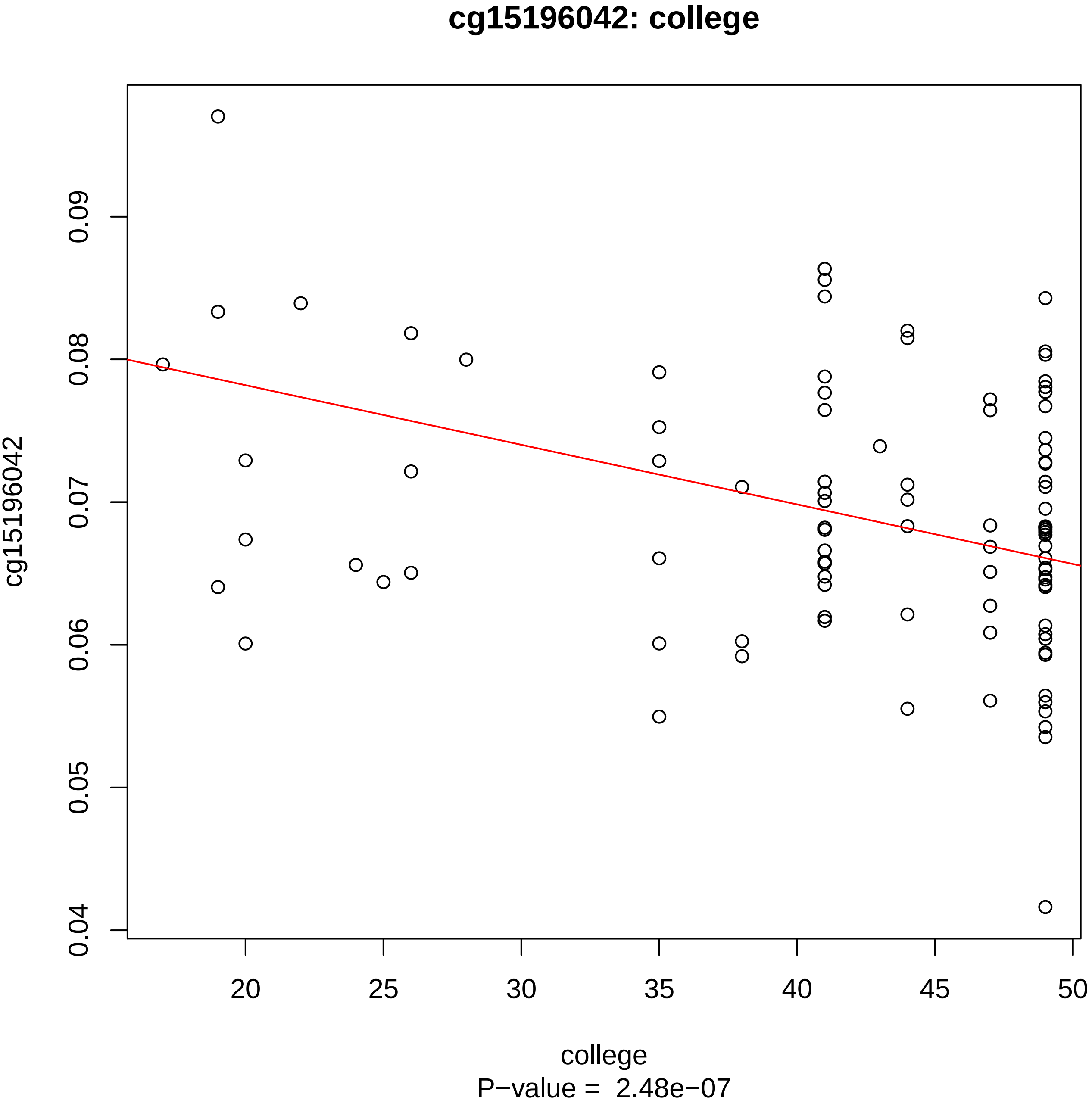

Single_Parent_Household
Median Household Income (2008-2016)
% College Graduates
% Non-White
Neighborhood Poverty Rates
Psychosocial Stress
DNA Methylation
Job_Growth_Rate
Average Neighborhood Rent
Population_Density
Job_Density

EWAS Scatterplots

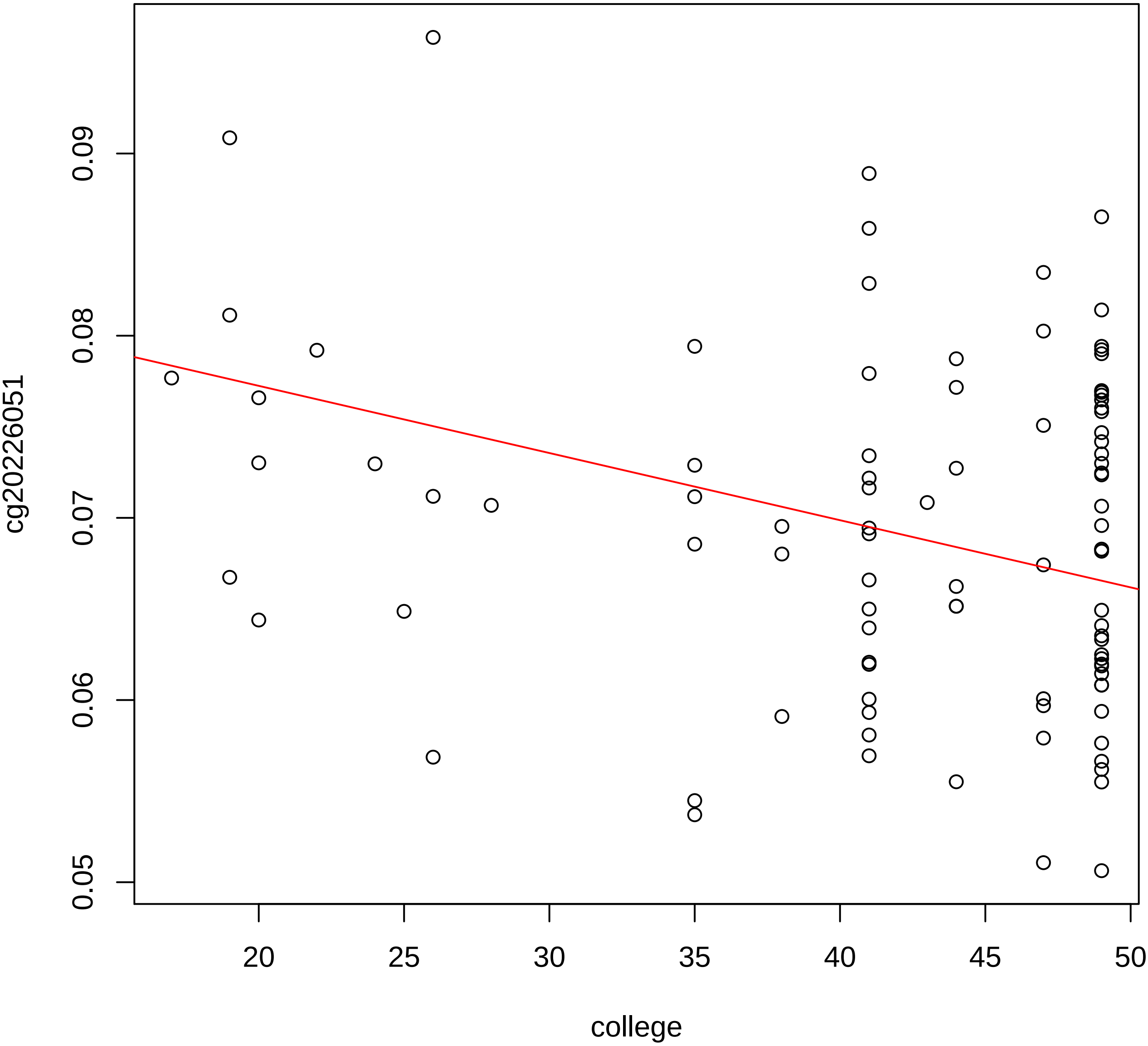
Graphing the association between neighborhood factors and DNA methylation at CpG sites


cg04734977: college
cg04734977
0.07
0.08
0.09
0.10
0.11
20
25
30
35
40
45
50
college
P−value = 1.7e−07

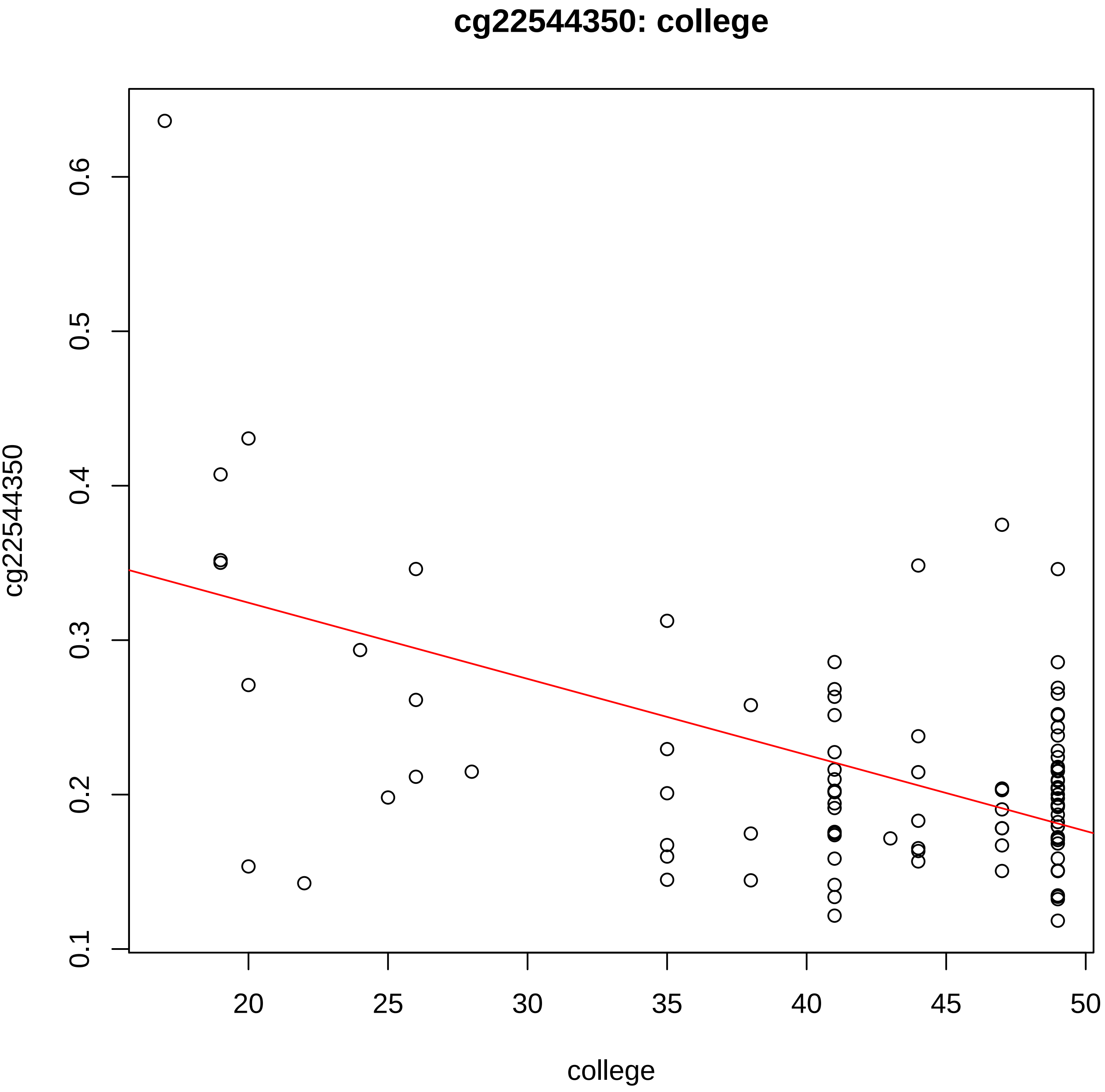

cg09254001: college
cg09254001
0.08
0.07
0.06
0.05
0.04
20
25
30
35
40
45
50
college
P−value = 2.16e−07


cg15196042: college
cg15196042
0.04
0.05
0.06
0.07
0.08
0.09
20
25
30
35
40
45
50
college
P−value = 2.48e−07

cg20226051: college

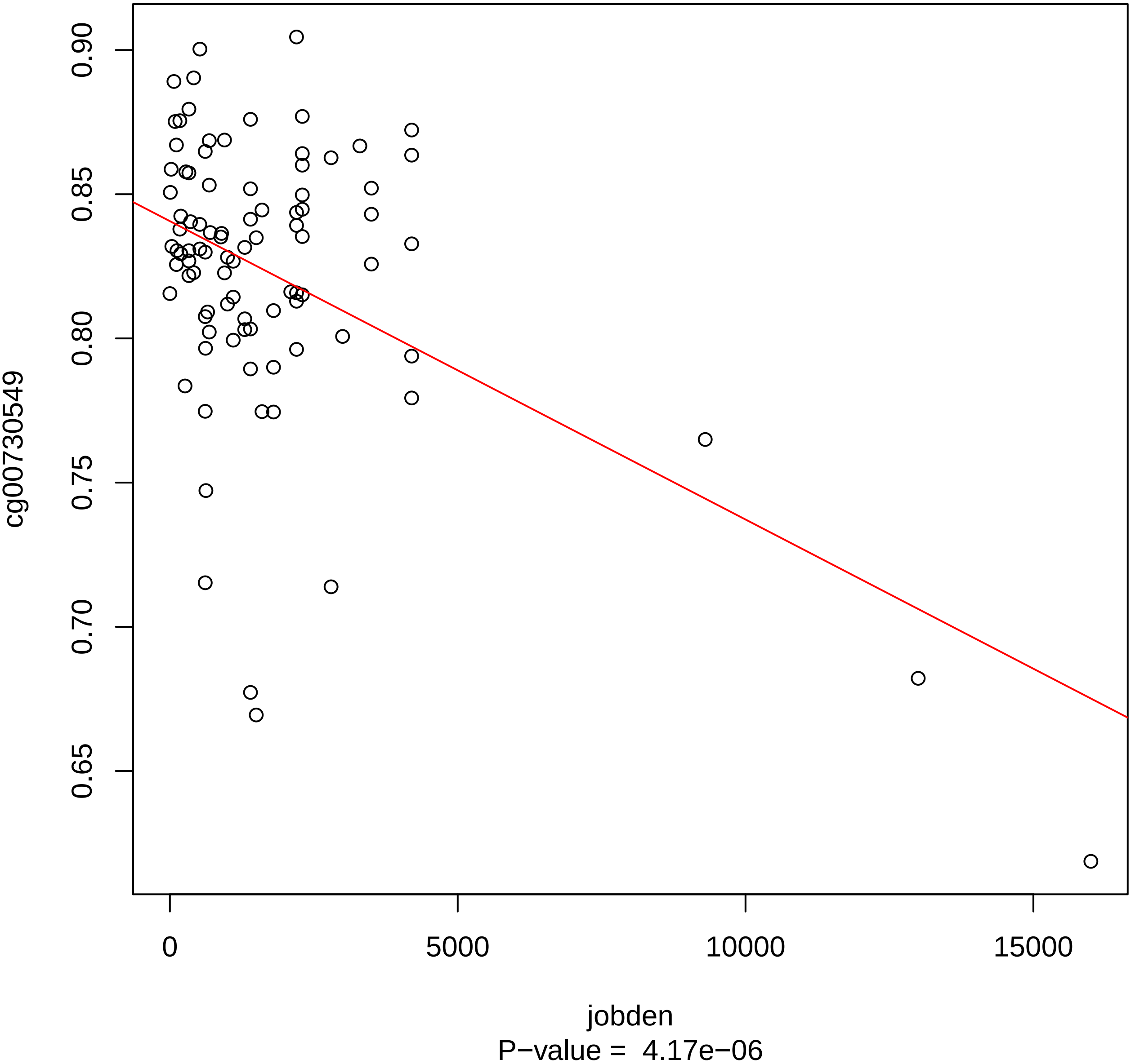


P−value = 2.37e−07

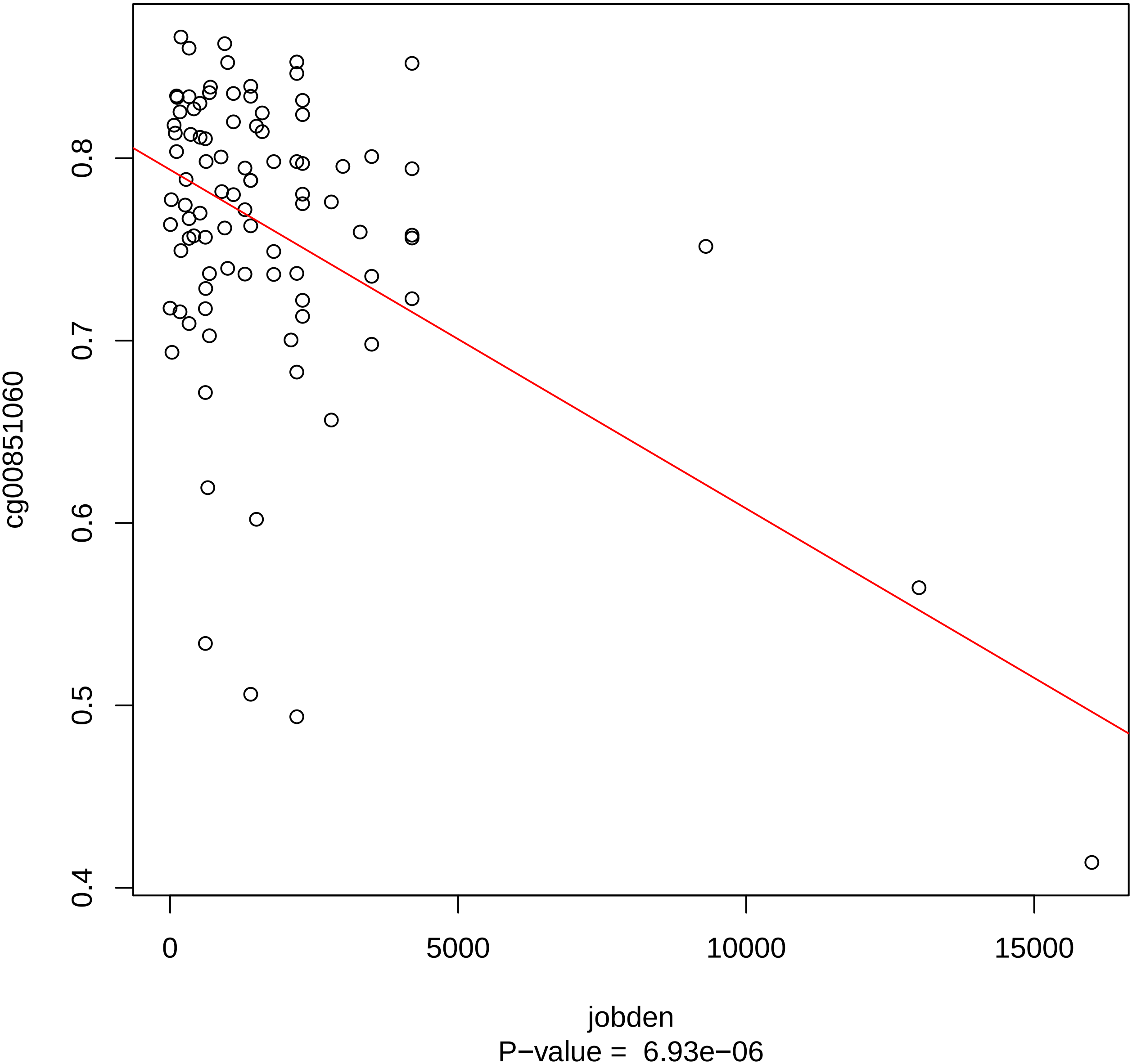


P−value = 1.14e−07

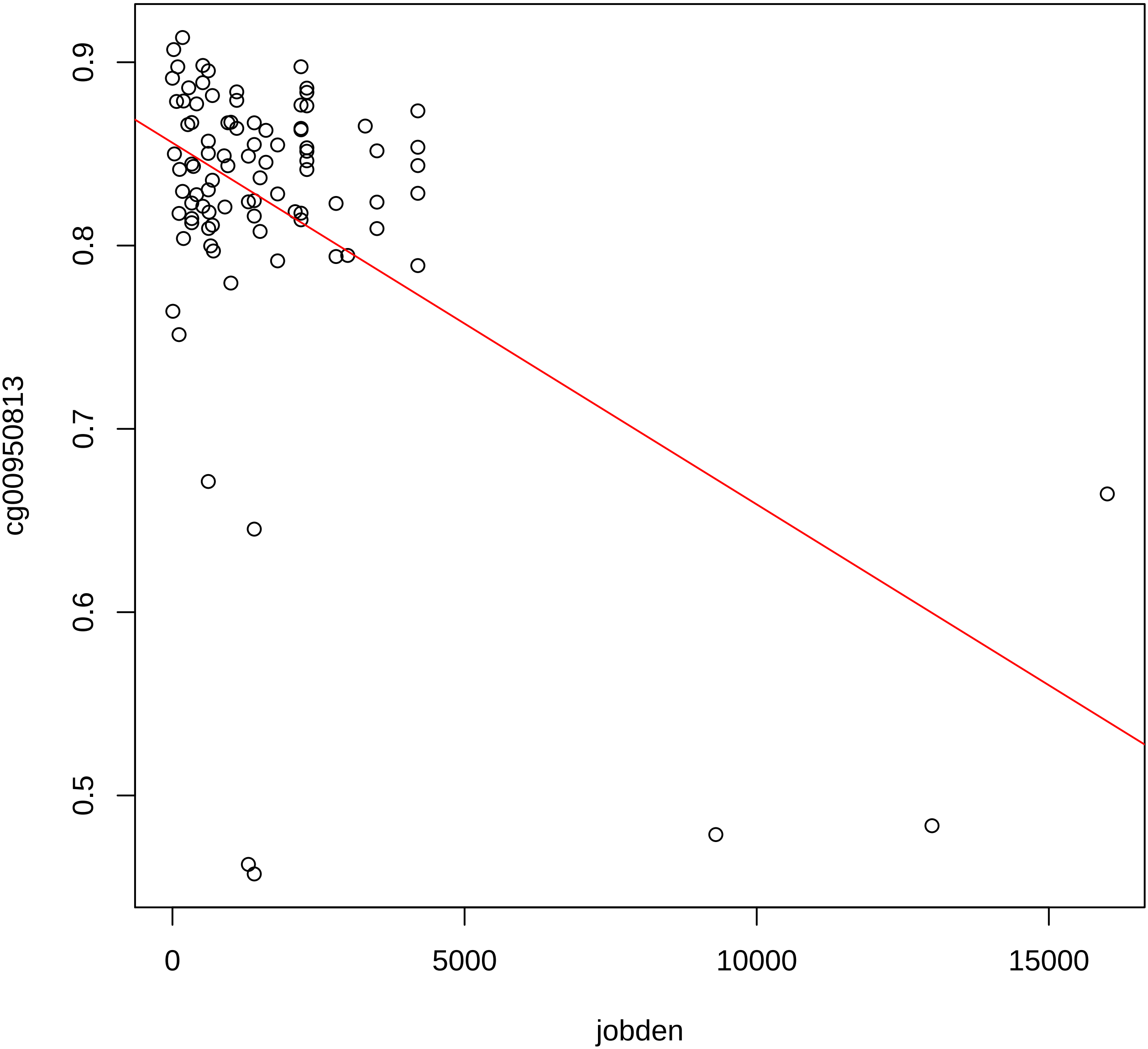
cg00730549: jobdensity



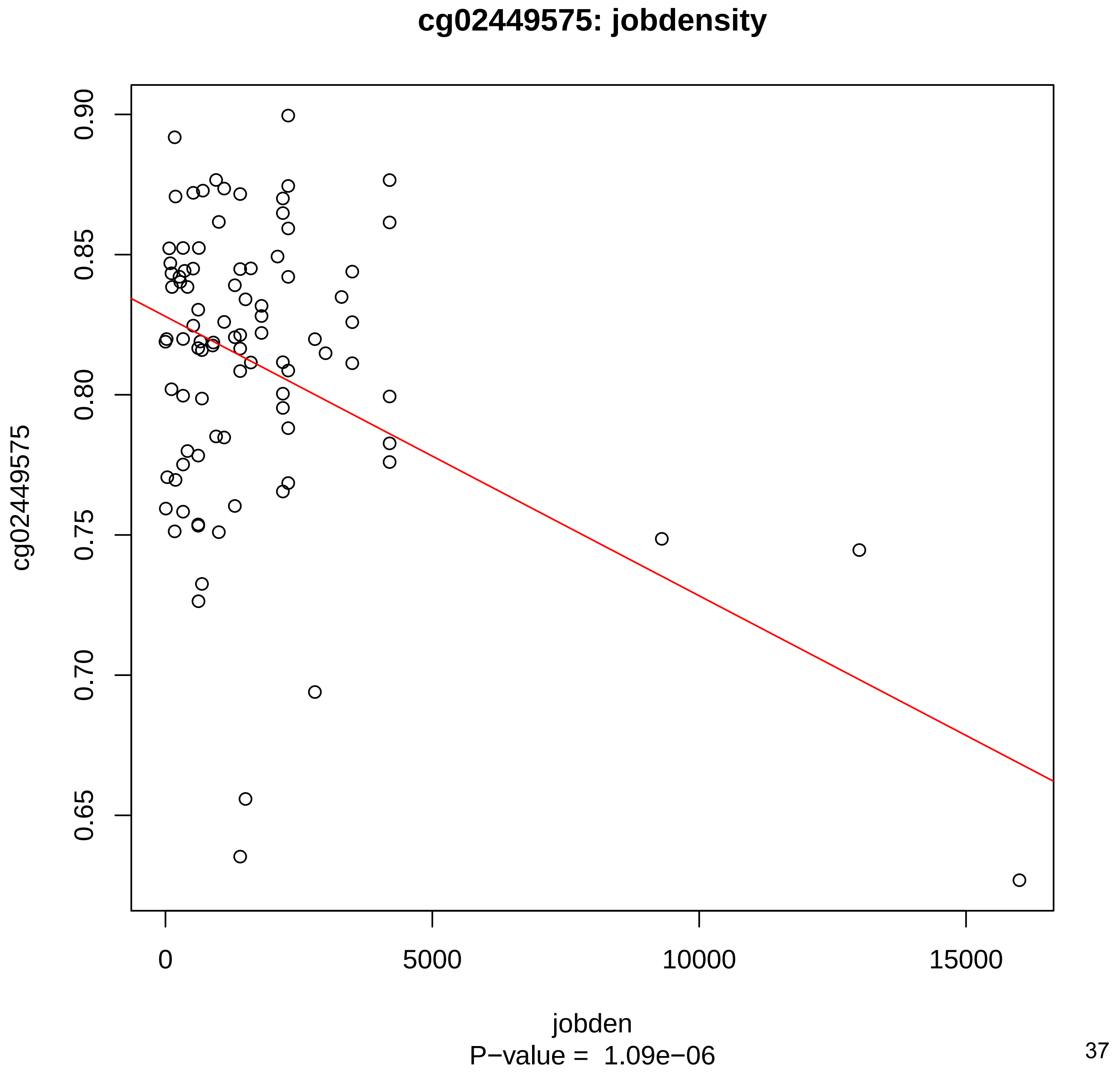
cg00851060: jobdensity

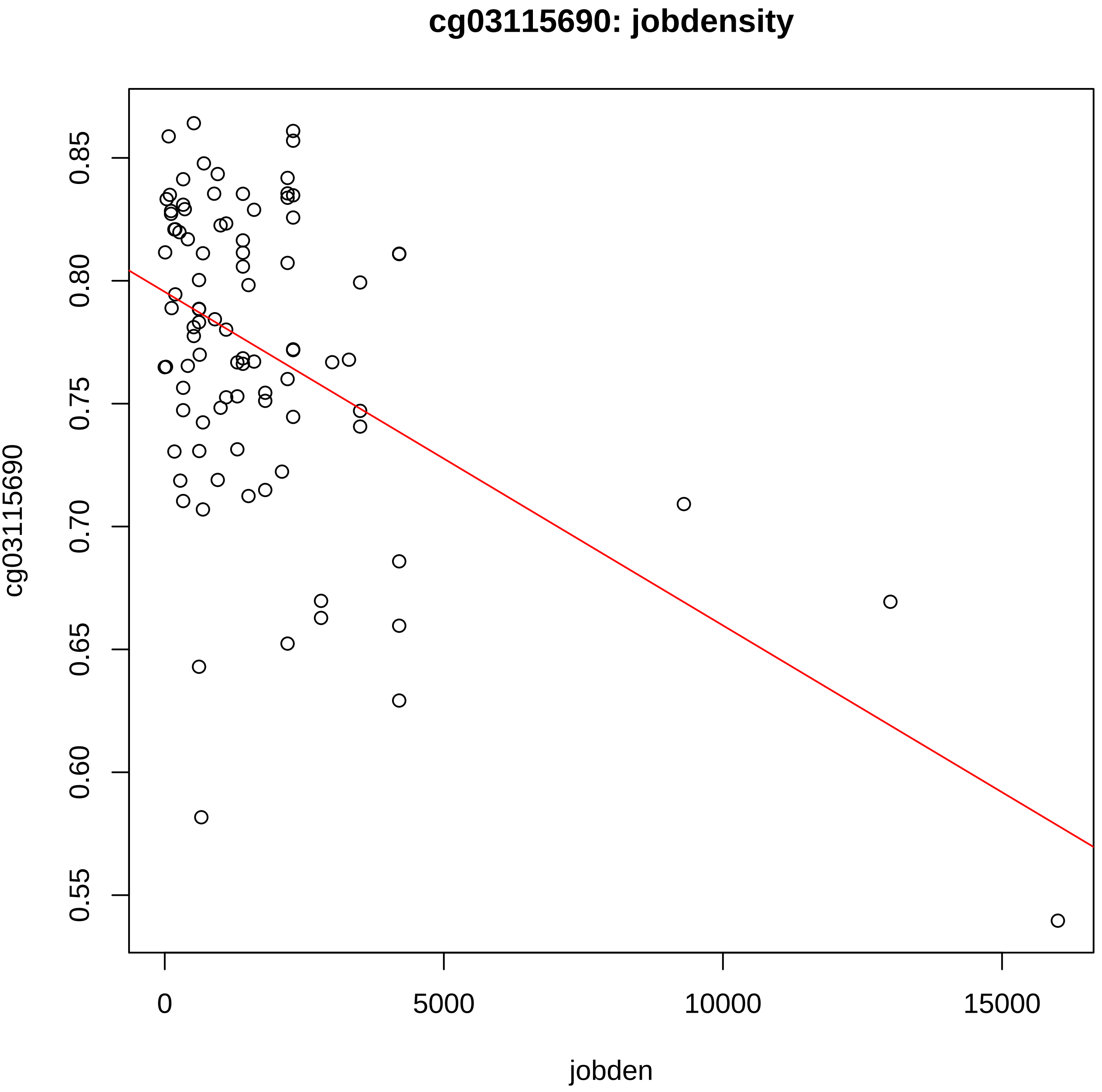


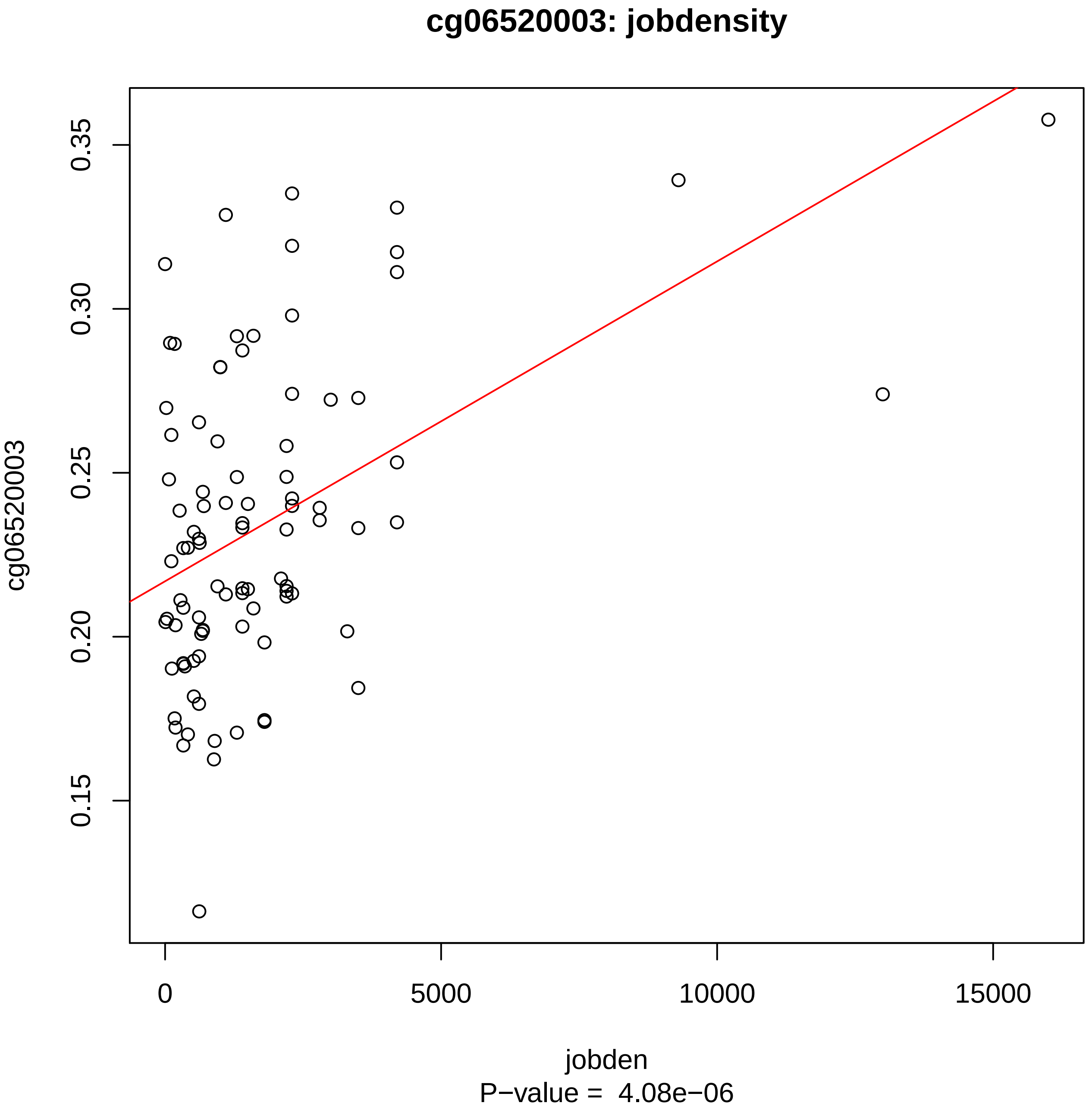
cg00950813: jobdensity

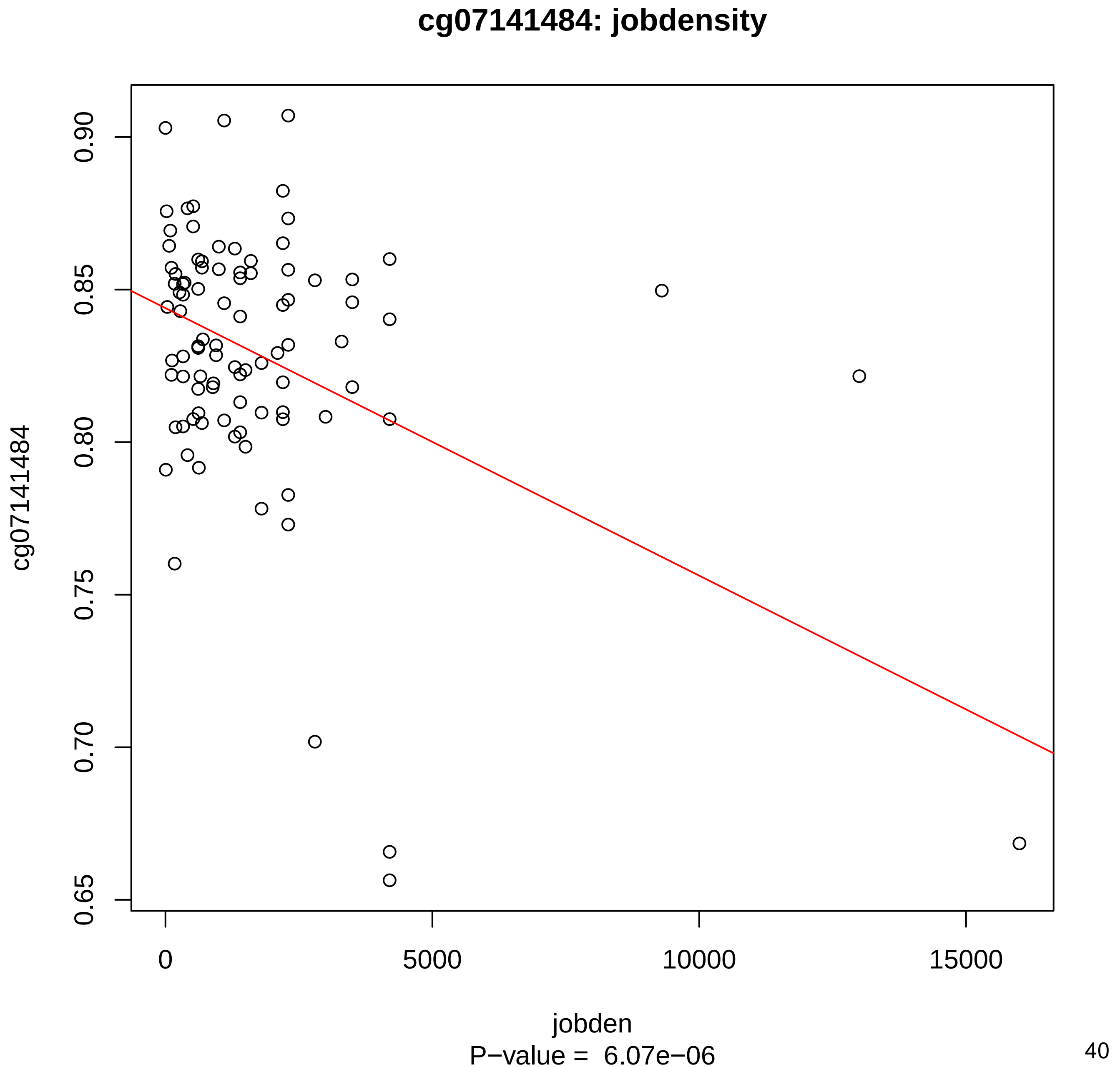


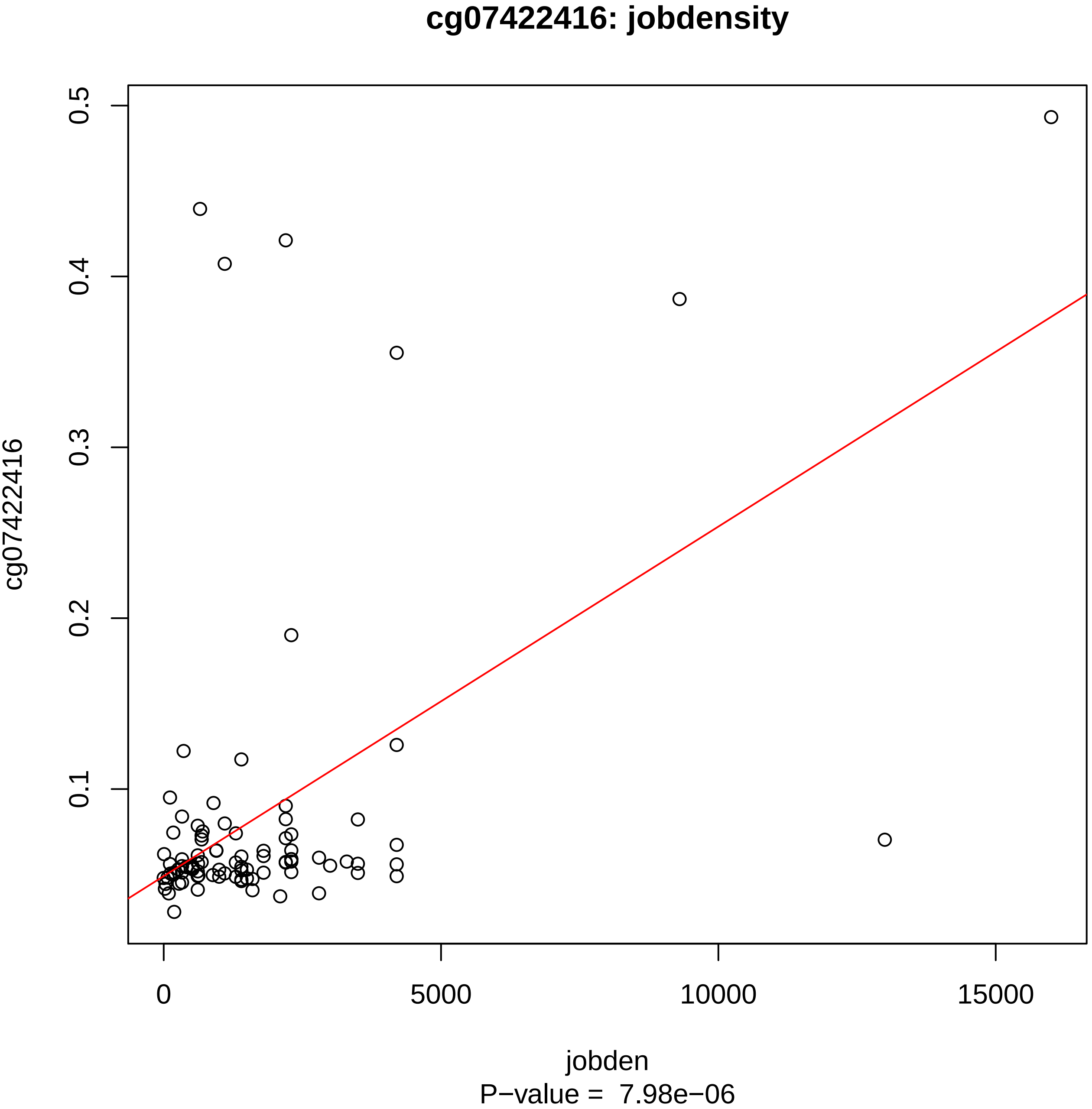
P−value = 1.85e−06

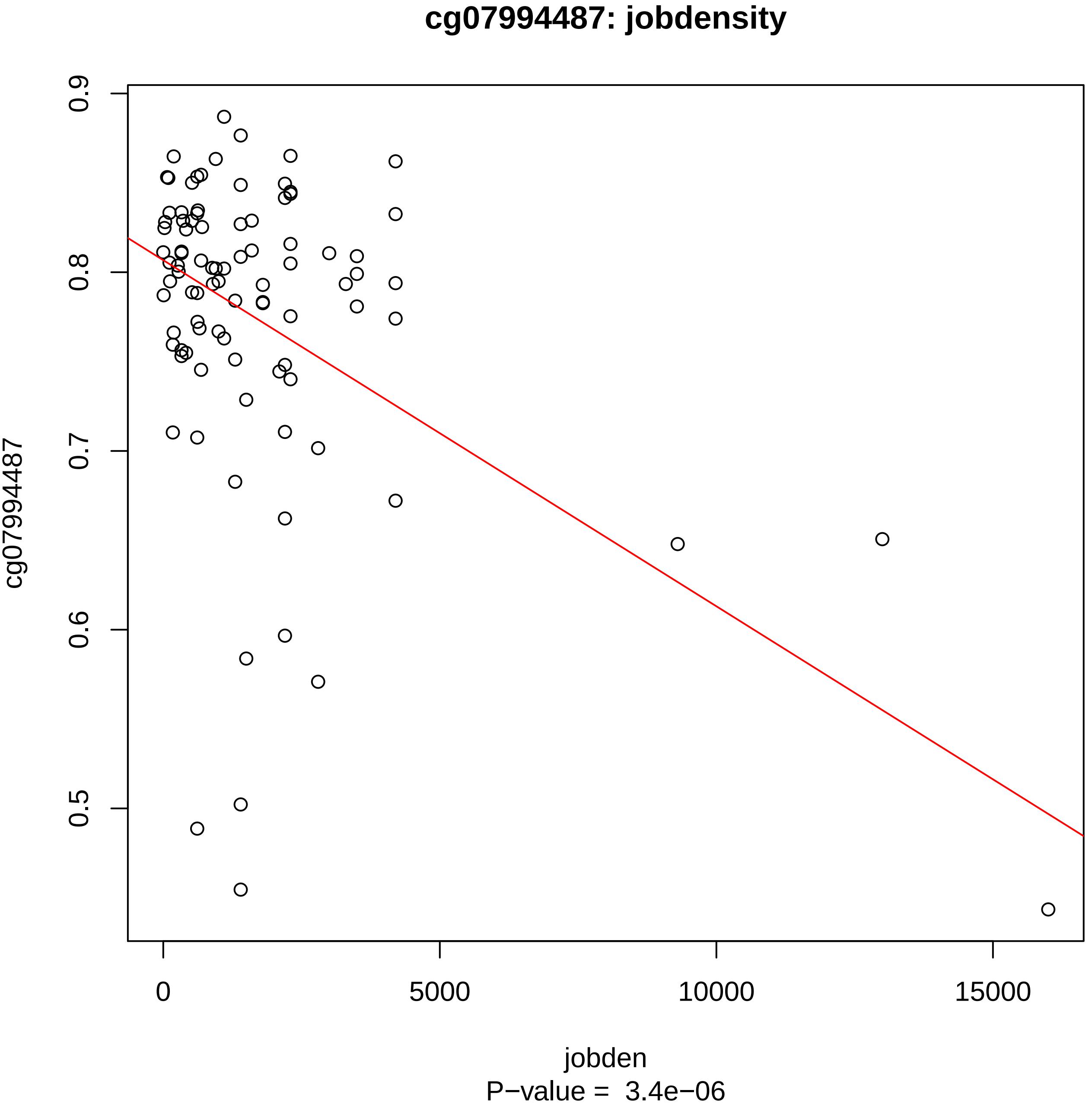

cg02449575: jobdensity
cg02449575
0.90
0.85
0.80
0.75
0.70
0.65
0
5000
10000
15000
jobden
P−value = 1.09e−06

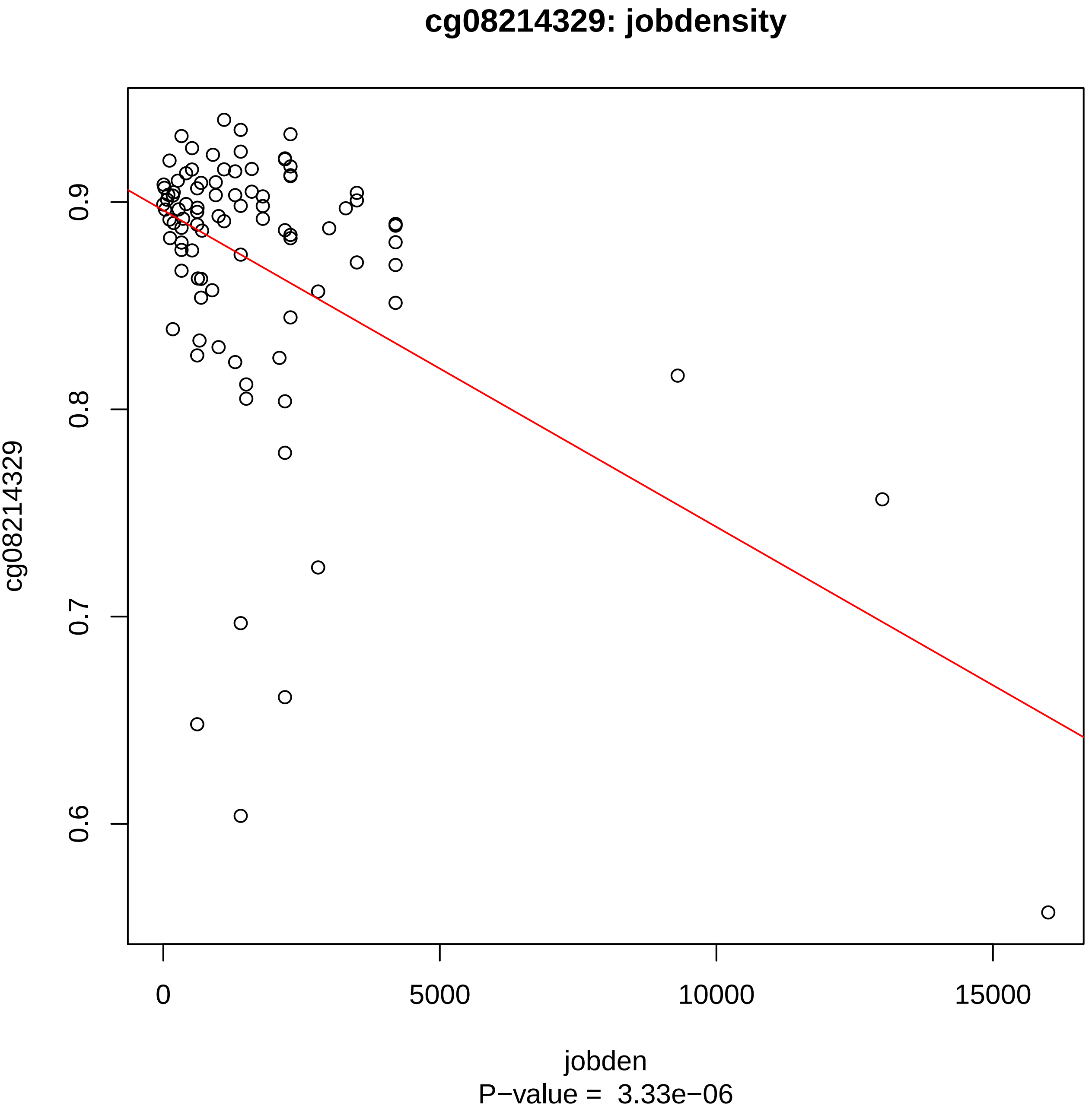

cg03115690: jobdensity
cg03115690
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0
5000
10000
15000
jobden
P−value = 3.16e−06


cg06520003: jobdensity
cg06520003
0.15
0.20
0.25
0.30
0.35
0
5000
10000
15000
jobden
P−value = 4.08e−06

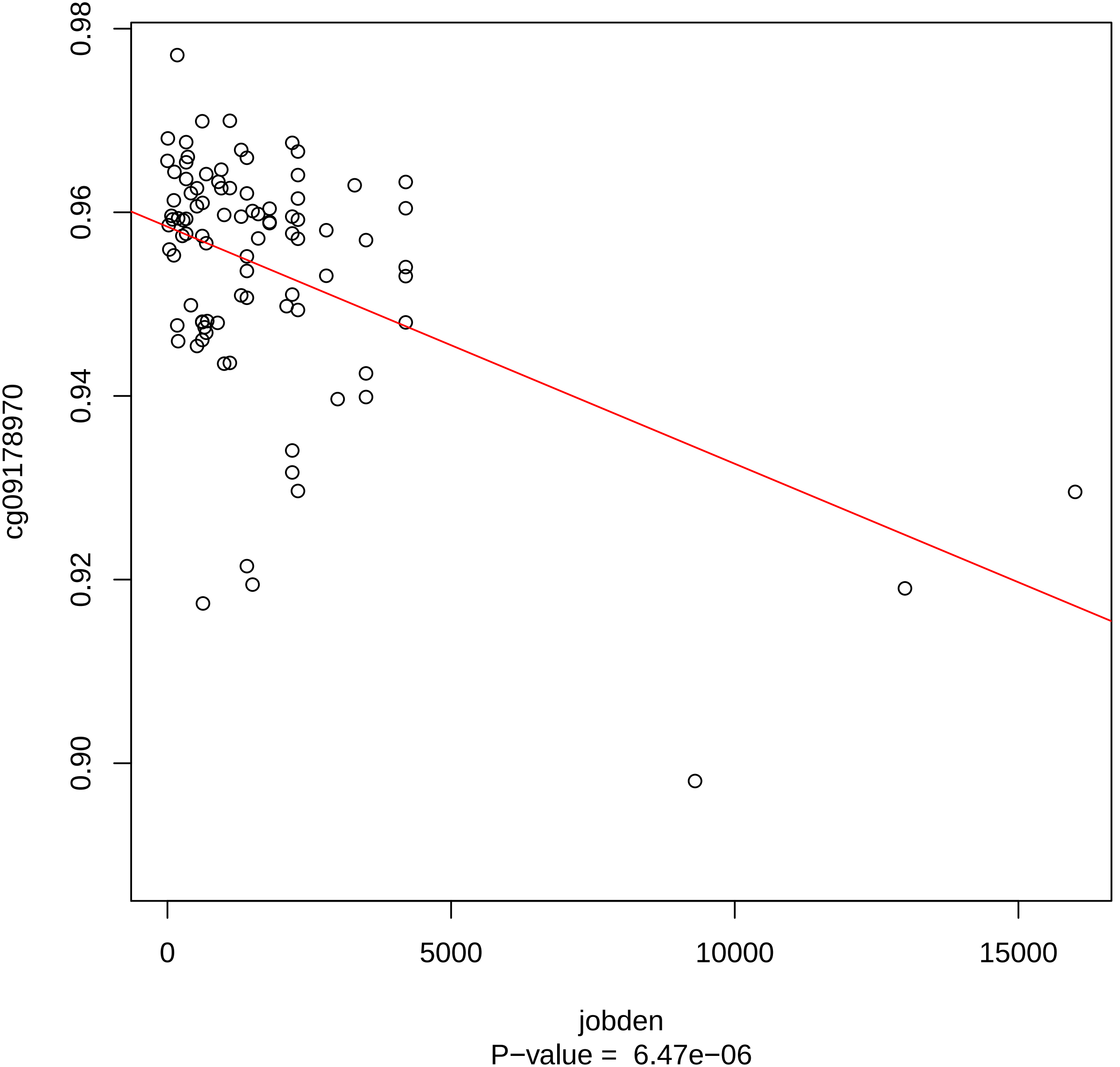

cg07141484: jobdensity
cg07141484
0.65
0.70
0.75
0.80
0.85
0.90
0
5000
10000
15000
jobden
P−value = 6.07e−06

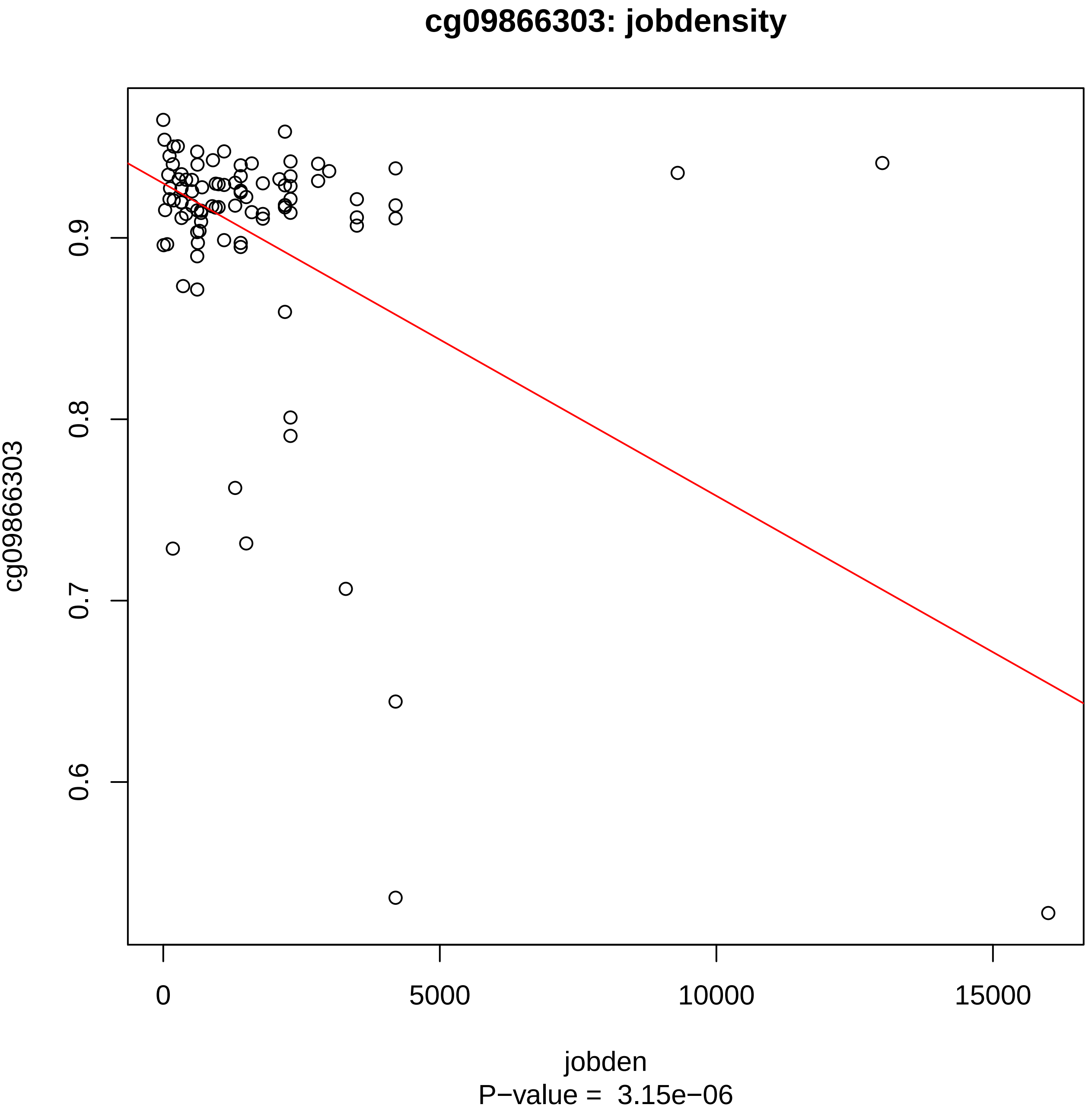

cg07422416: jobdensity
cg07422416
0.5
0.4
0.3
0.2
0.1
0
5000
10000
15000
jobden
P−value = 7.98e−06

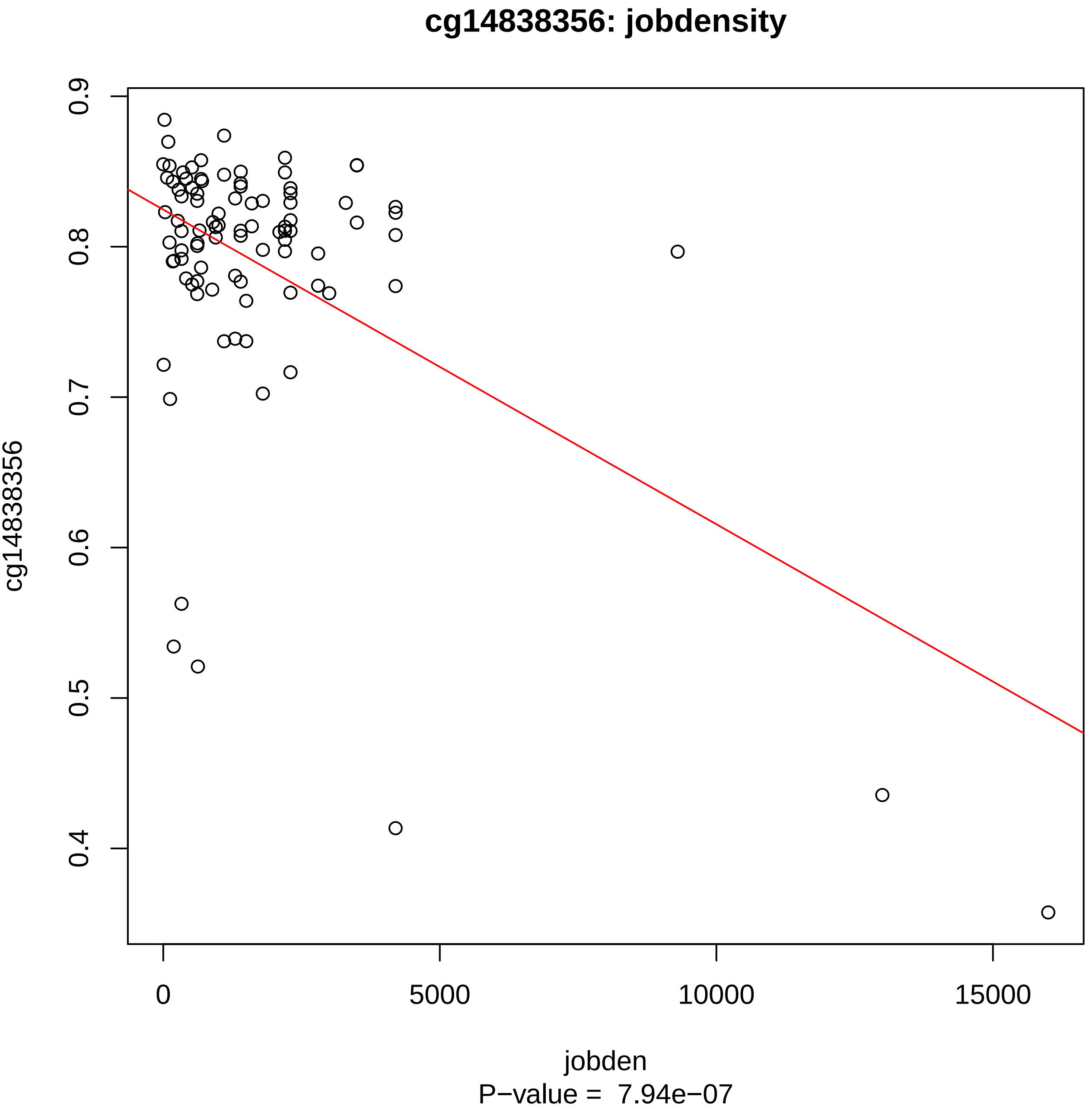

cg07994487: jobdensity
cg07994487
0.9
0.8
0.7
0.6
0.5
0
5000
10000
15000
jobden
P−value = 3.4e−06

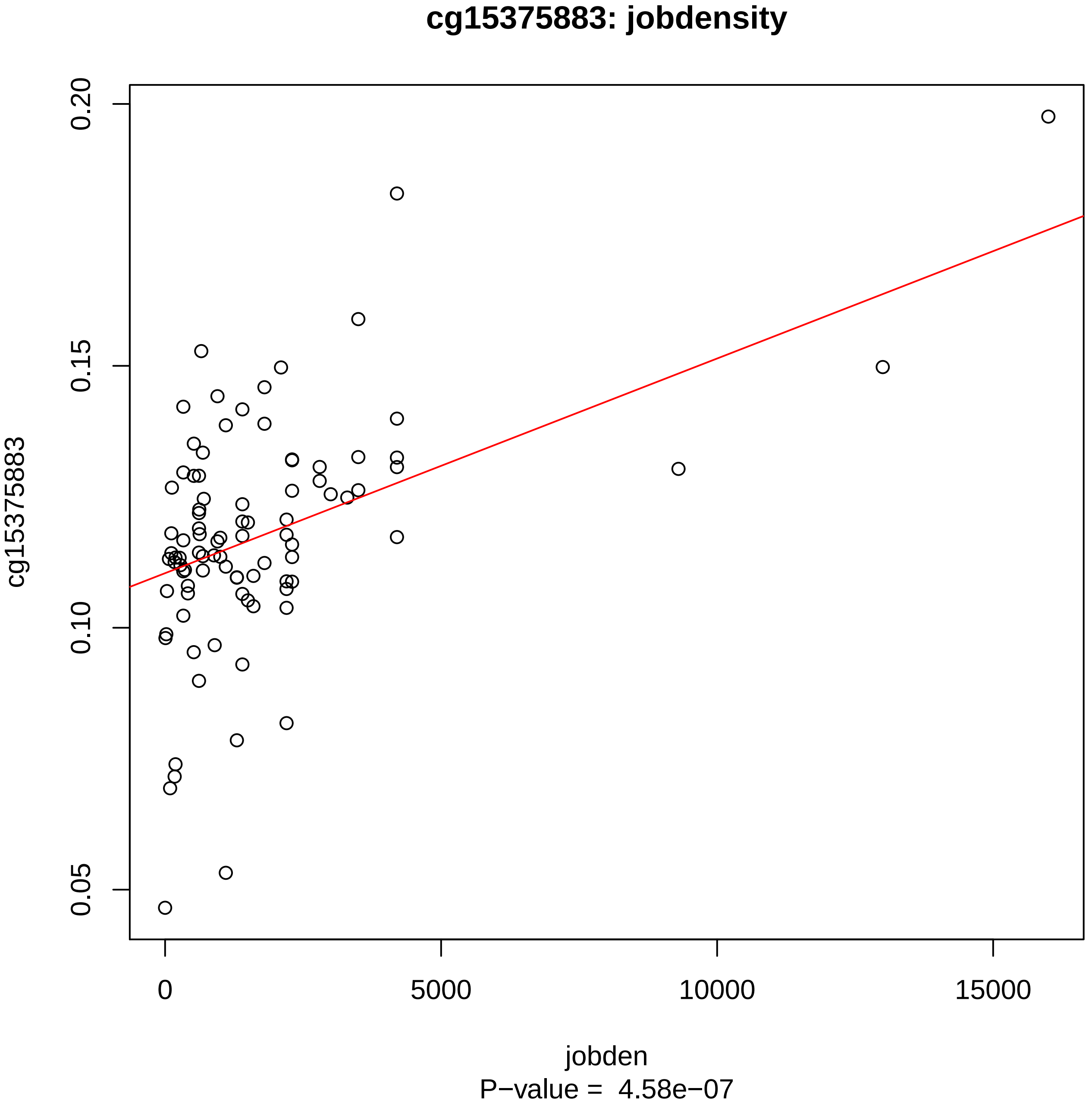

cg08214329: jobdensity
cg08214329
0.6
0.7
0.8
0.9
0
5000
10000
15000
jobden
P−value = 3.33e−06

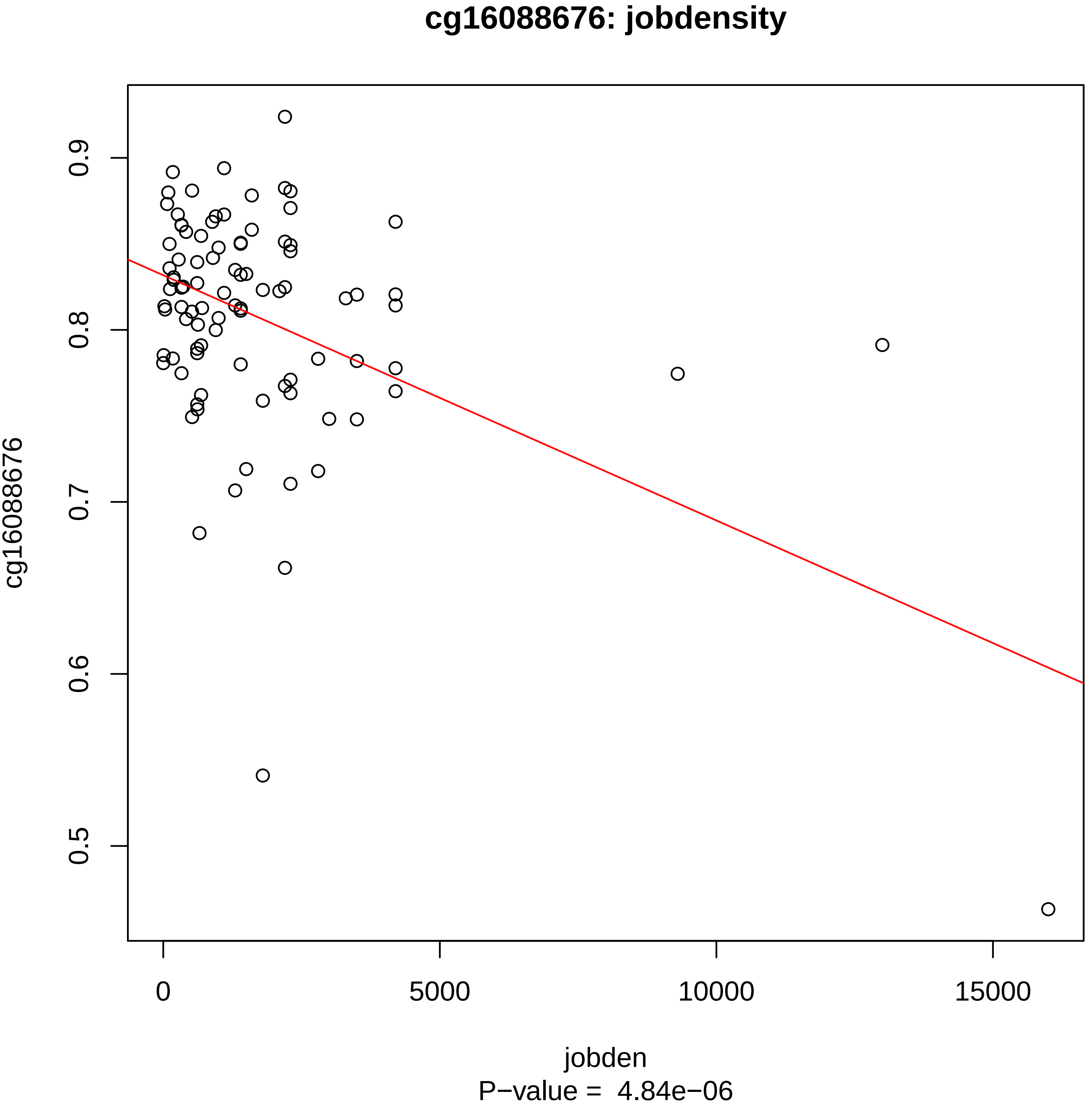
cg09178970: jobdensity

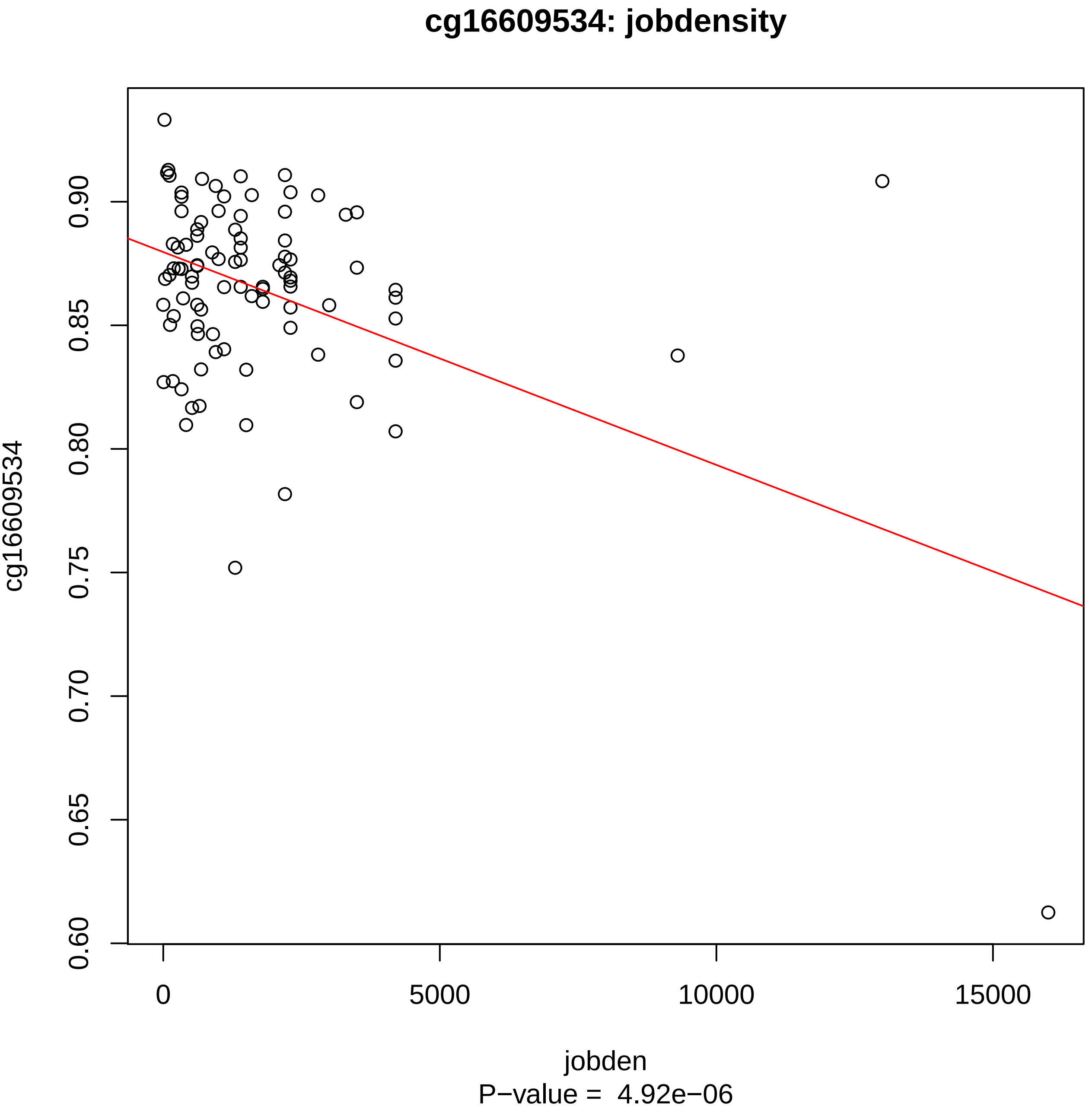



cg09866303: jobdensity
cg09866303
0.6
0.7
0.8
0.9
0
5000
10000
15000
jobden
P−value = 3.15e−06

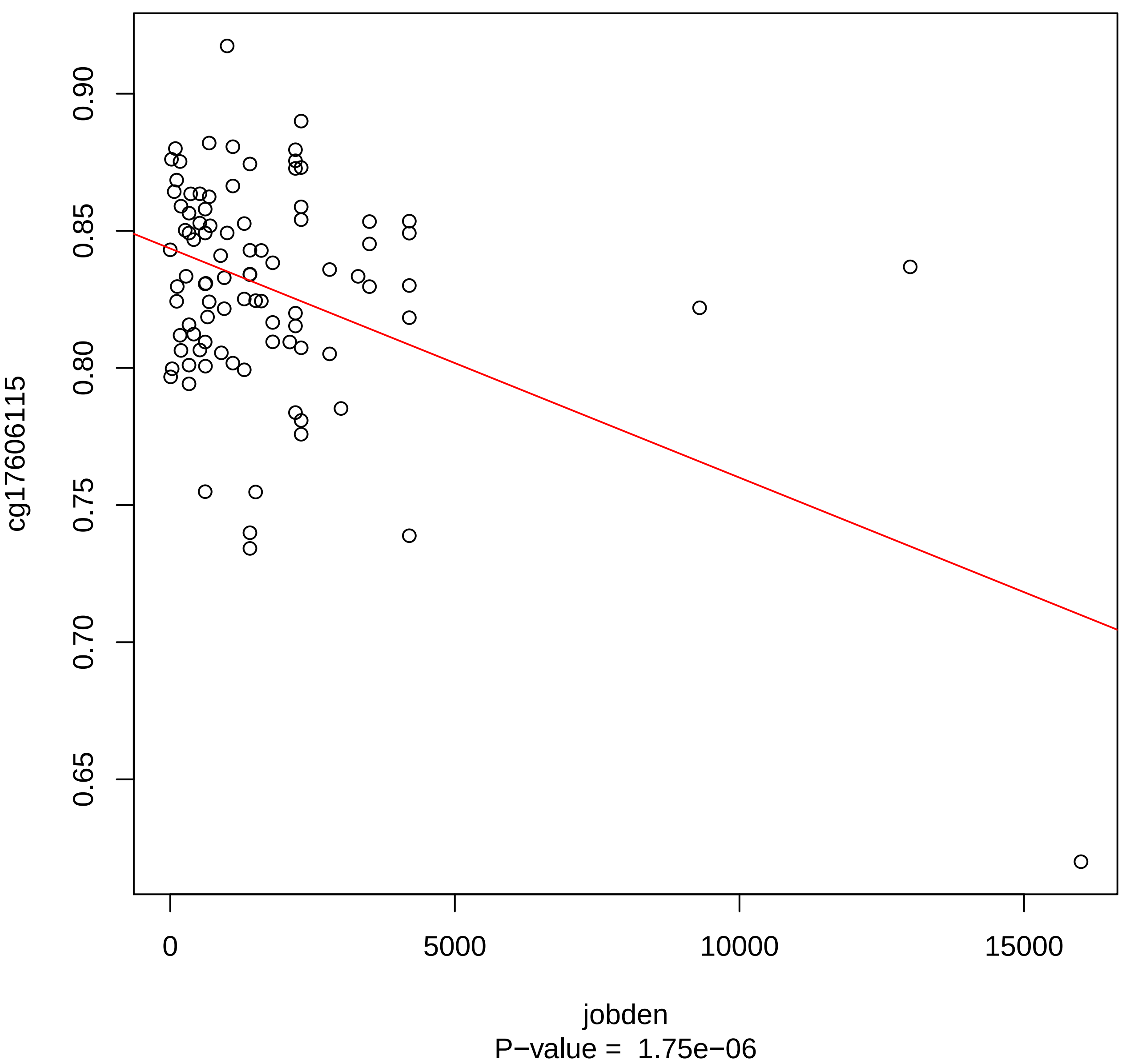

cg14838356: jobdensity
cg14838356
0.9
0.8
0.7
0.6
0.5
0.4
0
5000
10000
15000
jobden
P−value = 7.94e−07


cg15375883: jobdensity
cg15375883
0.05
0.10
0.15
0.20
0
5000
10000
15000
jobden
P−value = 4.58e−07

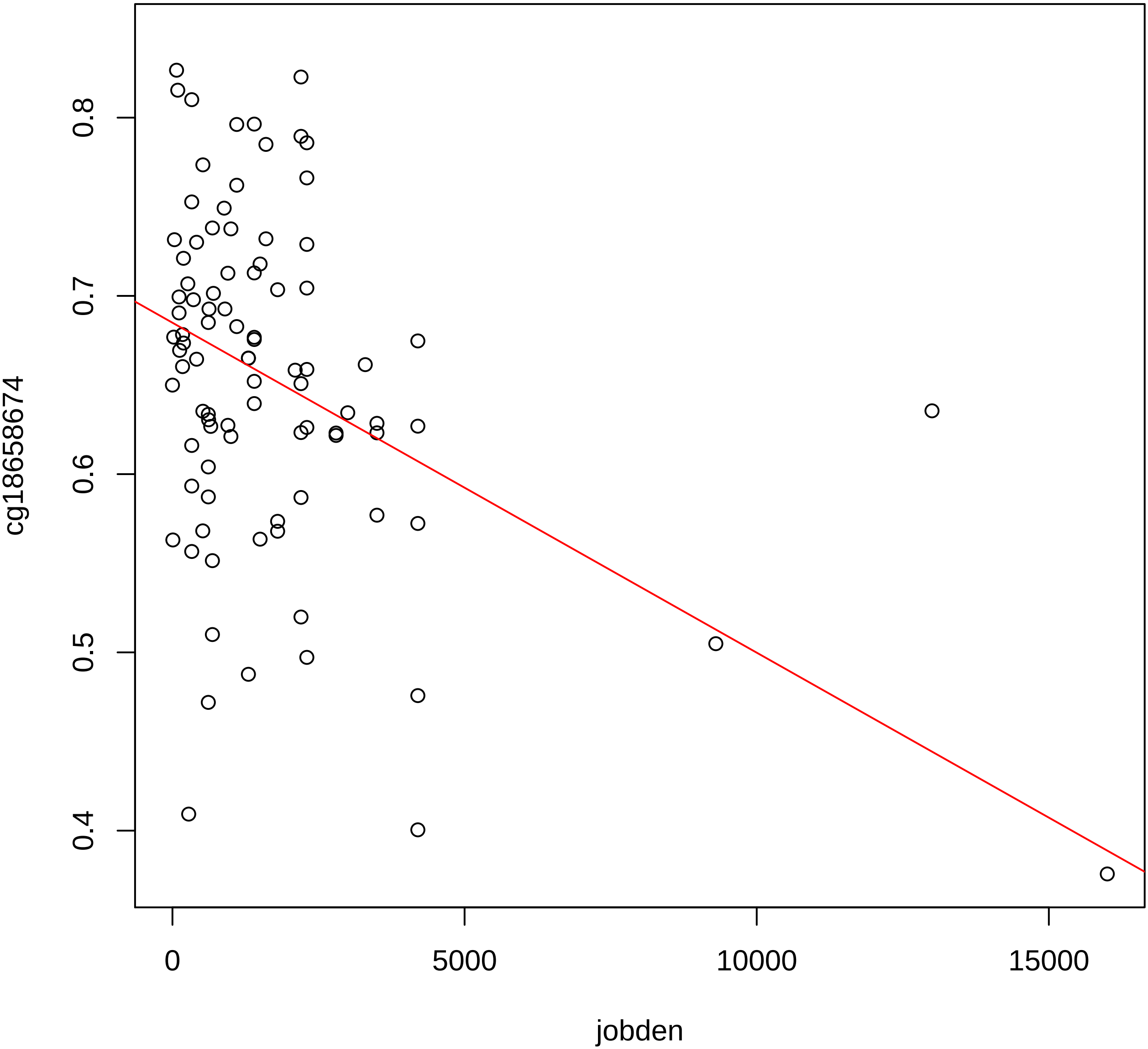

cg16088676: jobdensity
cg16088676
0.5
0.6
0.7
0.8
0.9
0
5000
10000
15000
jobden
P−value = 4.84e−06


cg16609534: jobdensity
cg16609534
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0
5000
10000
15000
jobden
P−value = 4.92e−06

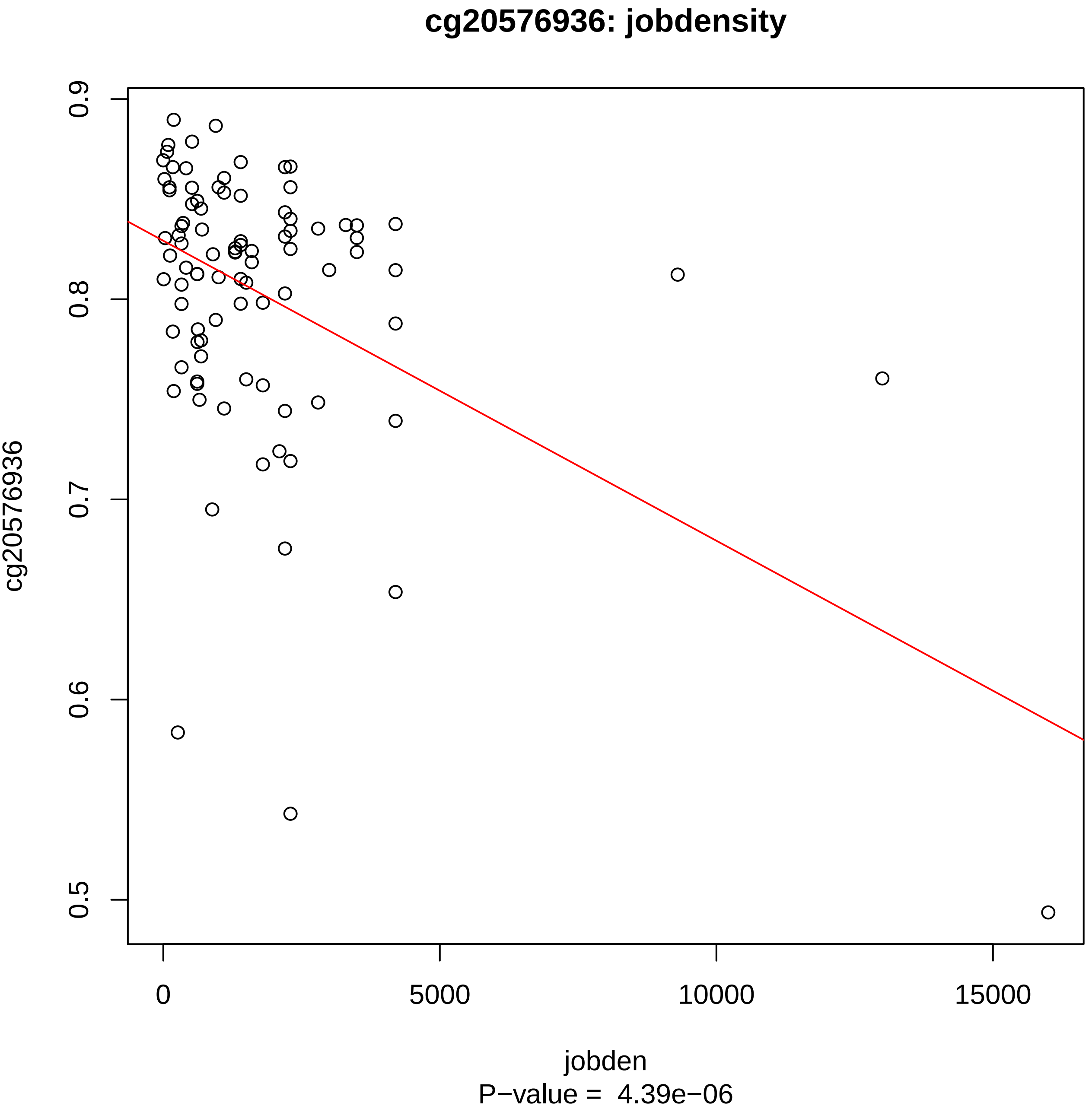
cg17606115: jobdensity

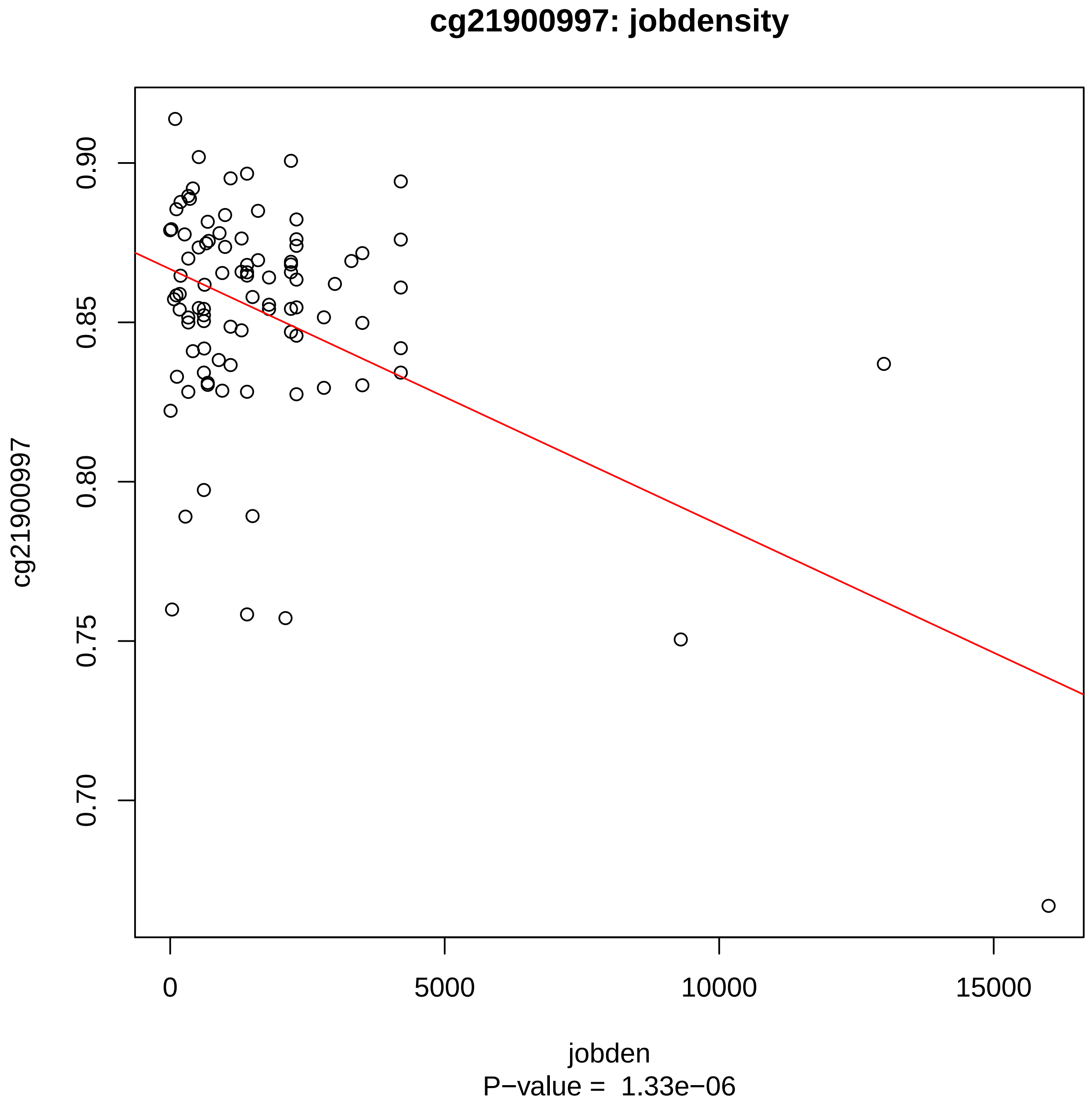


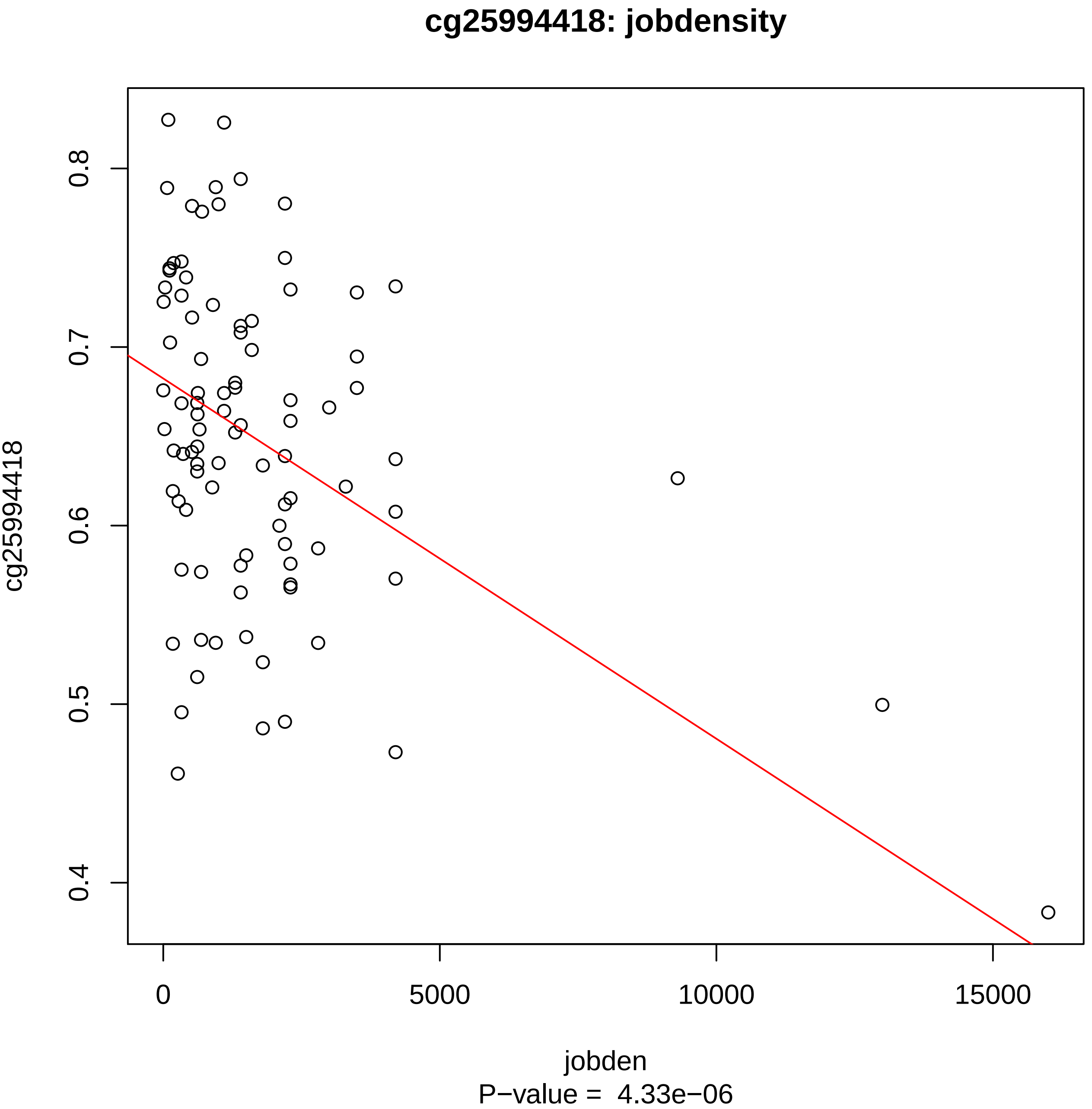
cg18658674: jobdensity



P−value = 7.82e−06


cg20576936: jobdensity
cg20576936
0.9
0.8
0.7
0.6
0.5
0
5000
10000
15000
jobden
P−value = 4.39e−06

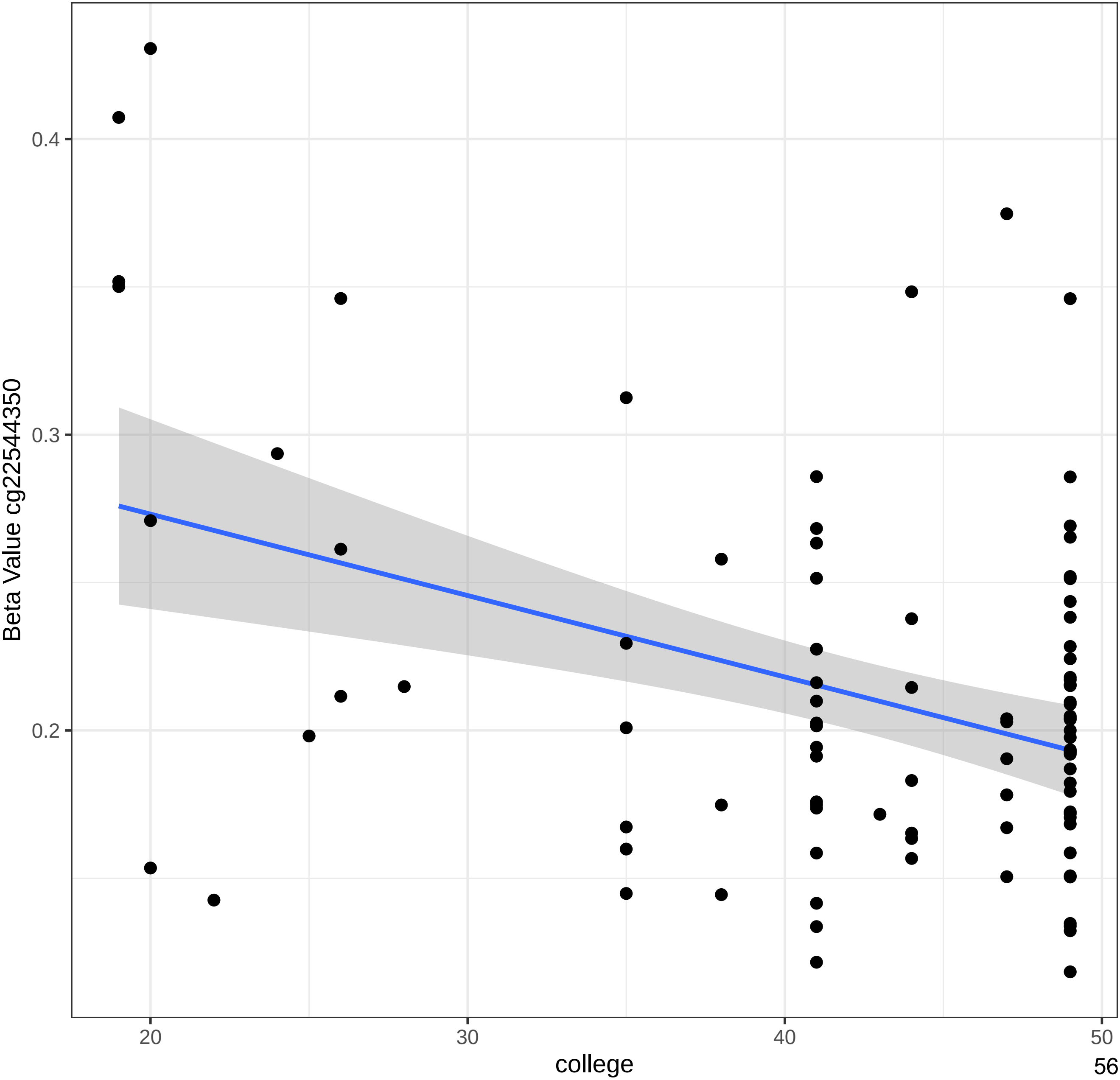

cg21900997: jobdensity
0.90
0.85
0.80
0.75
0.70
cg21900997
0
5000
10000
15000
jobden
P−value = 1.33e−06


cg25994418: jobdensity
cg25994418
0.4
0.5
0.6
0.7
0.8
0
5000
10000
15000
jobden
P−value = 4.33e−06

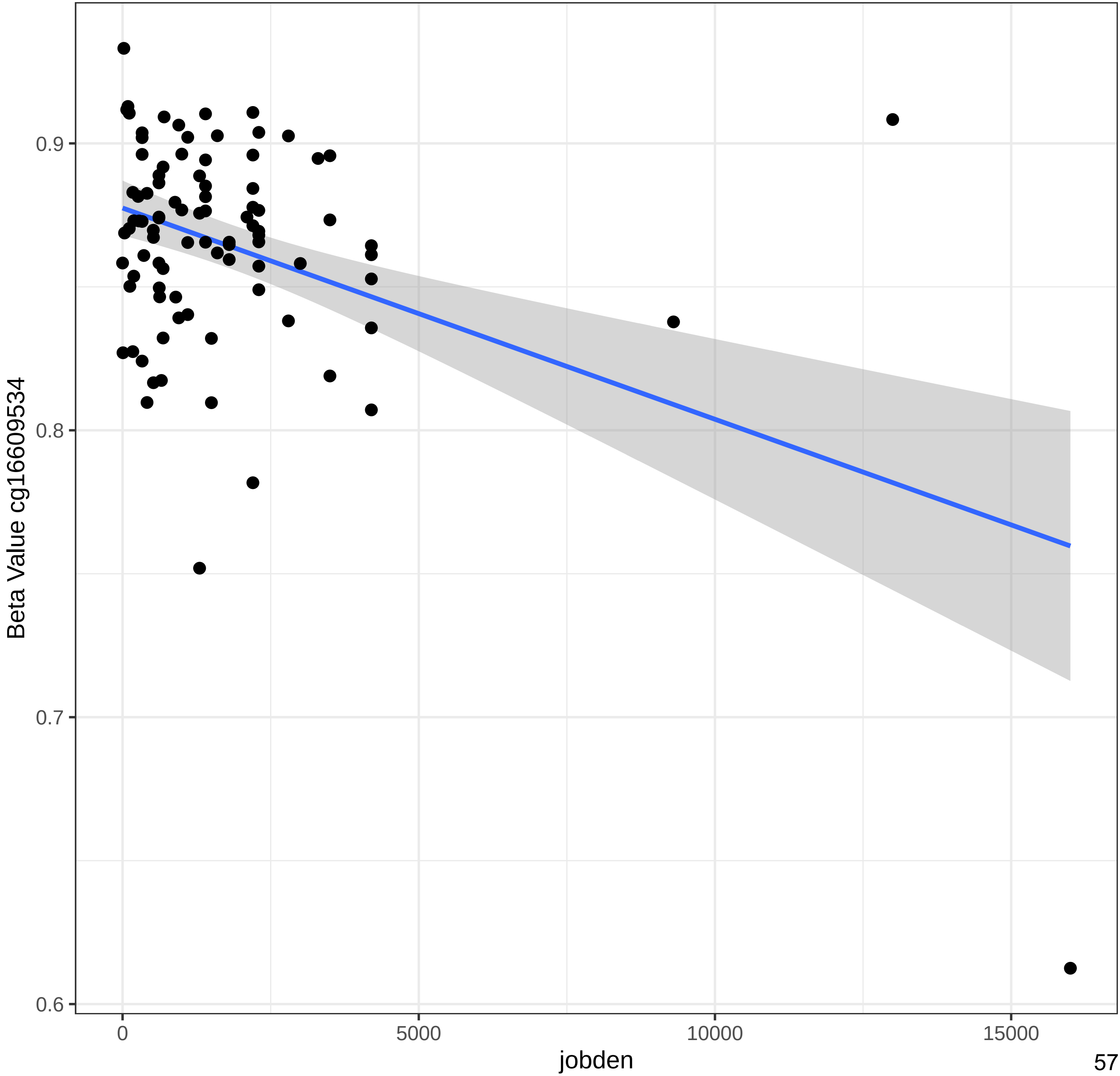
EWAS Scatterplots (Post-Sensitivity Analysis)

Removing outliers in the association between college graduation rates and methylation at cg22544350, job density and methylation at cg16609534

Methylation by college

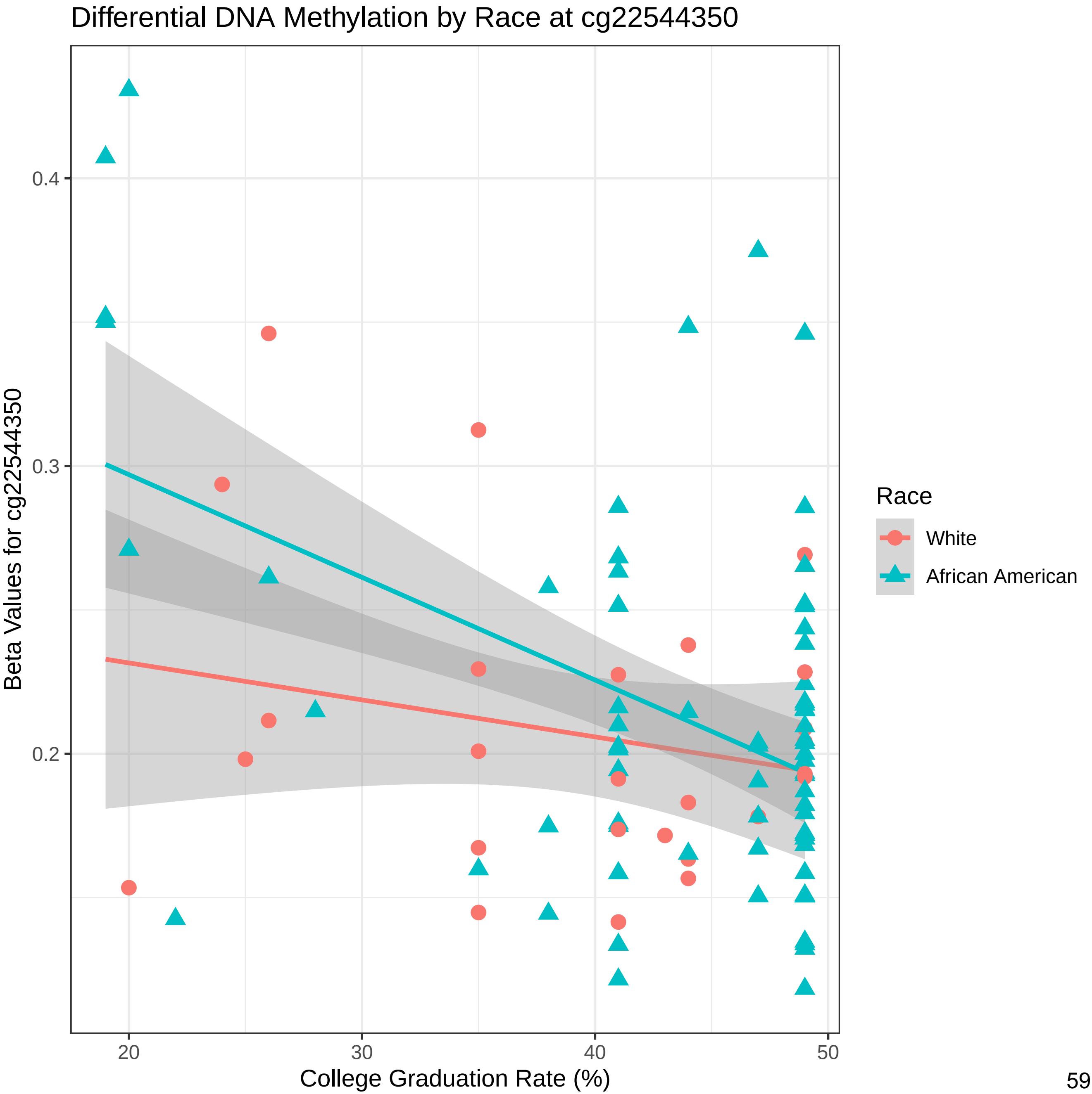


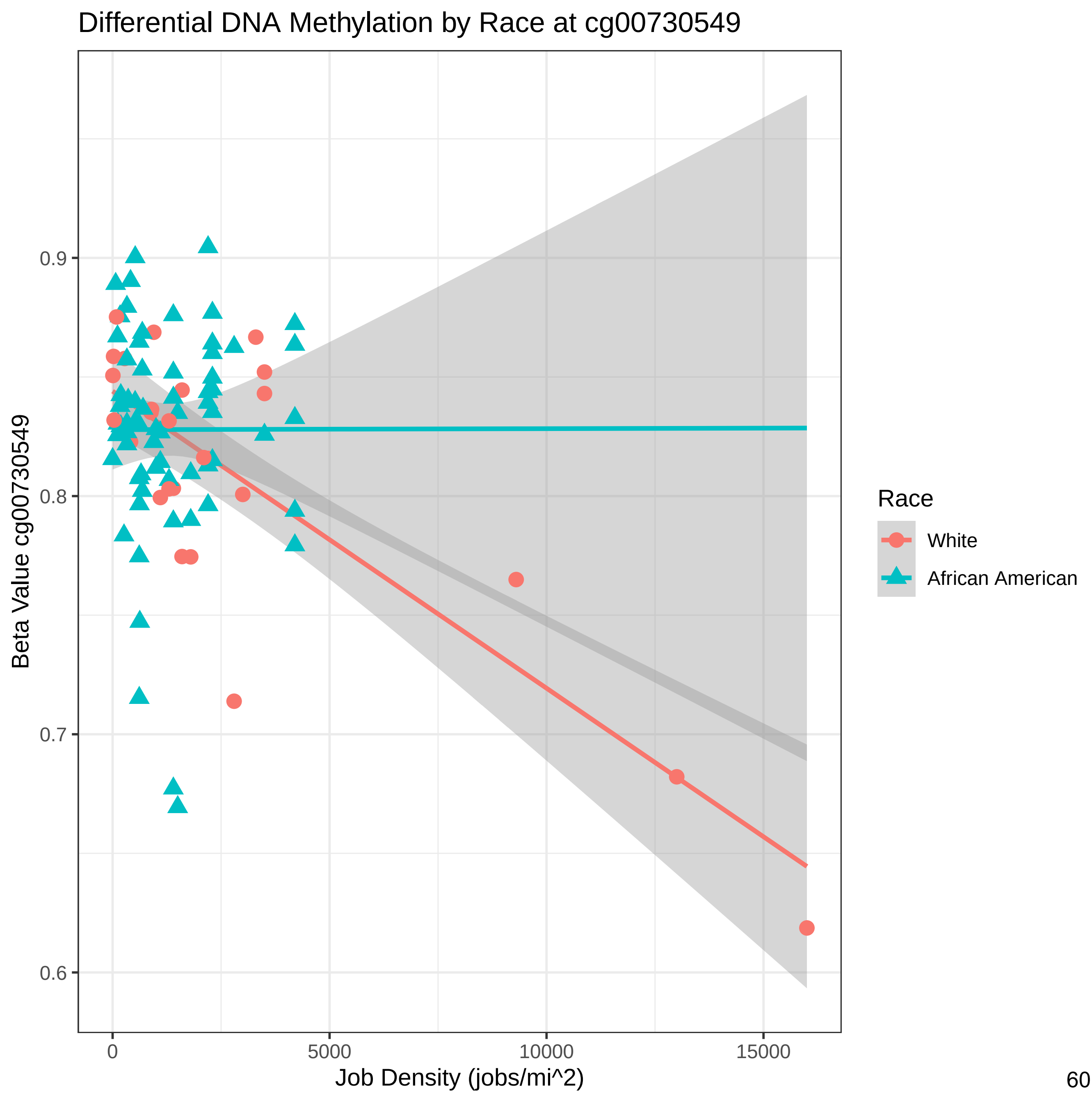
Methylation by Job Density

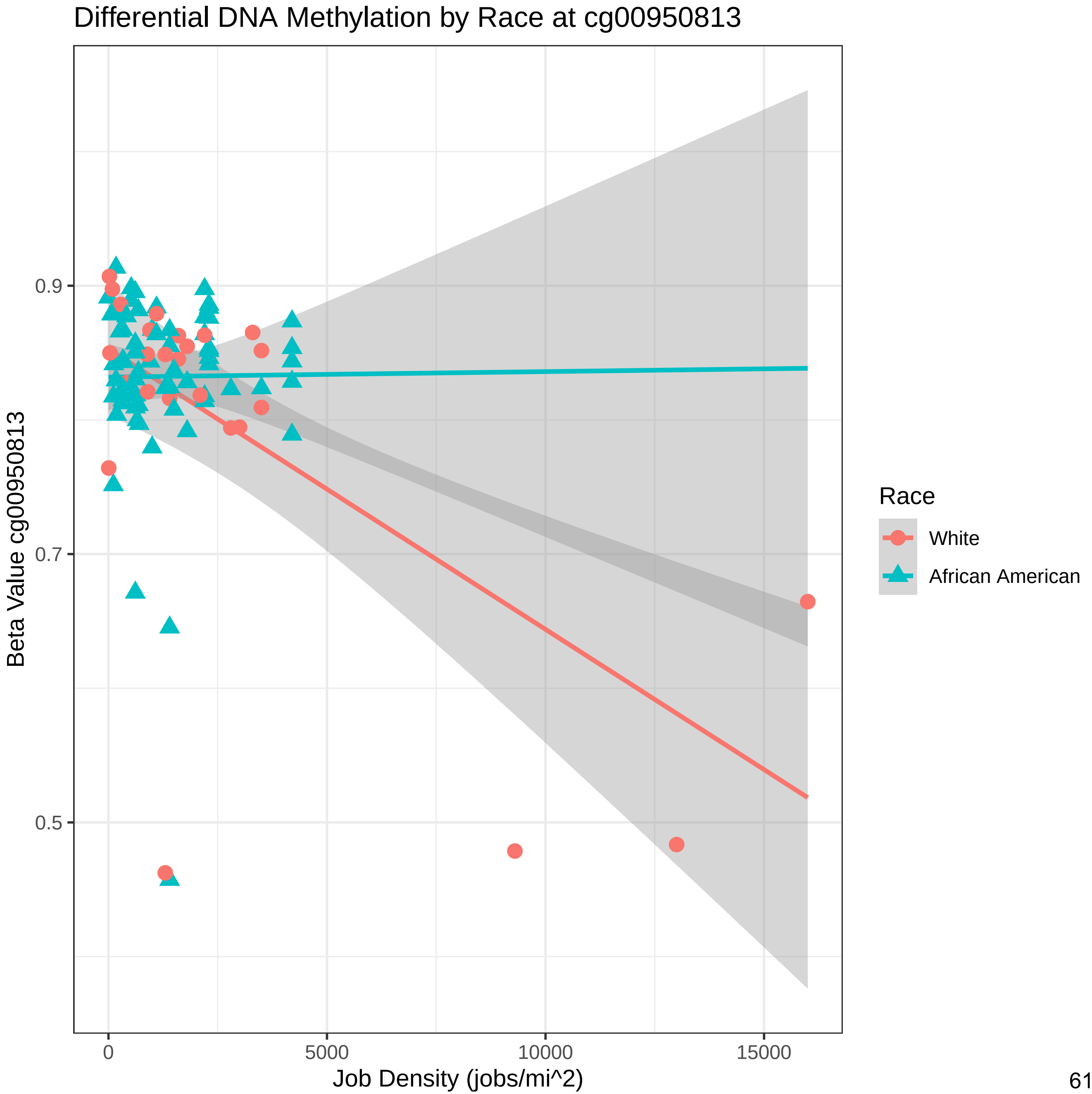


Interaction Analysis

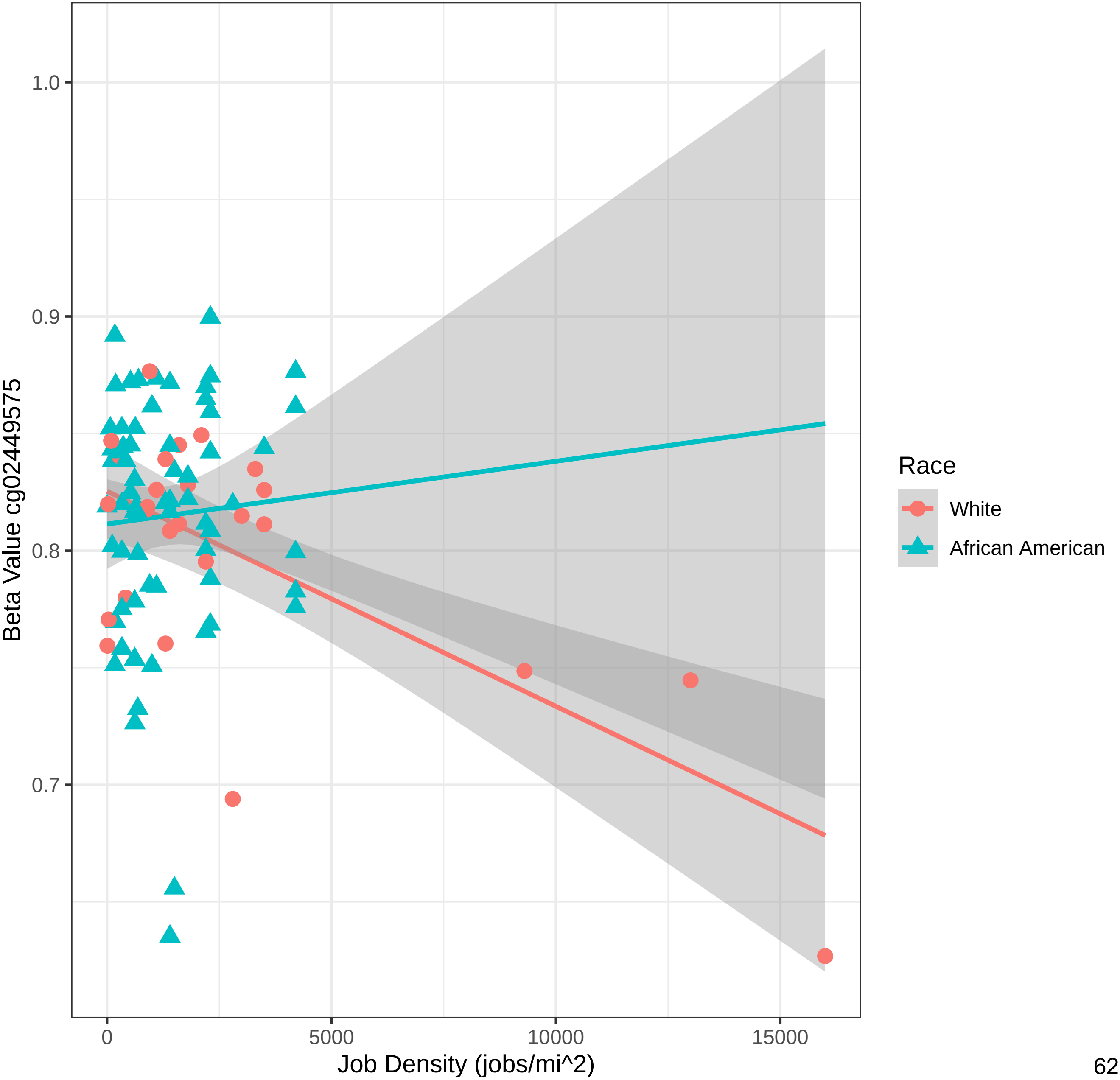
Graphing the association between the interaction term of race and neighborhood factors and DNA methylation at CpG sites


Differential DNA Methylation by Race at cg22544350
Beta Values for cg22544350
0.4
0.3
0.2
20
30
40
50
College Graduation Rate (%)
Race
White
African American


Differential DNA Methylation by Race at cg00730549
Beta Value cg00730549
0.9
0.8
0.7
0.6
0
5000
10000
15000
Job Density (jobs/mi^2)
Race
White
African American


Differential DNA Methylation by Race at cg00950813
Beta Value cg00950813
0.9
0.7
0.5
0
5000
10000
15000
Job Density (jobs/mi^2)
Race
White
African American

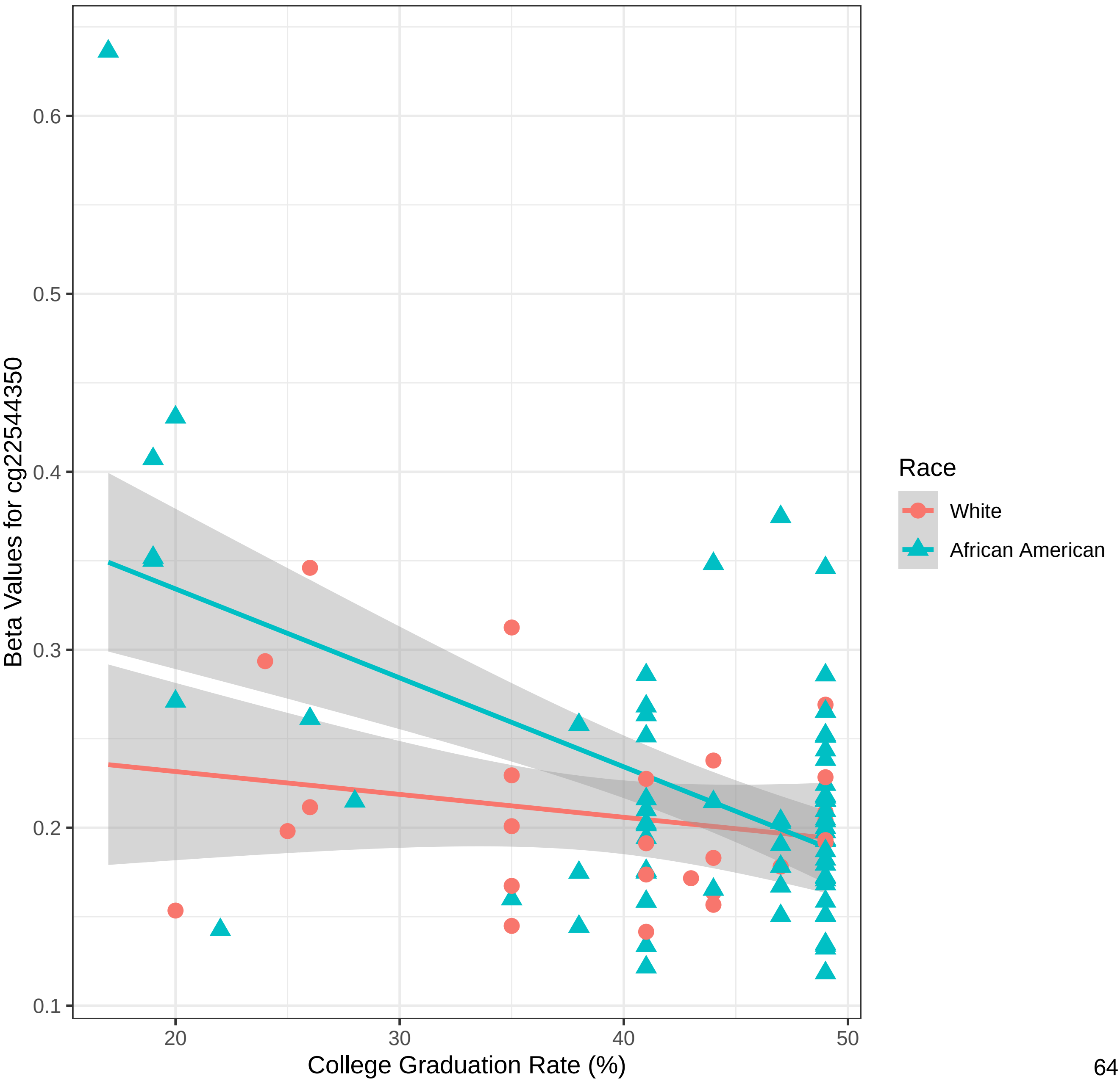
Differential DNA Methylation by Race at cg00950813



Interaction Analysis Scatterplots (Post-Sensitivity Analysis)

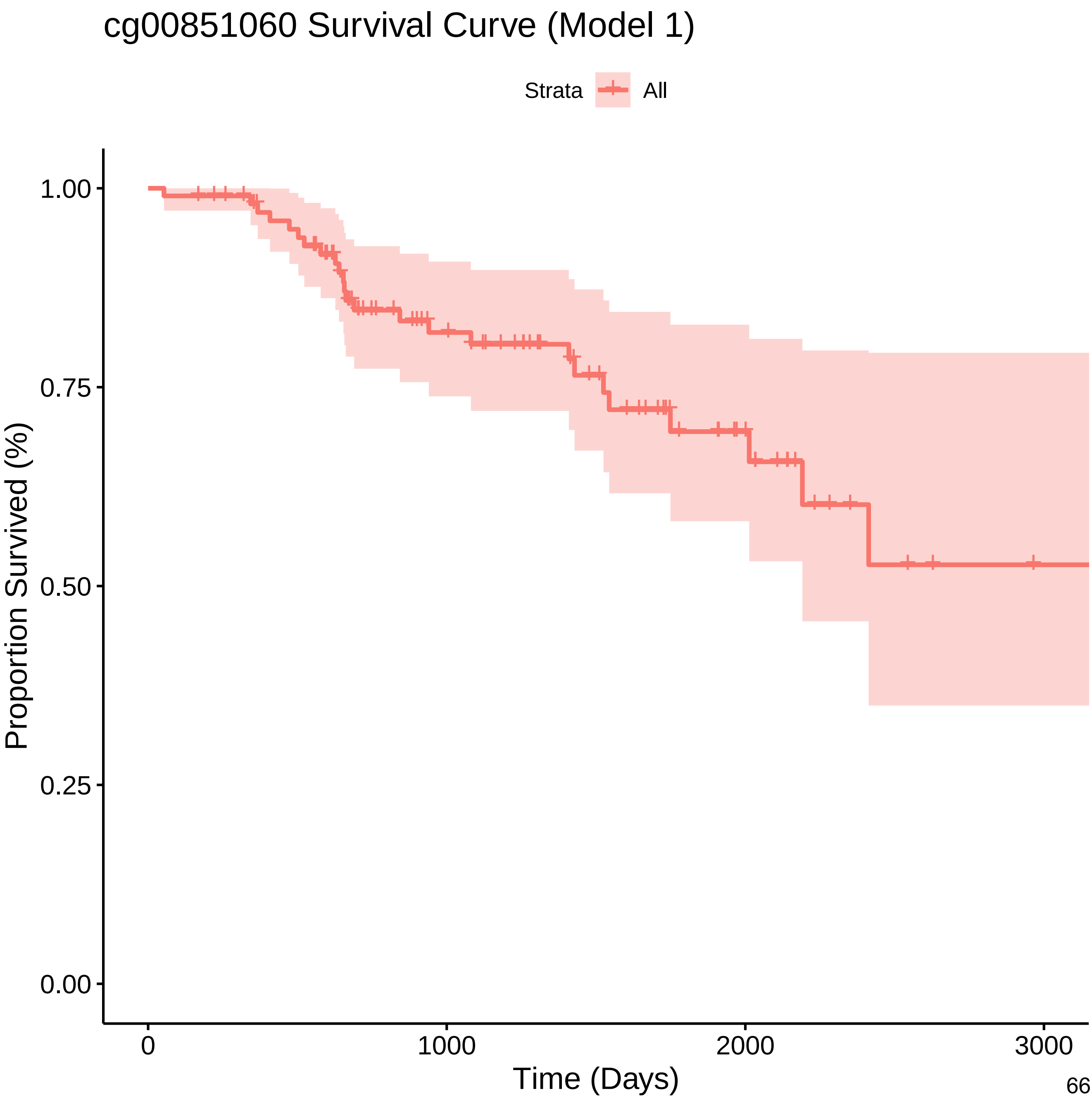
Graphing the association between the interaction term of race and neighborhood factors and DNA methylation at CpG sites cg22544350 and cg16609534 after removing outliers

Differential DNA Methylation by Race at cg22544350

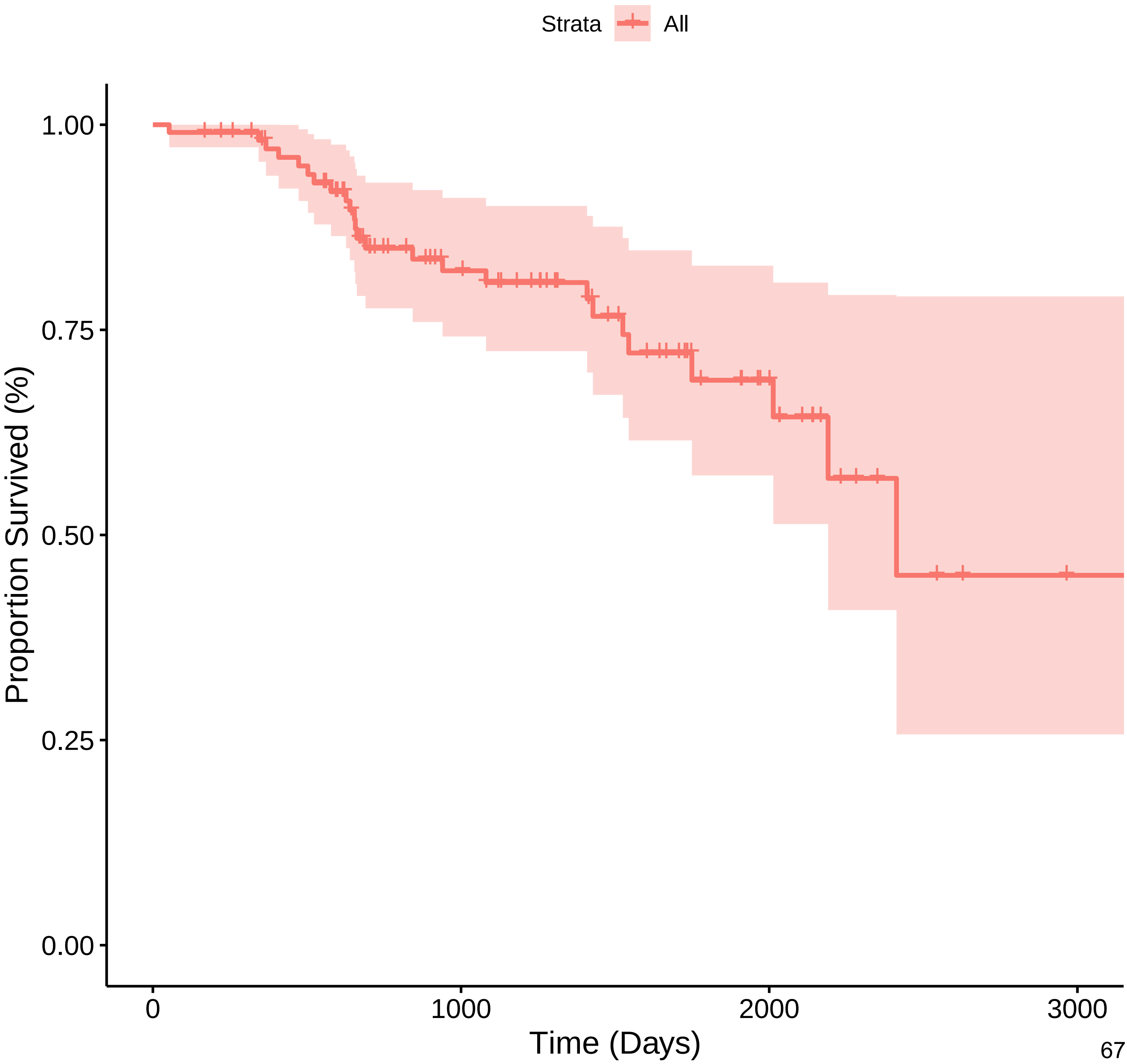


Hazard Analyses (Model 1)

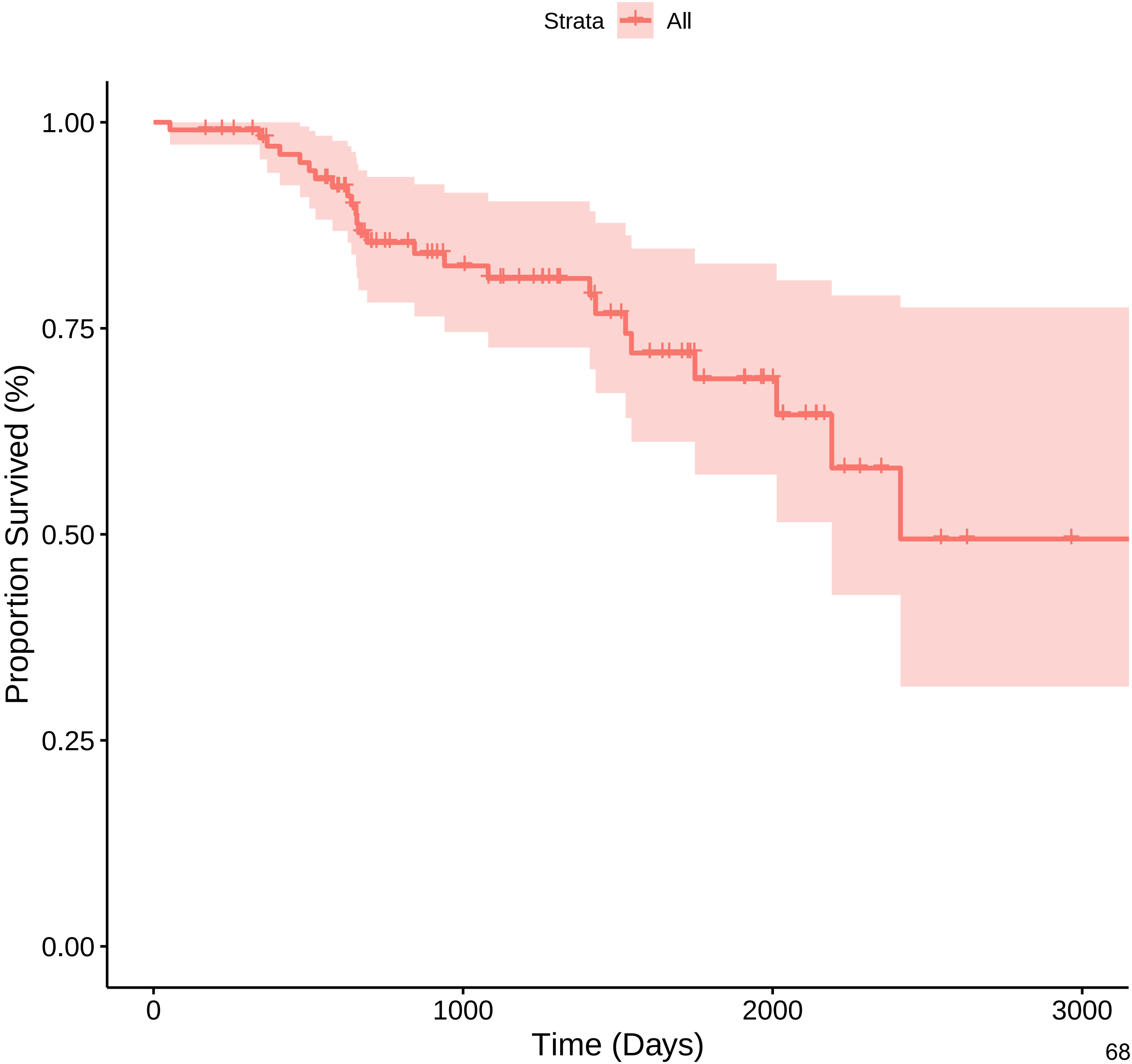
Graphing the association between DNA methylation at CpG sites and all cause mortality, adjusting for age

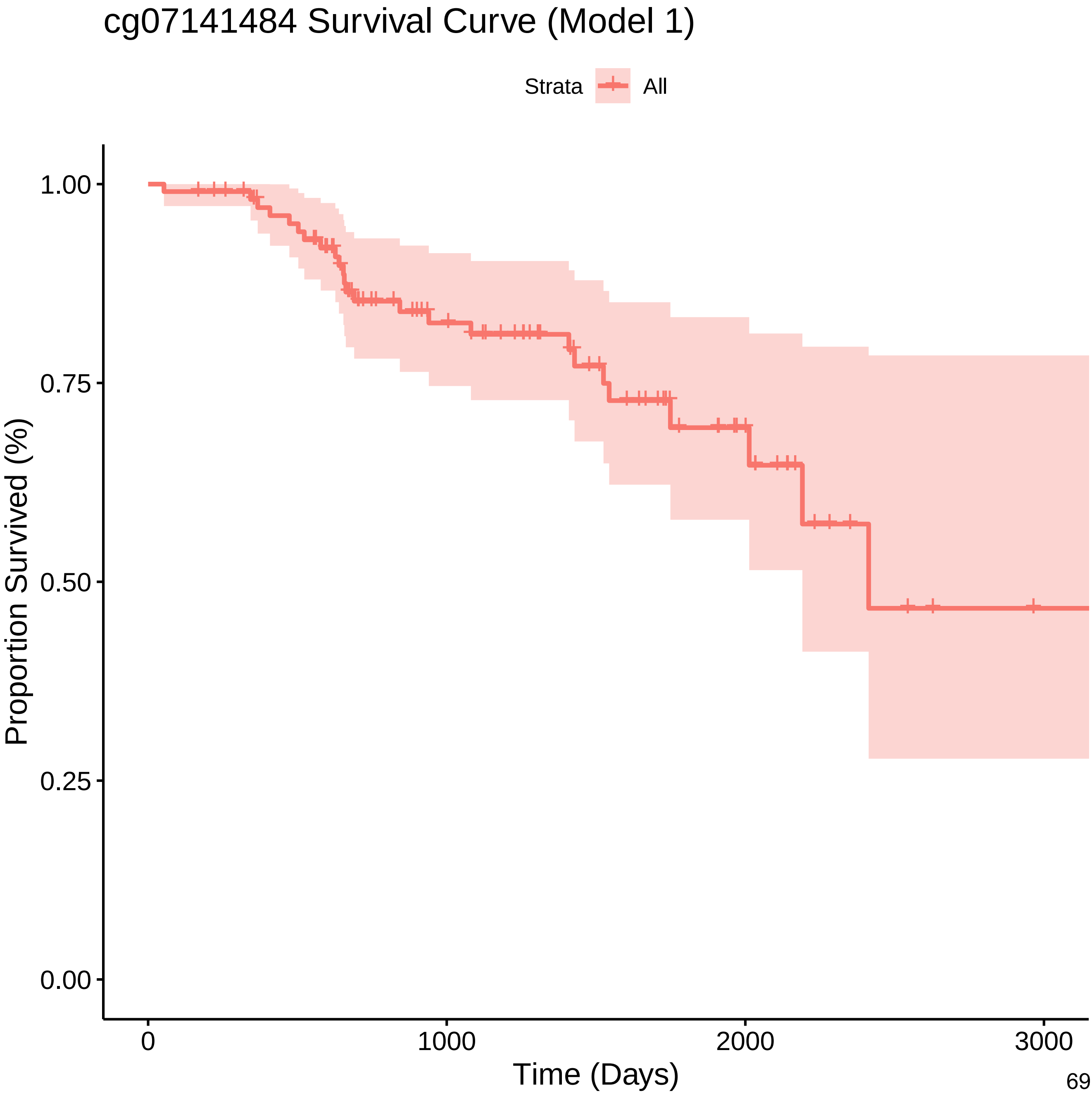

cg00851060 Survival Curve (Model 1)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)

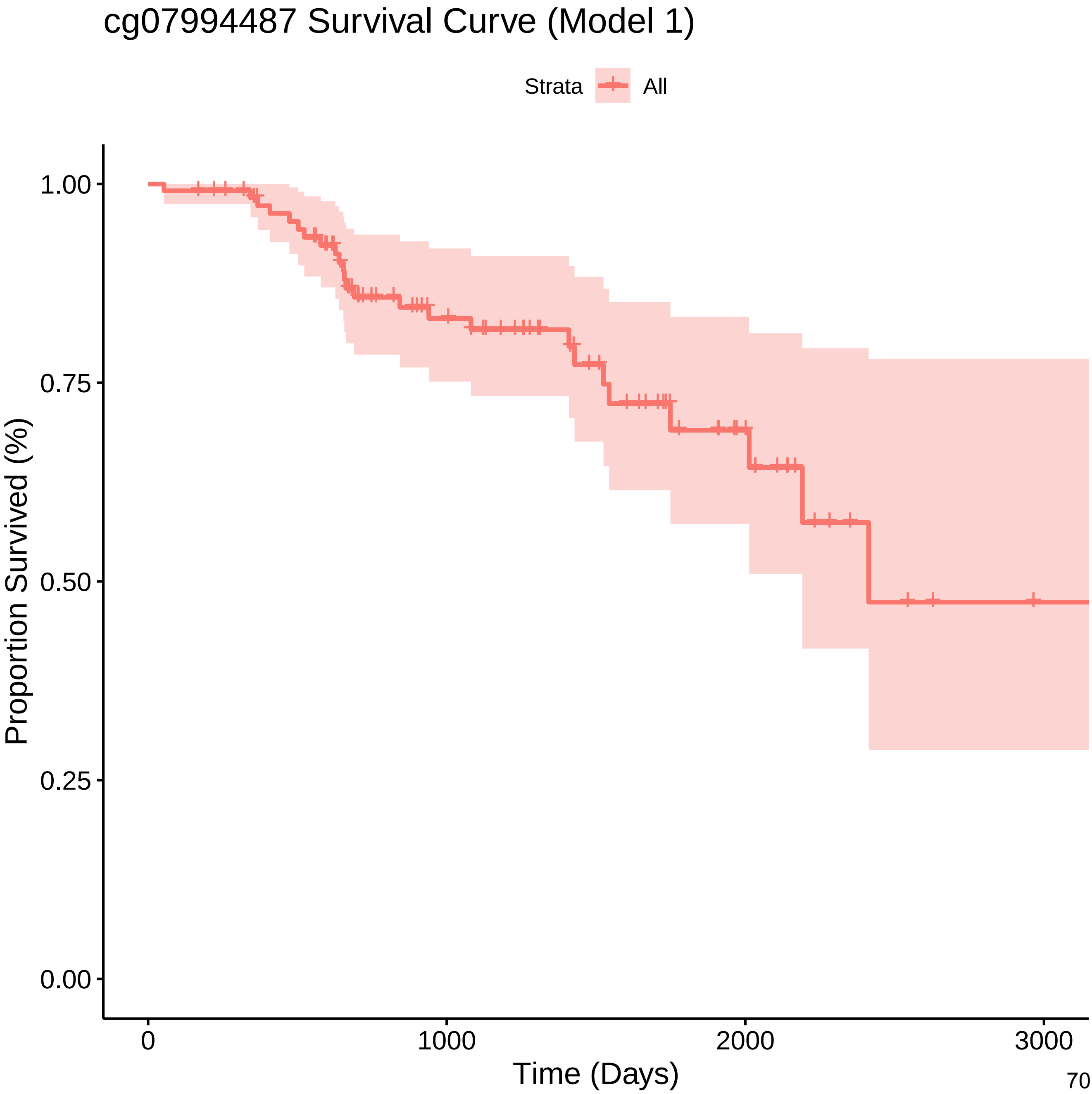
cg00950813 Survival Curve (Model 1)

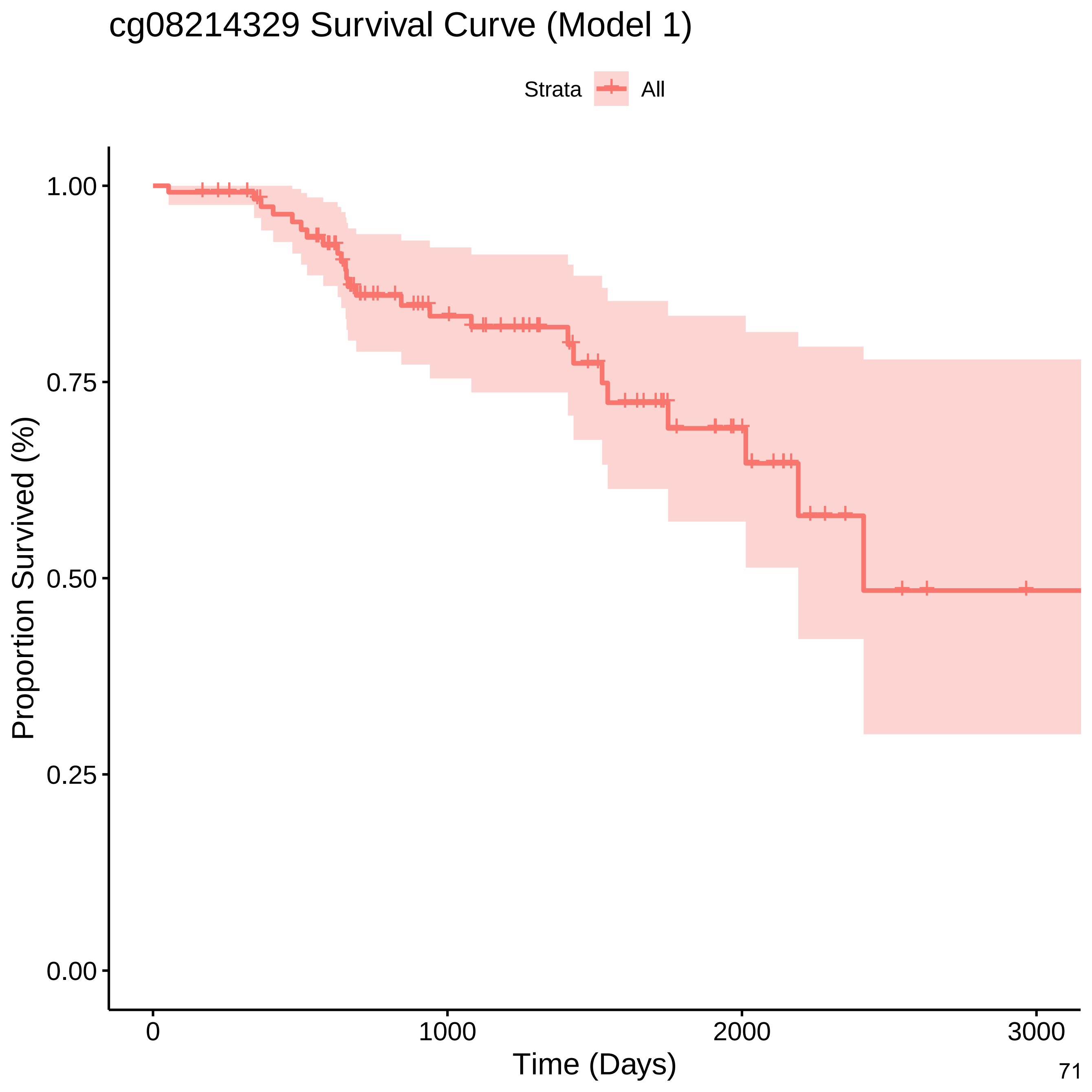


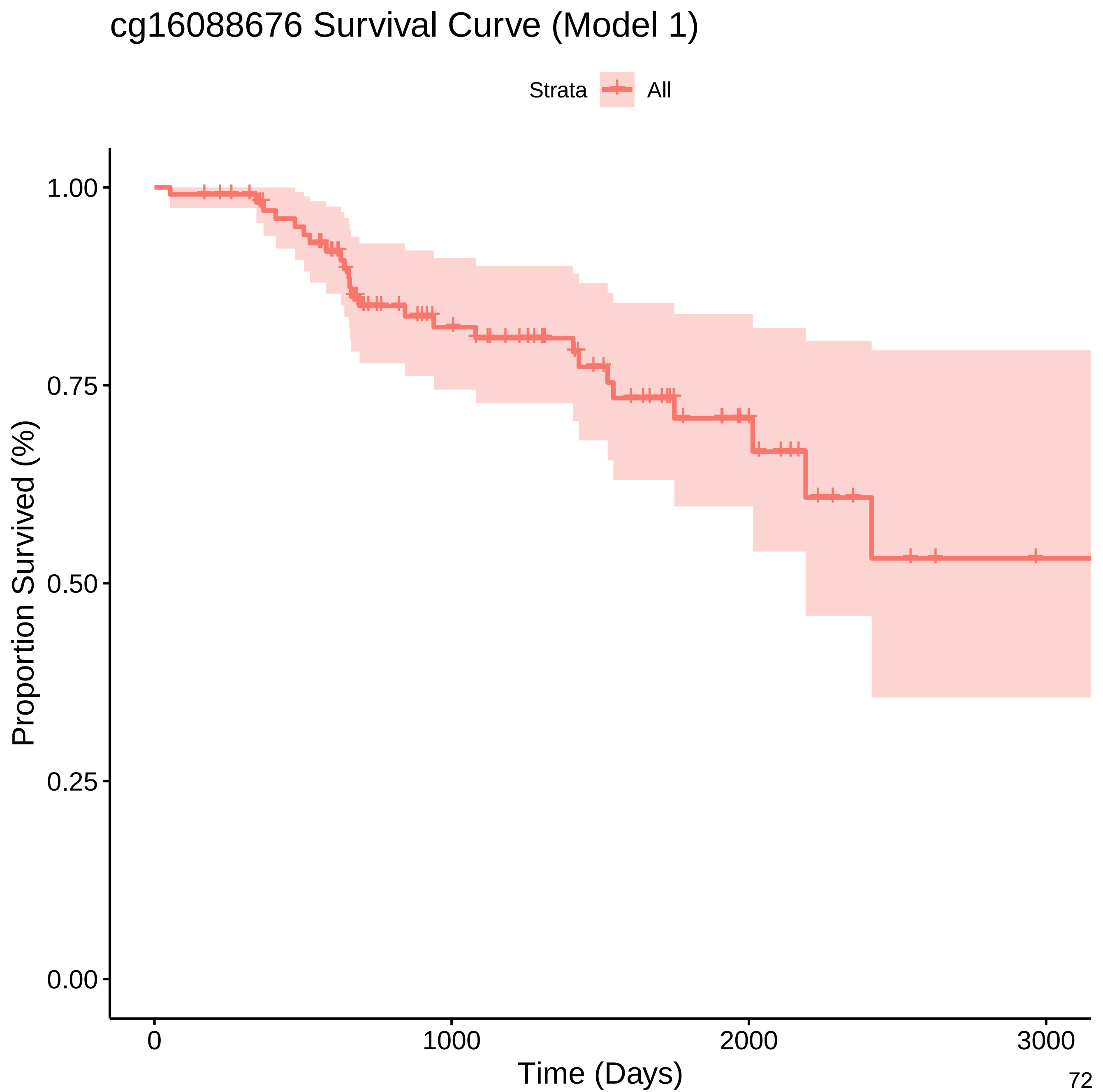
cg03115690 Survival Curve (Model 1)

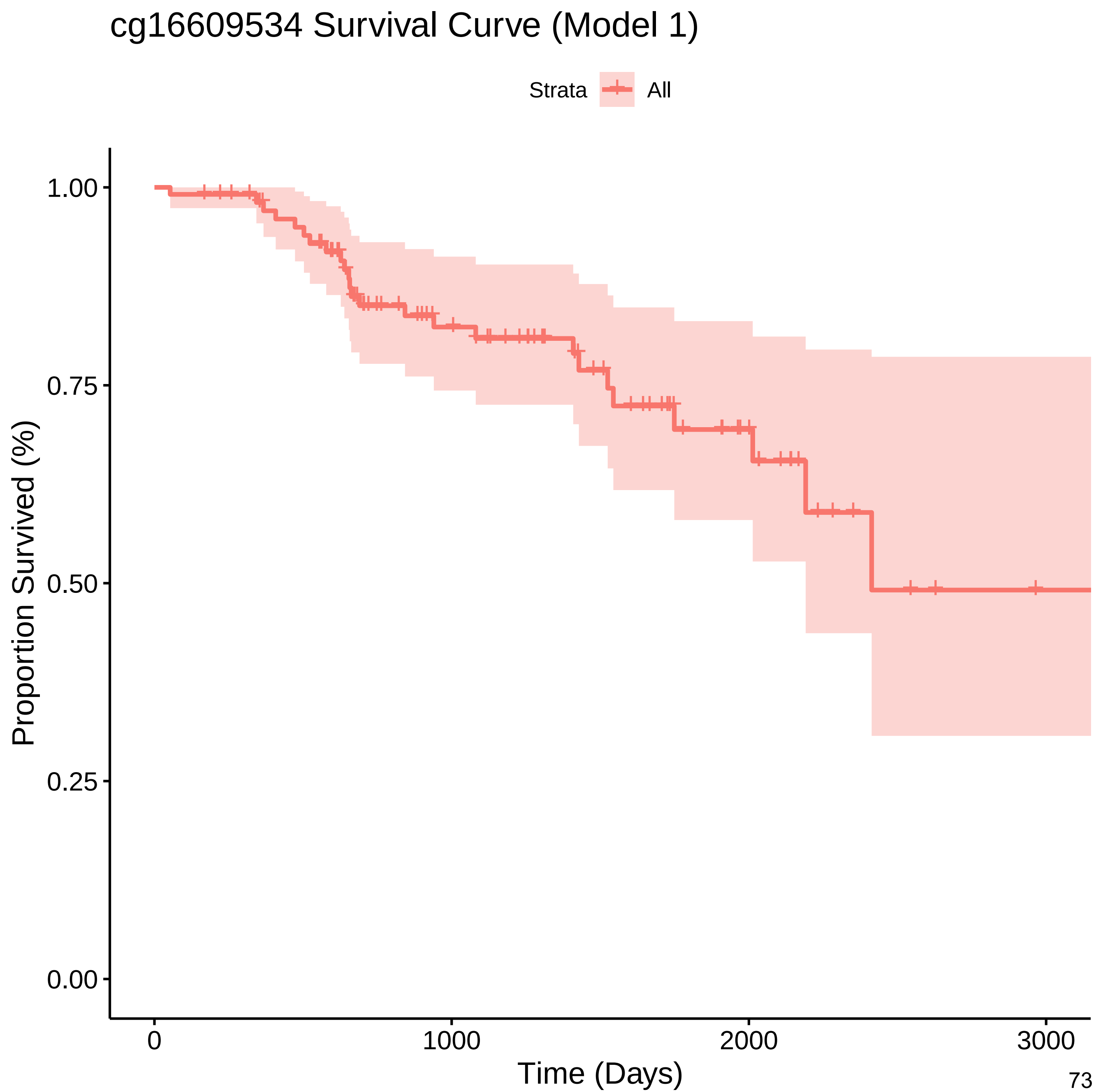


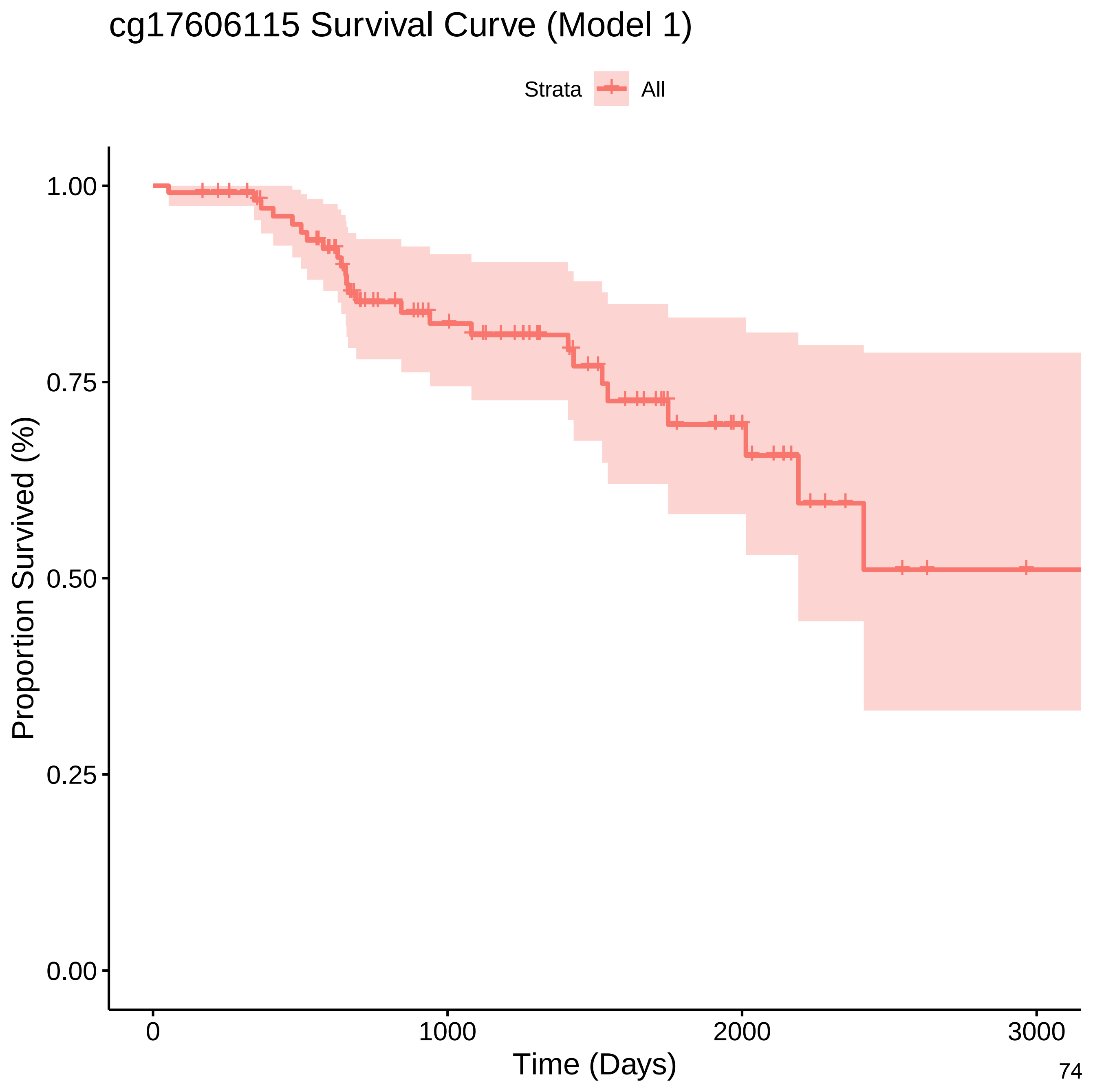

cg07141484 Survival Curve (Model 1)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)


cg07994487 Survival Curve (Model 1)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)


cg08214329 Survival Curve (Model 1)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)

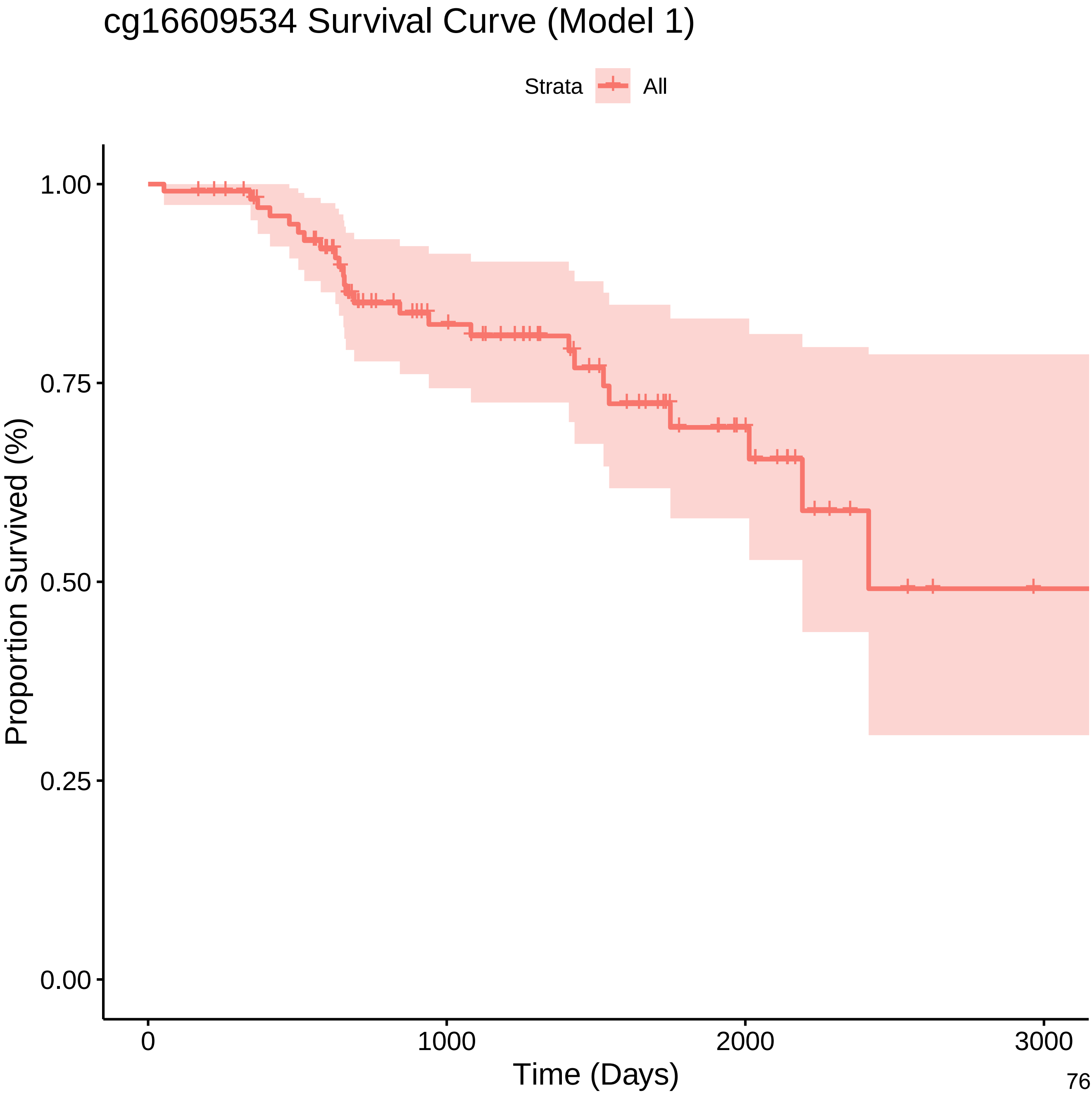

cg16088676 Survival Curve (Model 1)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)


cg16609534 Survival Curve (Model 1)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)


cg17606115 Survival Curve (Model 1)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)

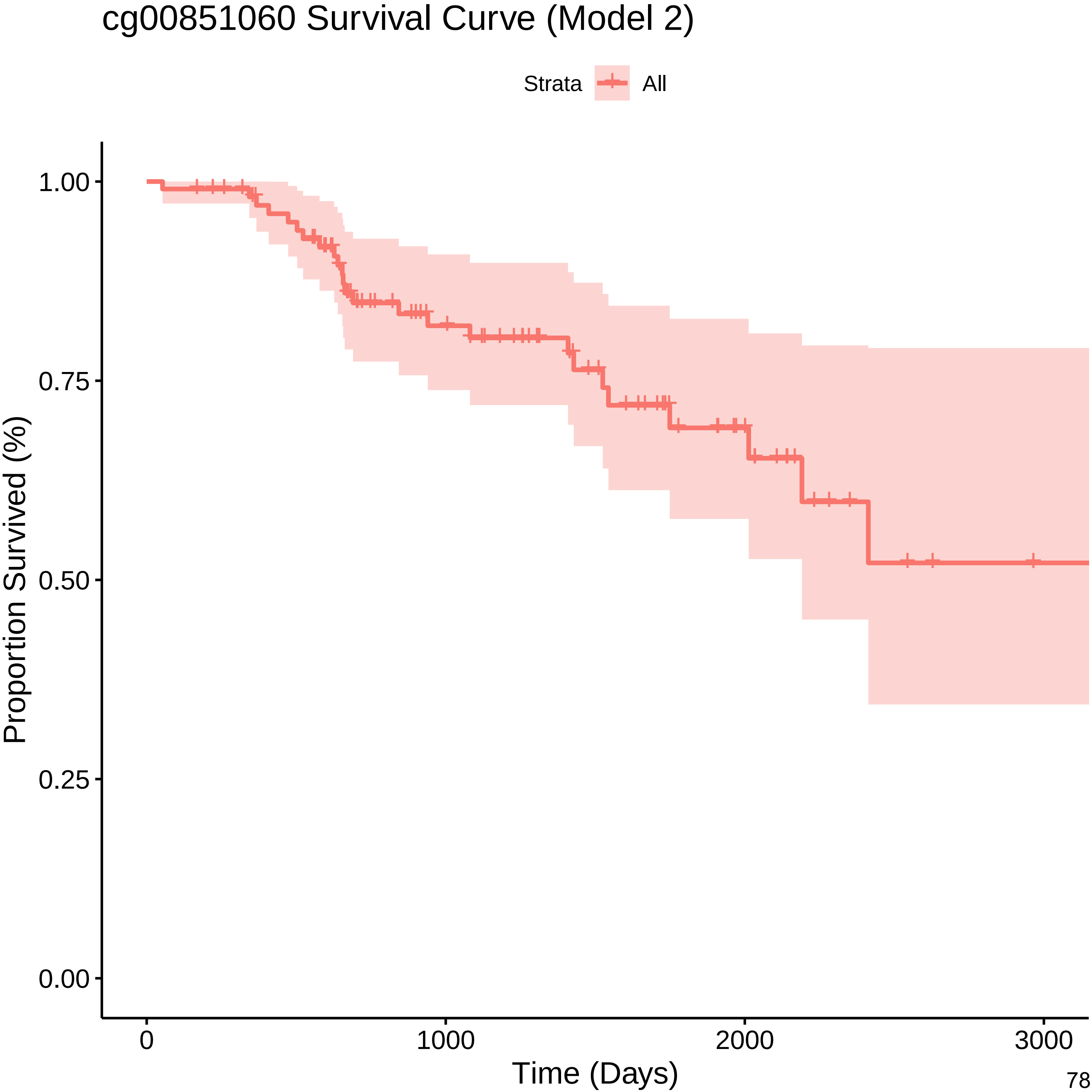
Hazard Analysis Scatterplots (Model 1, Post-Sensitivity)

Graphing the association between DNA methylation and all-cause mortality at CpG sites cg22544350 and at cg16609534 after removing outliers, adjusting for age


cg16609534 Survival Curve (Model 1)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)

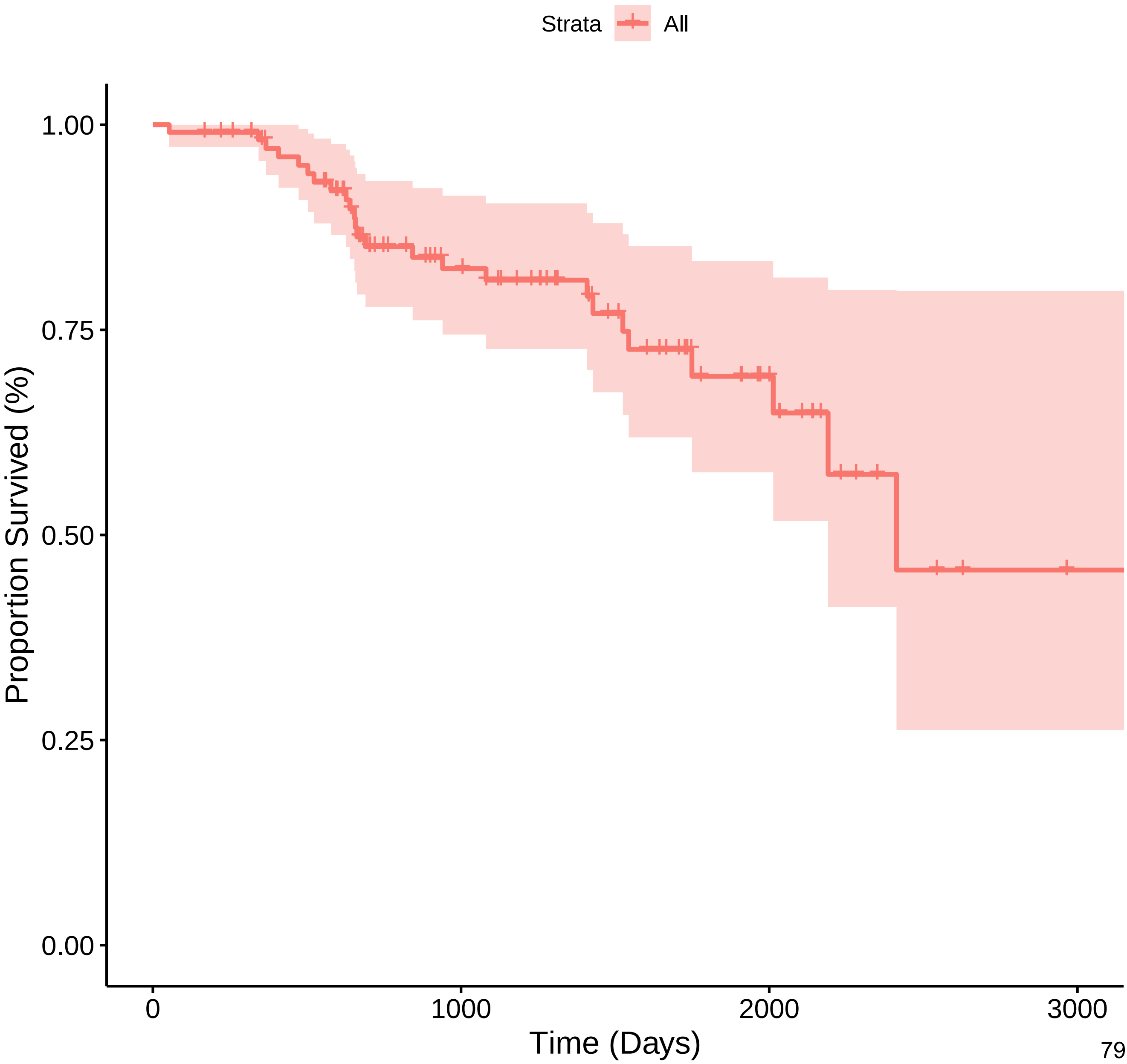
Hazard Analyses (Model 2)

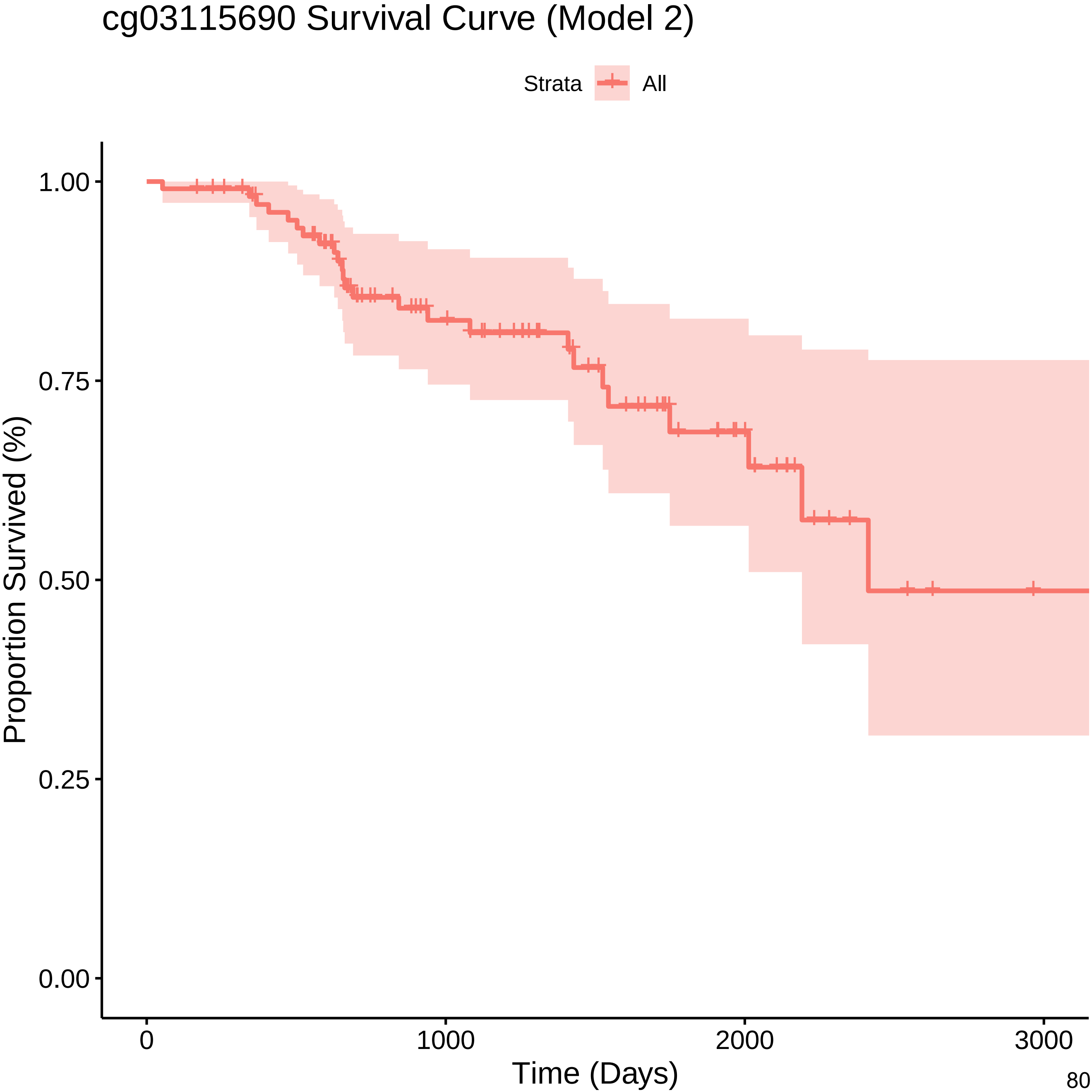
Graphing the association between DNA methylation at CpG sites and all cause mortality, adjusting for age and race



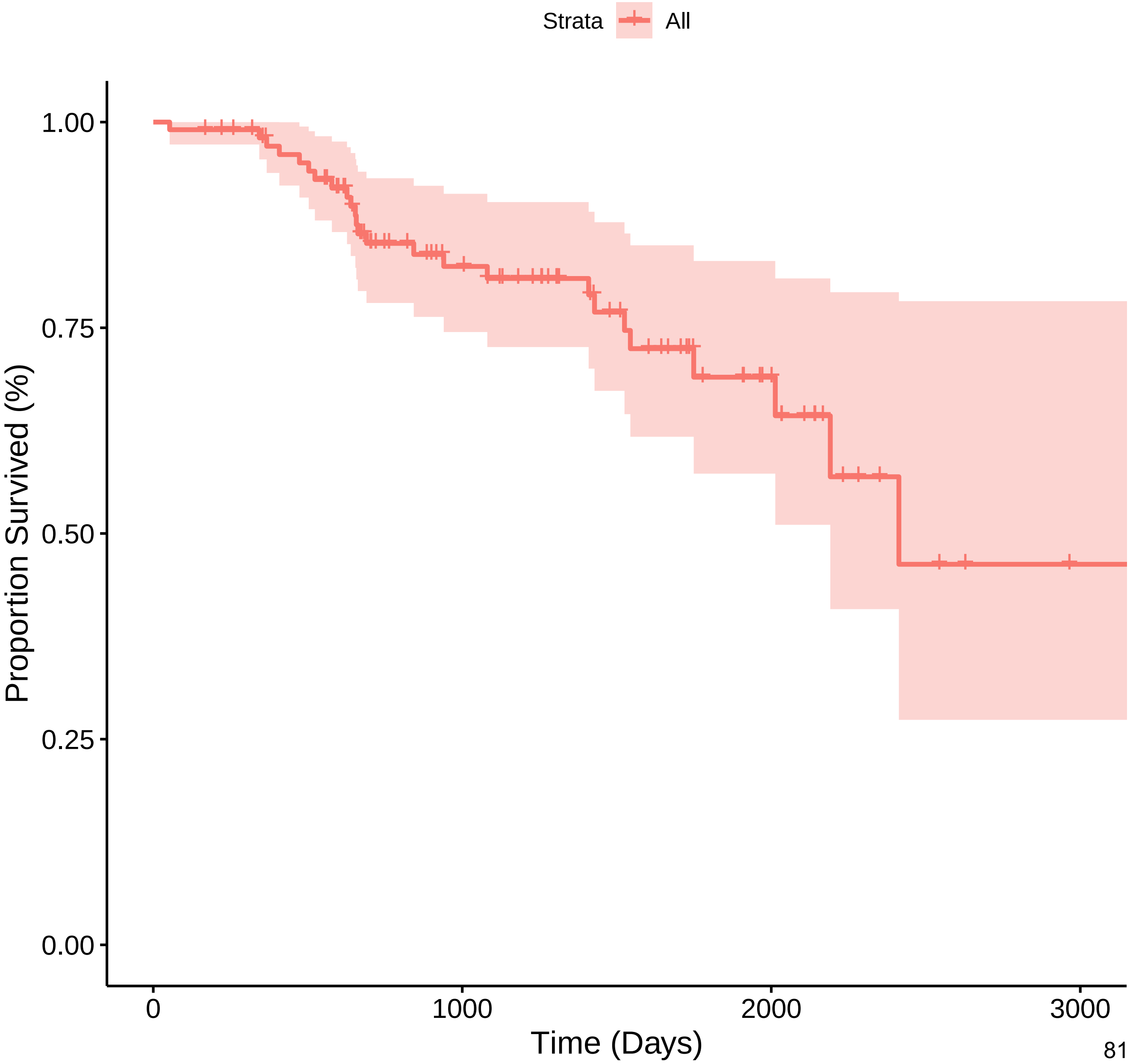
cg00851060 Survival Curve (Model 2)

cg00950813 Survival Curve (Model 2)

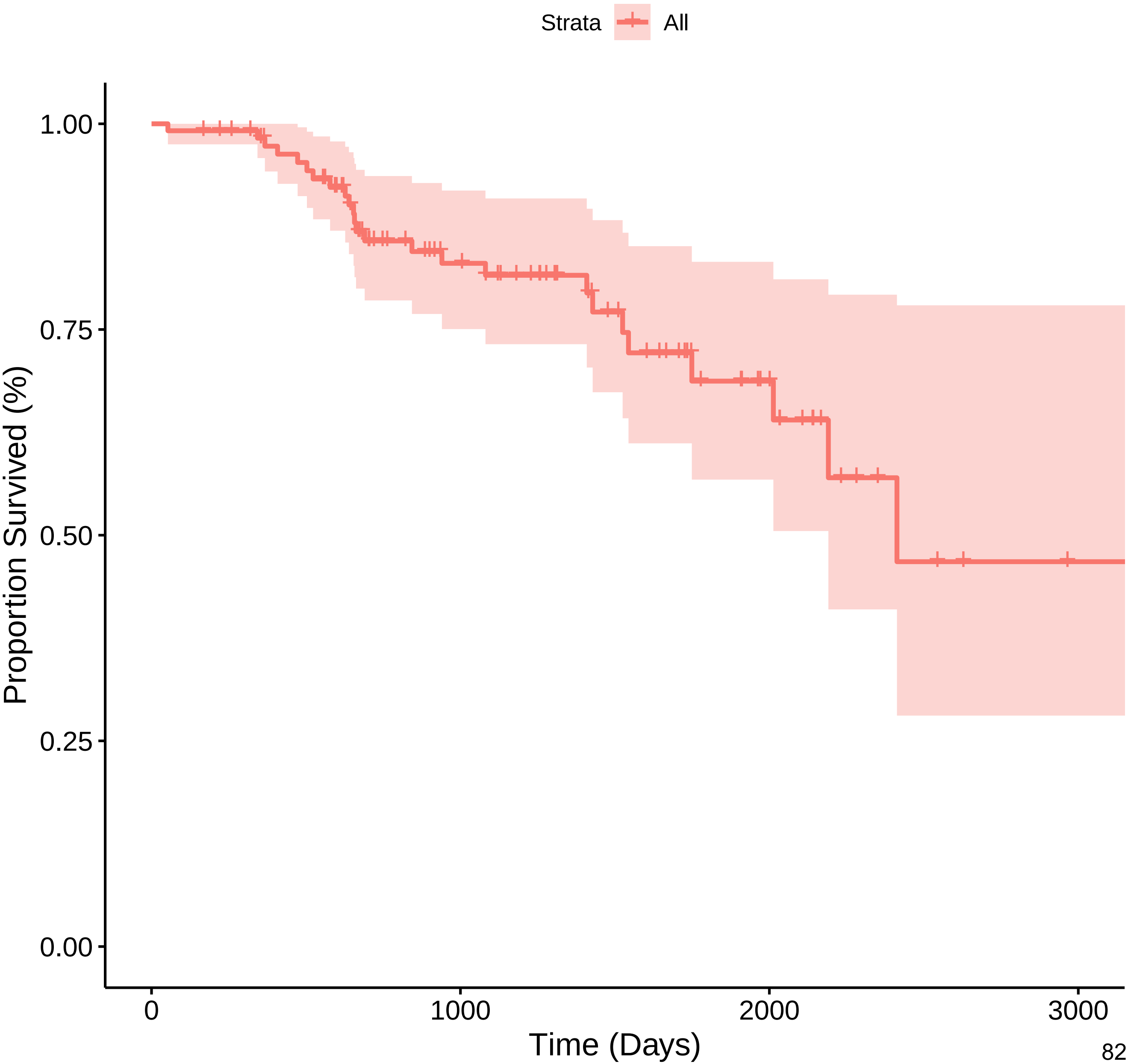



cg03115690 Survival Curve (Model 2)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)

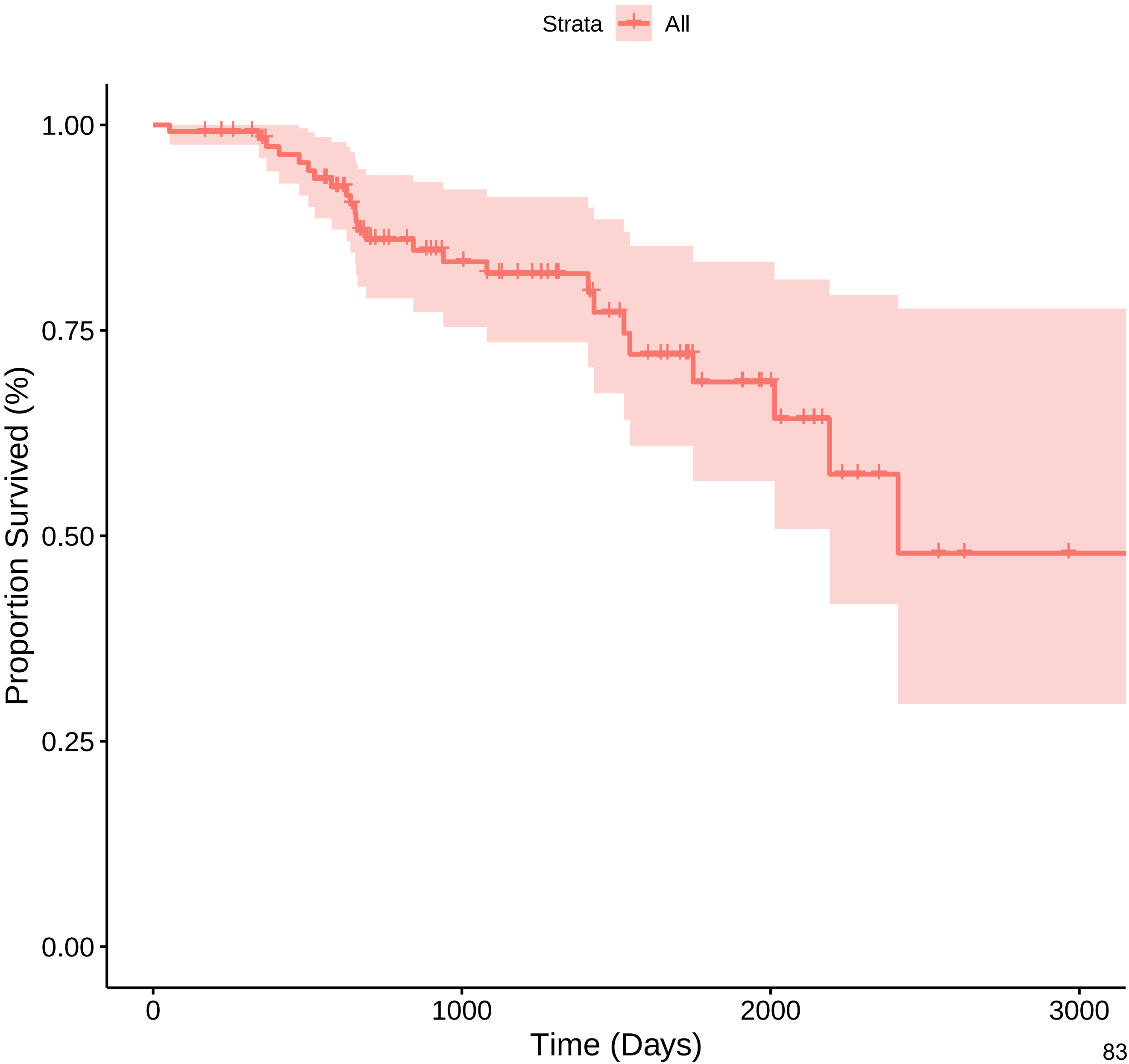
cg07141484 Survival Curve (Model 2)



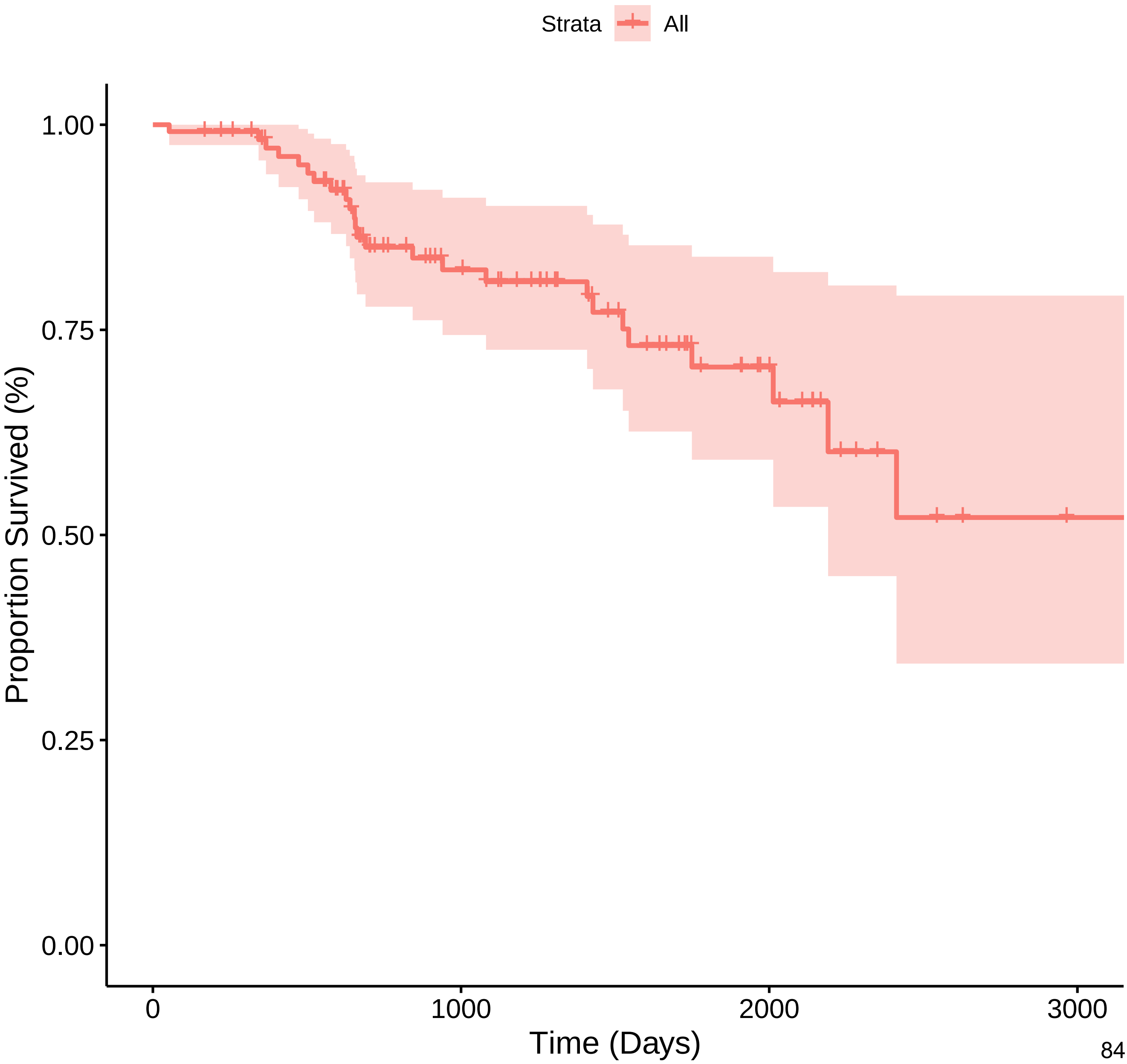
cg07994487 Survival Curve (Model 2)



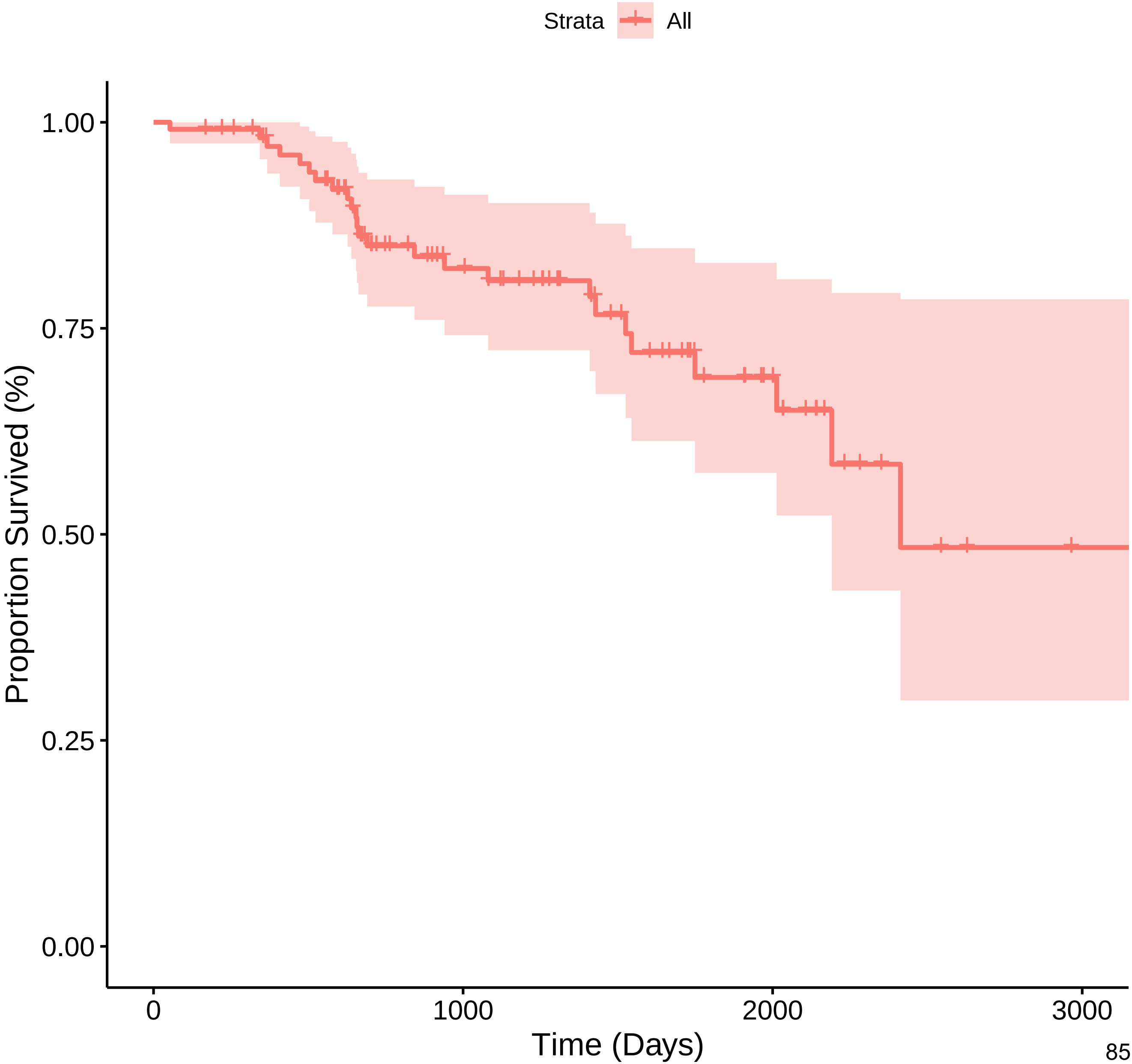
cg08214329 Survival Curve (Model 2)

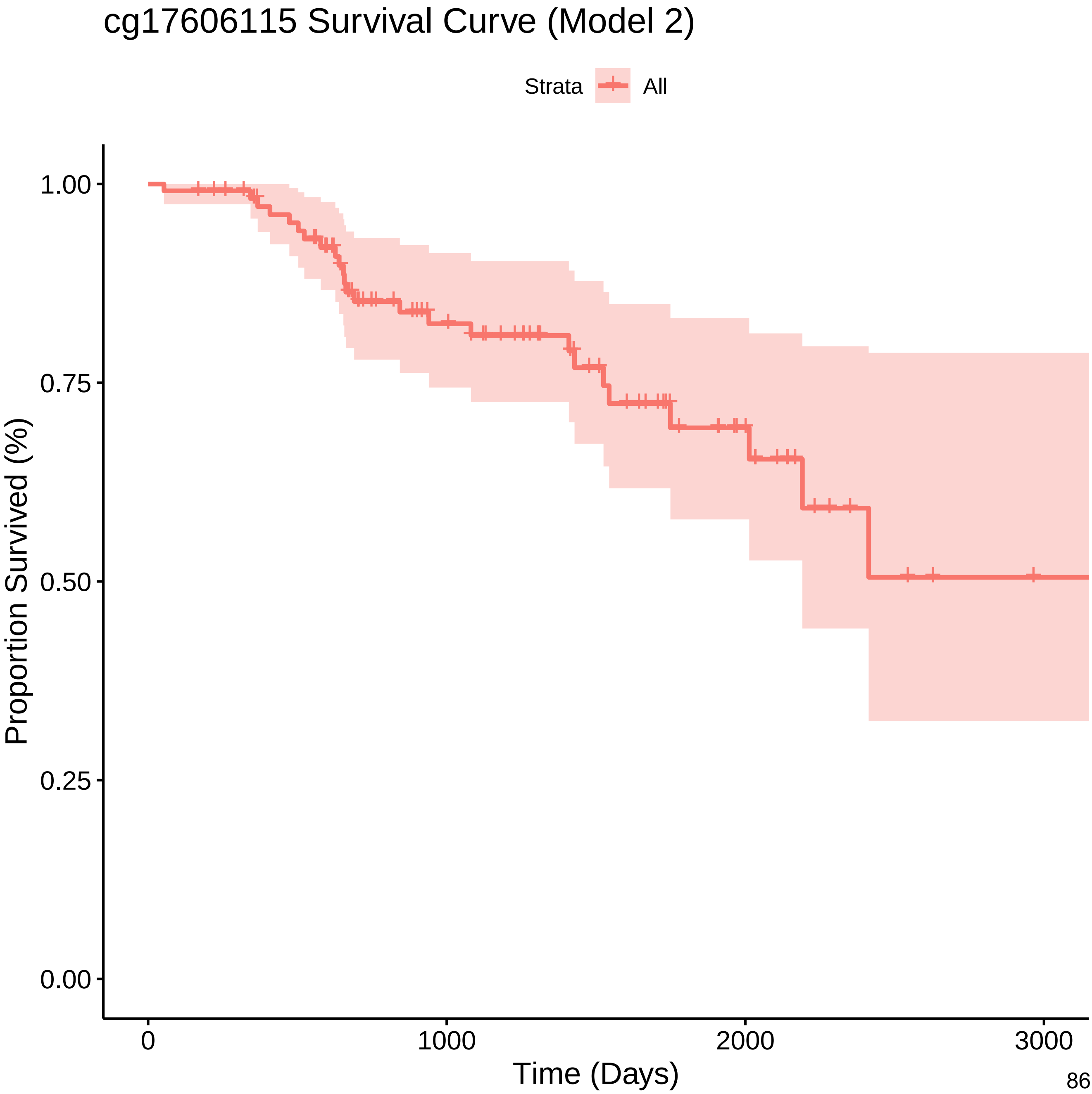


cg16088676 Survival Curve (Model 2)



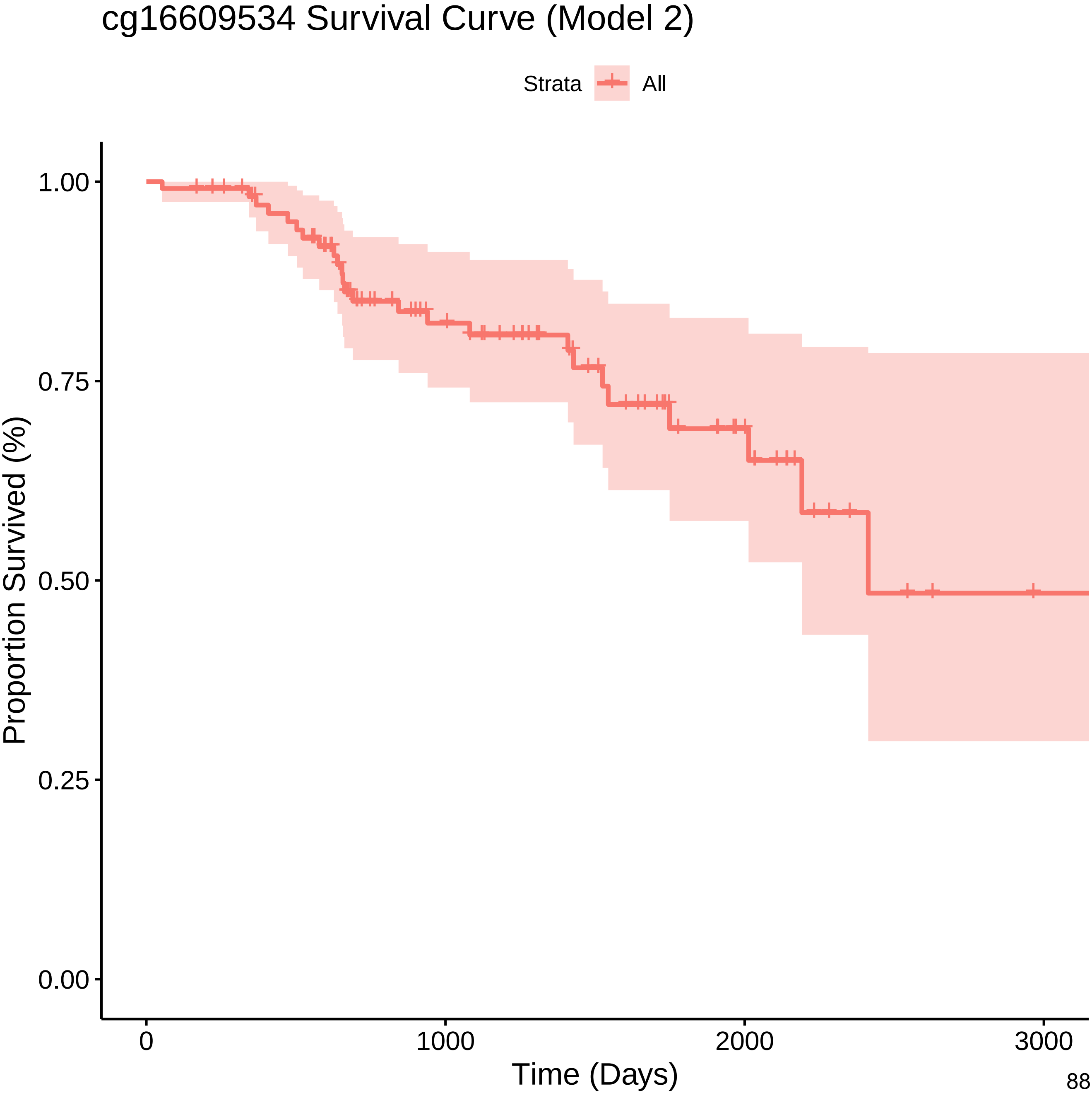
cg16609534 Survival Curve (Model 2)




cg17606115 Survival Curve (Model 2)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)

Hazard Analysis Scatterplots (Model 2, Post-Sensitivity)

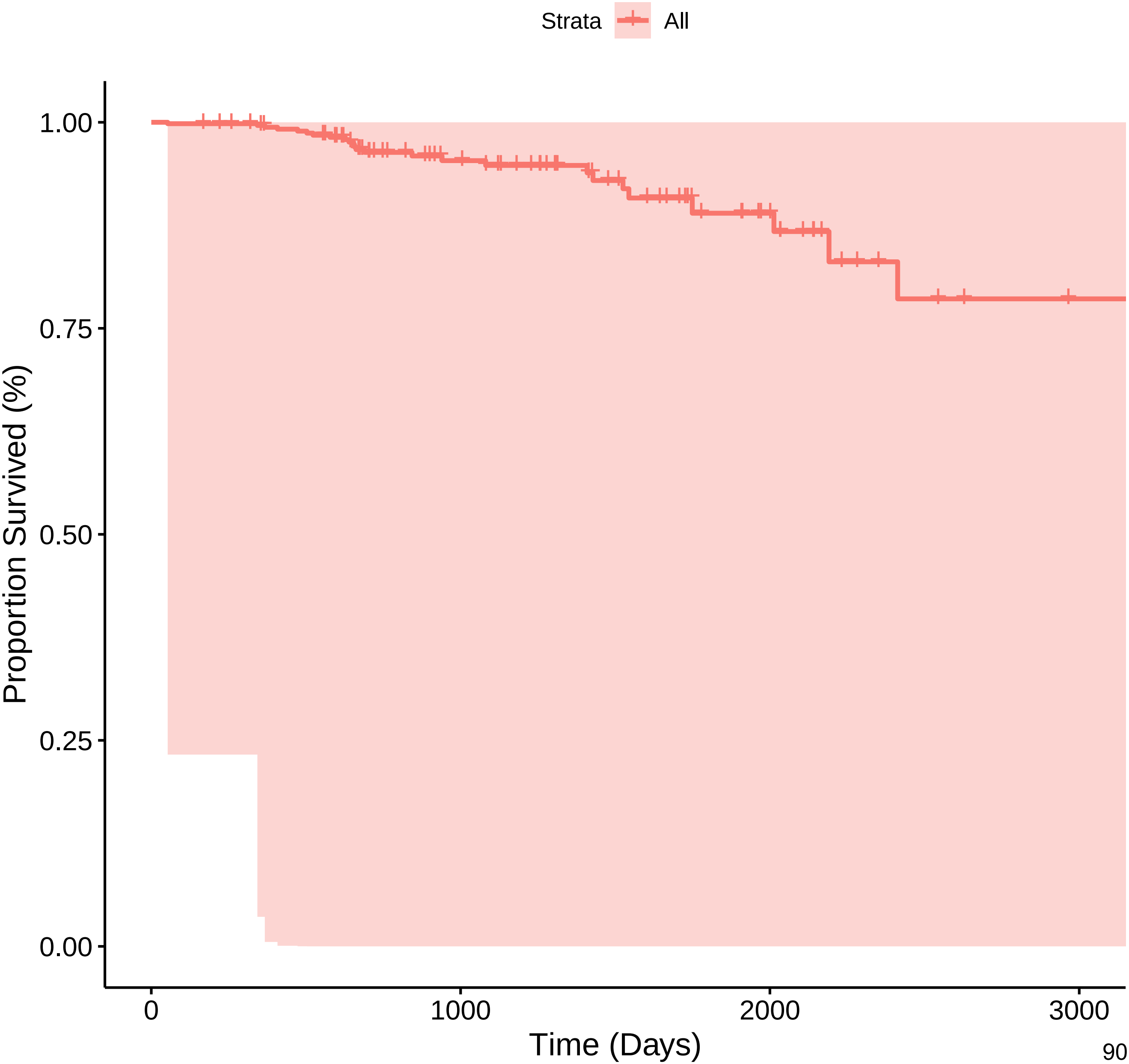
Graphing the association between DNA methylation and all-cause mortality at CpG sites cg22544350 and at cg16609534 after removing outliers, adjusting for age and race


cg16609534 Survival Curve (Model 2)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)

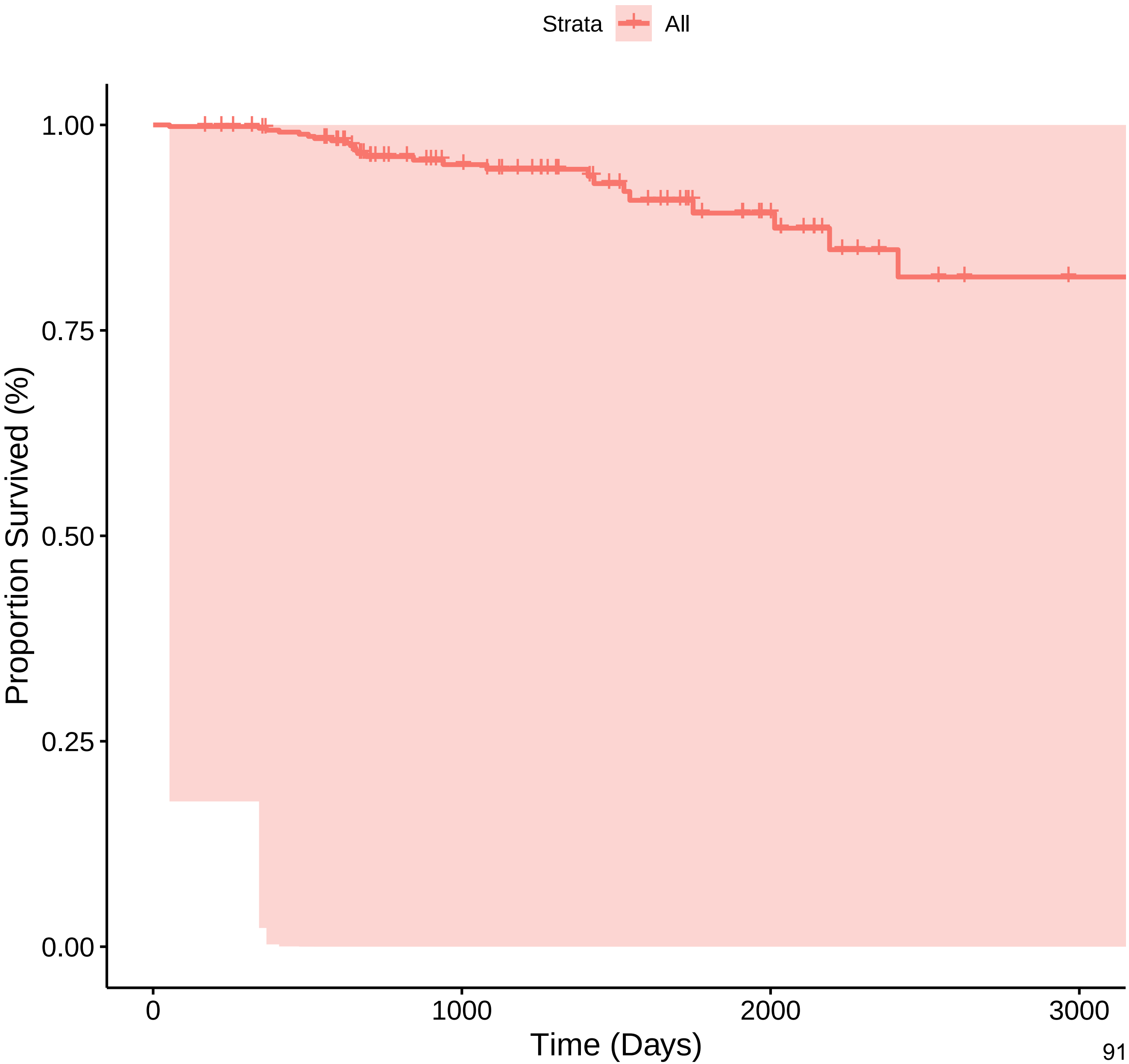
Hazard Analyses (Model 3)

Graphing the association between DNA methylation at CpG sites and all cause mortality, adjusting for age, race, stage, and subtype

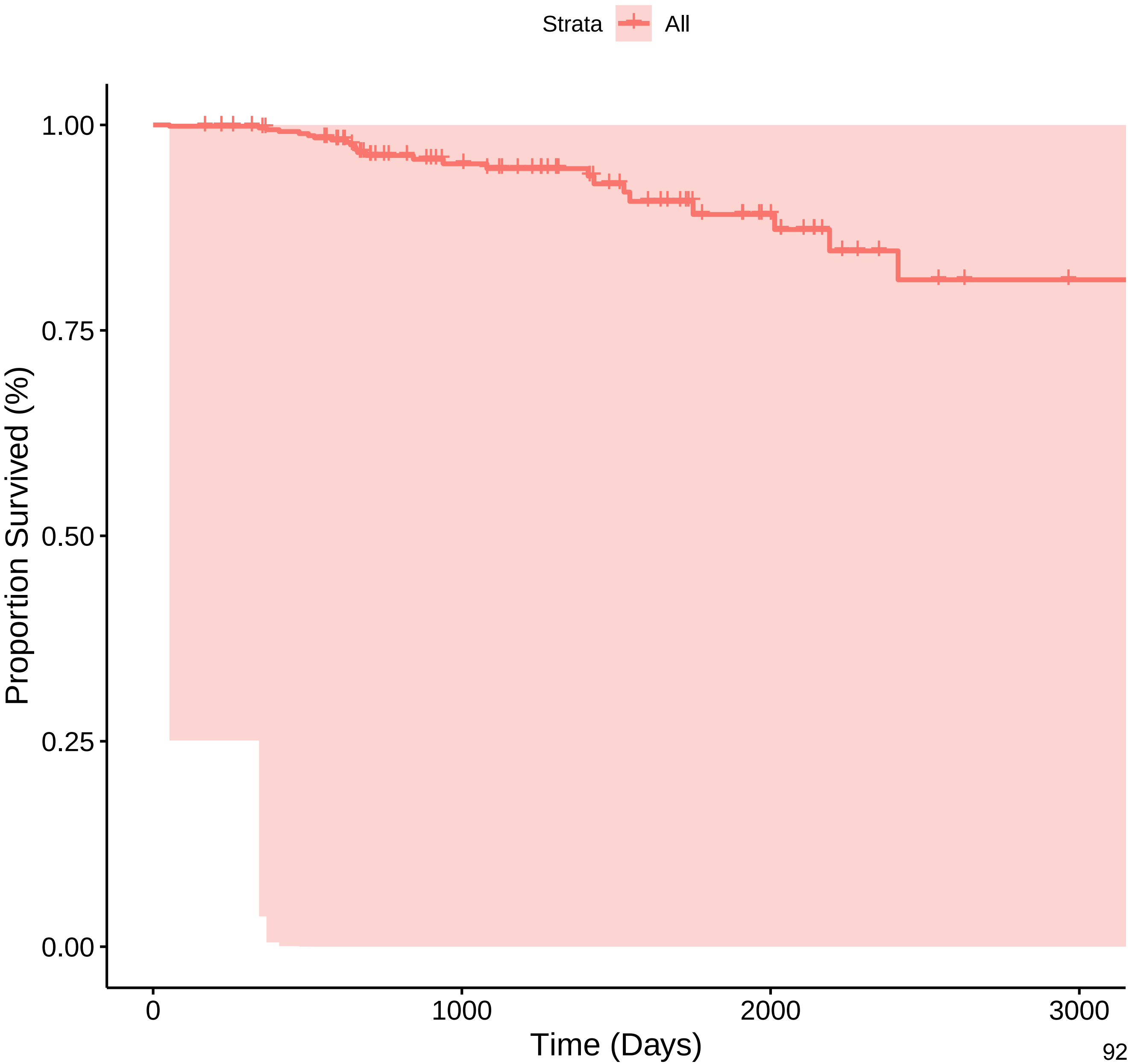
cg07141484 Survival Curve (Model 3)

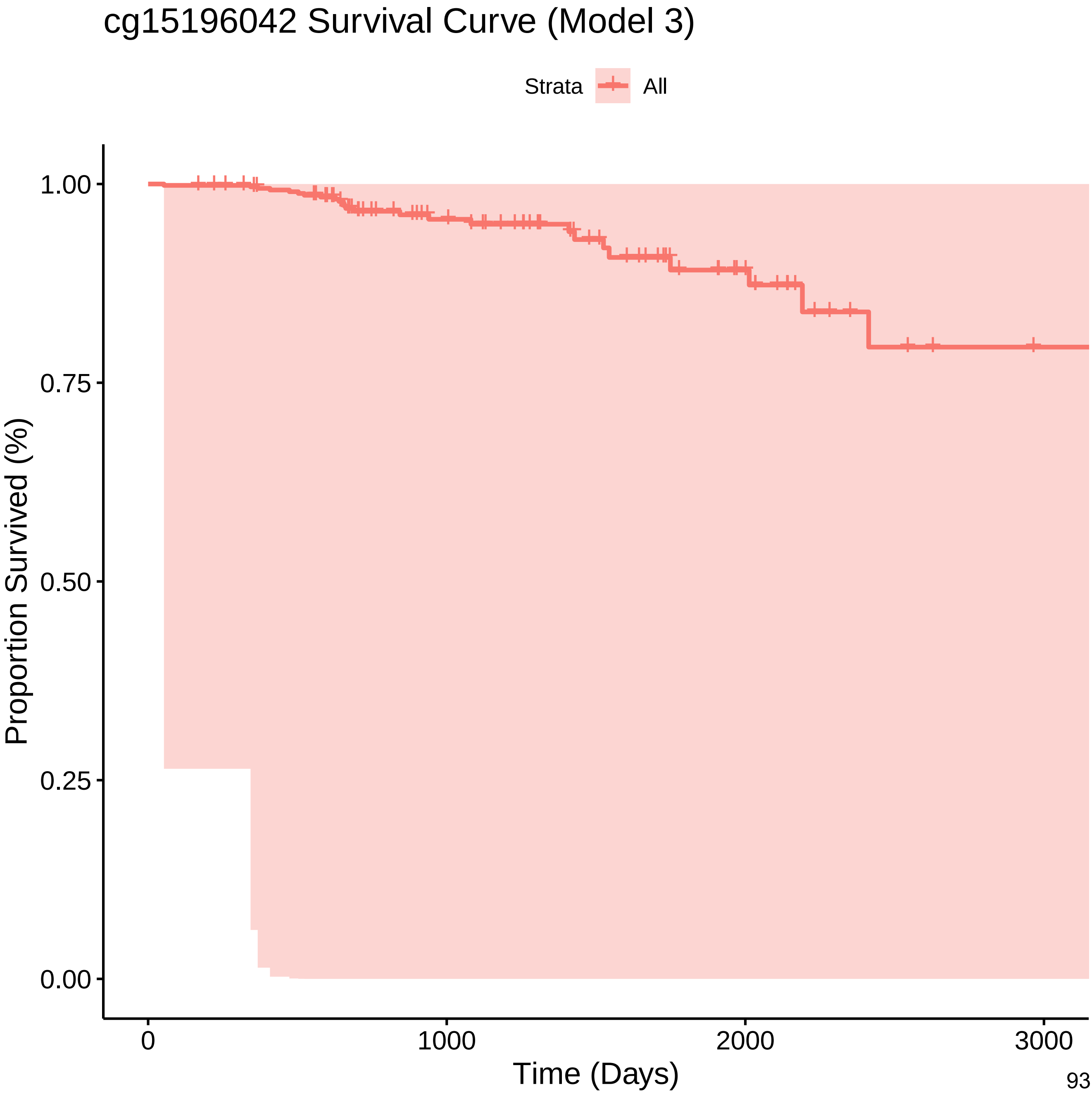


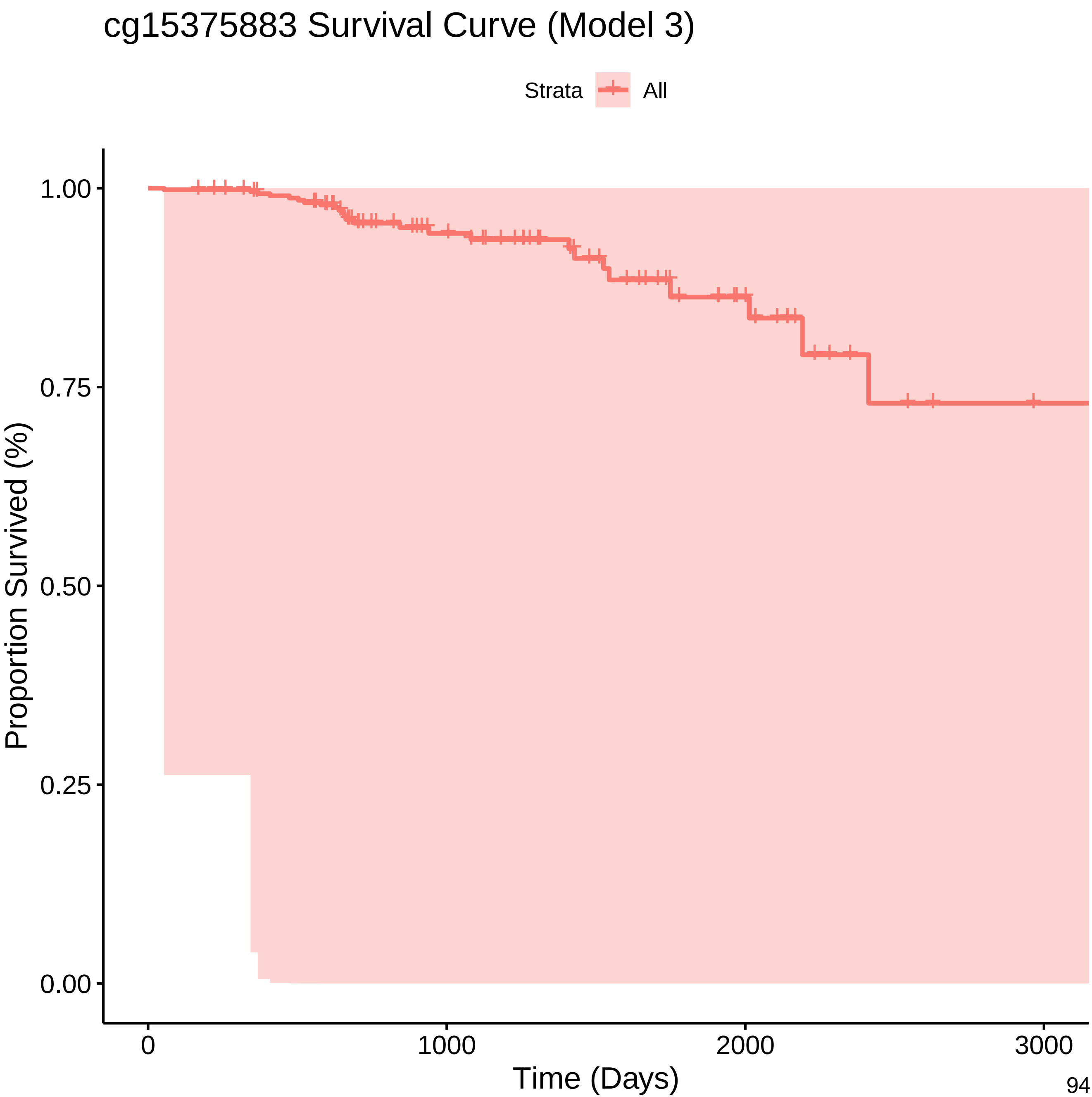
cg07994487 Survival Curve (Model 3)

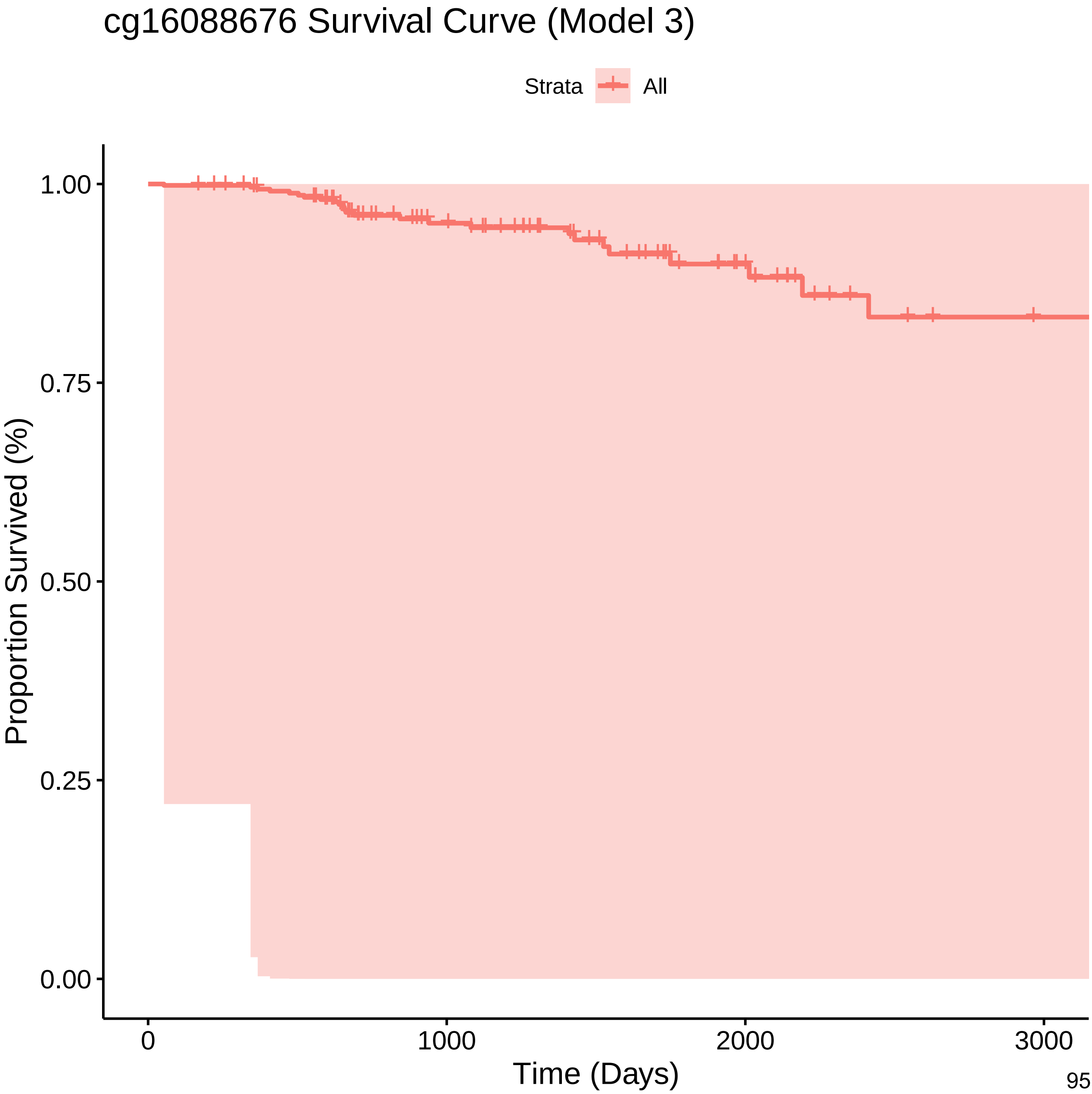


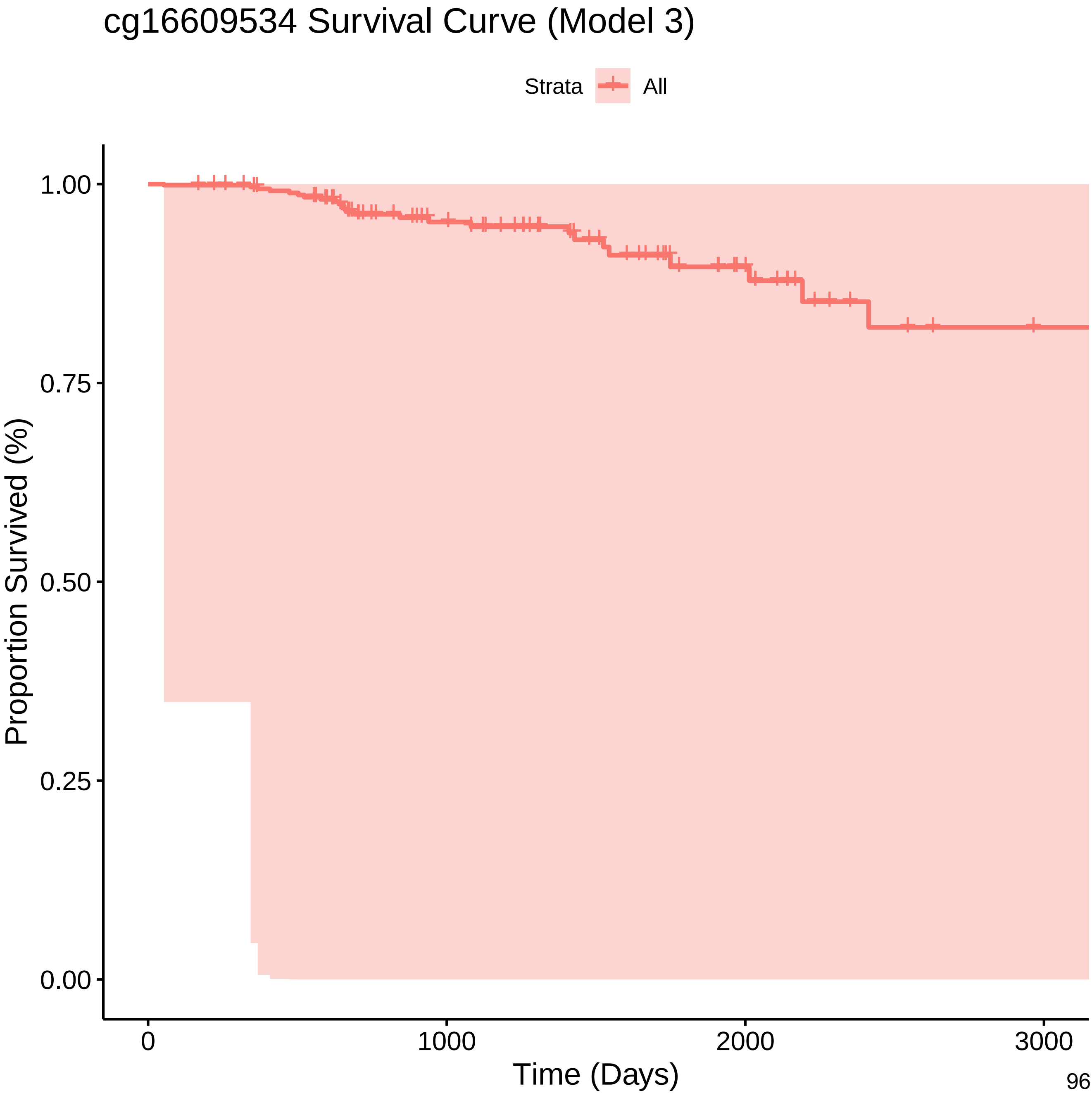
cg08214329 Survival Curve (Model 3)




cg15196042 Survival Curve (Model 3)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)

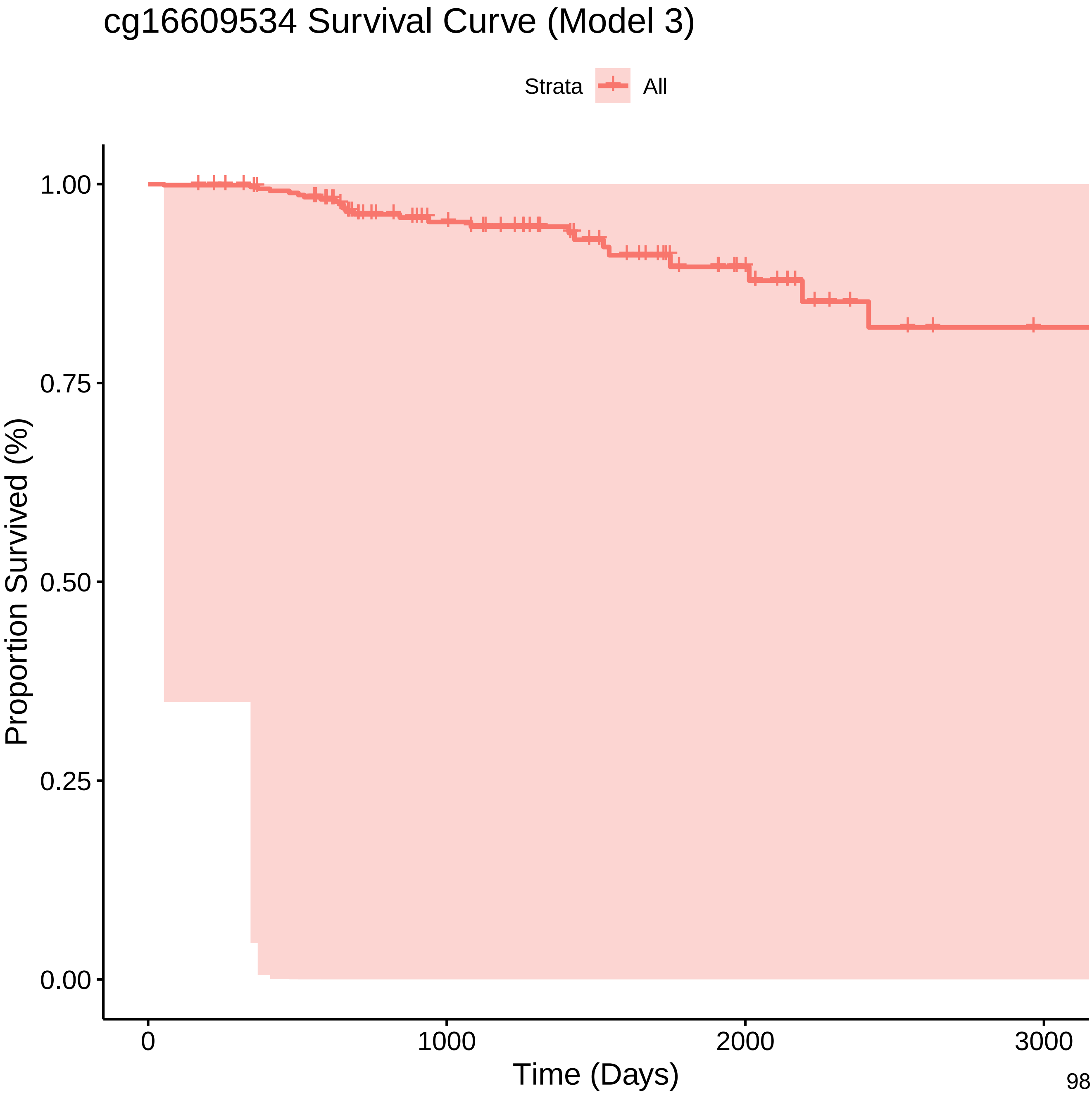

cg15375883 Survival Curve (Model 3)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)


cg16088676 Survival Curve (Model 3)
Strata
All
Proportion Survived (%)
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time (Days)


cg16609534 Survival Curve (Model 3)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)

Hazard Analysis Scatterplots (Model 3, Post-Sensitivity)

Graphing the association between DNA methylation and all-cause mortality at CpG sites cg22544350 and at cg16609534 after removing outliers, adjusting for age, race, stage, and subtype


cg16609534 Survival Curve (Model 3)
Strata
All
1.00
0.75
0.50
0.25
0.00
Proportion Survived (%)
0
1000
2000
3000
Time (Days)

Results Tables

EWAS Significant CpGs Results

Exposure	CPG.Labels	T.stat	P.value	FDR	Bon.	effect.size	std.error
College	cg04734977	-5.7742	1.703E-07	0.03764	0.129219	-0.00048637	8.423E-05
College	cg09254001	-5.7163	2.156E-07	0.03764	0.163652	-0.00036396	6.367E-05
College	cg15196042	-5.682	2.48E-07	0.03764	0.188206	-0.00041763	7.35E-05
College	cg20226051	-5.6931	2.371E-07	0.03764	0.179916	-0.00036878	6.478E-05
College	cg22544350	-5.8718	1.141E-07	0.03764	0.086573	-0.00492858	0.0008394
Job Density	cg00038239	-6.5672	7.61E-09	0.00058	0.005776	8.20725E-07	5.649E-06
Job Density	cg00042994	-6.1629	4.032E-08	0.00146	0.030597	-2.1168E-07	2.018E-07
Job Density	cg00052865	-4.8688	6.711E-06	0.03833	1	1.35714E-07	4.577E-06
Job Density	cg00341089	-6.1271	4.667E-08	0.00154	0.035417	-3.6726E-06	5.355E-06
Job Density	cg00443451	-5.1352	2.426E-06	0.0227	1	2.09823E-06	6.111E-06
Job Density	cg00548173	-5.4742	6.454E-07	0.00891	0.489823	-4.6449E-06	7.559E-06
Job Density	cg00657582	5.32412	1.164E-06	0.01403	0.88361	-8.1504E-06	7.118E-06
Job Density	cg00730549	-4.9939	4.172E-06	0.03057	1	1.74259E-07	2.729E-06
Job Density	cg00773475	-5.8253	1.589E-07	0.00365	0.120605	5.11666E-06	7.294E-06
Job Density	cg00851060	-4.8601	6.933E-06	0.03898	1	1.03376E-05	8.083E-06
Job Density	cg00950813	-5.2049	1.853E-06	0.01926	1	2.08755E-06	5.454E-06
Job Density	cg01154248	-5.3879	9.068E-07	0.01147	0.688171	-3.7187E-07	1.762E-06
Job Density	cg01359967	-6.8626	2.221E-09	0.00024	0.001686	-5.33E-06	5.178E-06
Job Density	cg01504472	-5.9305	1.039E-07	0.00282	0.078841	-2.2355E-06	2.224E-06
Job Density	cg01571625	5.50076	5.81E-07	0.00848	0.440945	-4.7078E-06	3.636E-06
Job Density	cg02352612	-6.516	9.41E-09	0.00065	0.007142	-4.228E-06	6.389E-06
Job Density	cg02449575	-5.3398	1.095E-06	0.0134	0.830934	4.61833E-07	9.738E-07
Job Density	cg02531277	-7.6659	7.527E-11	3.9E-05	5.71E-05	6.57957E-06	5.193E-06
Job Density	cg02631718	-4.9623	4.707E-06	0.03118	1	2.73938E-06	7.924E-06
Job Density	cg02847472	-5.5088	5.629E-07	0.00838	0.427213	1.34332E-07	4.524E-06
Job Density	cg02911248	-5.1368	2.411E-06	0.0227	1	-2.8592E-06	2.354E-06
Job Density	cg03115690	-5.0662	3.164E-06	0.02698	1	5.07162E-07	4.565E-06
Job Density	cg03195060	-4.9944	4.164E-06	0.03057	1	1.5115E-06	1.764E-06
Job Density	cg03637703	-6.1912	3.591E-08	0.00136	0.027253	4.05573E-07	3.438E-07
Job Density	cg03654391	-5.1157	2.615E-06	0.02372	1	1.08962E-07	9.714E-07
Job Density	cg03699958	4.92375	5.45E-06	0.03363	1	3.51843E-06	4.839E-06
Job Density	cg03936955	5.73507	2.284E-07	0.00456	0.173337	-1.1787E-06	1.567E-06
Job Density	cg04302567	4.87515	6.55E-06	0.03795	1	-3.607E-07	1.995E-06
Job Density	cg04432267	-4.8874	6.255E-06	0.0368	1	-2.8363E-08	2.588E-07
Job Density	cg04837991	-6.1364	4.493E-08	0.00154	0.034099	6.35641E-07	1.56E-06
Job Density	cg05069807	-5.0397	3.503E-06	0.02828	1	6.15289E-07	5.715E-06
Job Density	cg05181301	-4.9376	5.17E-06	0.03216	1	1.17961E-07	2.049E-07
Job Density	cg05268278	-6.9225	1.728E-09	0.00024	0.001312	1.27146E-07	8.312E-07
Job Density	cg05271910	-5.136	2.419E-06	0.0227	1	5.61956E-06	3.597E-06
Job Density	cg05342467	-6.3146	2.162E-08	0.00097	0.016411	-7.1727E-08	2.312E-07
Job Density	cg05409915	-4.8351	7.619E-06	0.04252	1	1.69824E-06	6.708E-06
Job Density	cg06014763	-5.0594	3.248E-06	0.02709	1	1.70771E-06	3.48E-06
Job Density	cg06334667	-5.0911	2.875E-06	0.02537	1	6.04221E-06	6.807E-06
Job Density	cg06520003	4.99948	4.085E-06	0.03057	1	-3.5054E-07	9.032E-07
Job Density	cg06823517	-5.0202	3.774E-06	0.02984	1	8.54764E-07	2.074E-06
Job Density	cg07141484	-4.8951	6.073E-06	0.03616	1	9.0158E-07	3.106E-06
Job Density	cg07379028	5.65013	3.209E-07	0.00594	0.243508	-1.2142E-06	5.98E-06
Job Density	cg07422416	4.82285	7.978E-06	0.04294	1	-3.2087E-06	4.291E-06
Job Density	cg07657131	5.7752	1.944E-07	0.0041	0.147537	3.98826E-06	4.609E-06
Job Density	cg07684879	-5.4938	6.162E-07	0.00882	0.46766	-3.4047E-06	7.923E-06
Job Density	cg07946827	-6.9409	1.6E-09	0.00024	0.001214	-1.1322E-05	8.103E-06
Job Density	cg07994487	-5.0474	3.4E-06	0.02775	1	5.23459E-06	3.587E-06
Job Density	cg08027369	5.55612	4.665E-07	0.00748	0.354073	-9.1E-06	6.008E-06
Job Density	cg08147226	-5.8691	1.332E-07	0.00326	0.101059	-3.263E-06	3.323E-06
Job Density	cg08214329	-5.0531	3.327E-06	0.02744	1	4.47238E-06	4.218E-06
Job Density	cg08429721	5.81282	1.671E-07	0.00373	0.126812	1.52213E-07	1.527E-07
Job Density	cg08550205	-4.9513	4.907E-06	0.03136	1	-1.6022E-05	7.219E-06
Job Density	cg08554114	-4.8279	7.828E-06	0.04274	1	9.80937E-07	1.015E-06
Job Density	cg08595995	-4.9719	4.537E-06	0.03109	1	8.56836E-07	2.349E-06
Job Density	cg09178970	-4.8786	6.466E-06	0.03775	1	-1.9411E-06	4.072E-06
Job Density	cg09384811	4.99524	4.151E-06	0.03057	1	1.34804E-08	8.839E-06
Job Density	cg09807821	-5.0769	3.037E-06	0.02649	1	1.5174E-06	2.191E-06
Job Density	cg09866303	-5.0674	3.15E-06	0.02698	1	7.24553E-07	1.868E-06
Job Density	cg09920043	-5.2748	1.411E-06	0.01599	1	-5.9291E-06	6.584E-06
Job Density	cg10319073	-6.462	1.177E-08	0.00074	0.008932	5.66864E-06	4.462E-06
Job Density	cg10695356	4.96903	4.588E-06	0.03109	1	1.79985E-06	2.179E-06
Job Density	cg11230447	-4.9702	4.568E-06	0.03109	1	-3.7485E-06	7.916E-06
Job Density	cg11275750	-6.1958	3.524E-08	0.00136	0.026744	-3.4985E-06	5.525E-06
Job Density	cg11295761	-6.3234	2.086E-08	0.00097	0.015829	-1.2334E-07	9.33E-07
Job Density	cg11601519	-5.8752	1.299E-07	0.00326	0.098609	5.22844E-06	2.95E-06
Job Density	cg11920325	5.57135	4.391E-07	0.00741	0.333276	1.24745E-06	3.98E-07
Job Density	cg12312131	5.2613	1.488E-06	0.01661	1	-2.6309E-06	6.573E-06
Job Density	cg12535551	-5.0615	3.222E-06	0.02709	1	-2.4093E-05	1.079E-05
Job Density	cg13249914	-5.5961	3.979E-07	0.00686	0.301997	-4.6216E-06	1.006E-05
Job Density	cg13256476	-6.3628	1.773E-08	0.00096	0.013455	-2.0564E-06	6.583E-06
Job Density	cg13625295	-5.01053	3.916E-06	0.03022	1	5.927E-07	2.85E-06
Job Density	cg13665866	5.01233	3.889E-06	0.03022	1	-8.69E-06	6.35E-06
Job Density	cg13774948	5.539	4.993E-07	0.00773	0.379	2.897E-06	1E-05
Job Density	cg13833988	-5.87596	1.295E-07	0.00326	0.0983	-1.237E-06	2.77E-06
Job Density	cg13927040	-4.9642	4.673E-06	0.03118	1	3.934E-07	1.3E-06
Job Density	cg14536353	-4.89402	6.099E-06	0.03616	1	-9.139E-06	5.53E-06
Job Density	cg14645721	-5.96801	8.922E-08	0.0026	0.0677	-8.216E-07	3.95E-06
Job Density	cg14838356	-5.4217	7.938E-07	0.01076	0.6025	-8.453E-07	6.2E-06
Job Density	cg14864022	-5.83228	1.545E-07	0.00365	0.1172	-1.214E-06	4.92E-06
Job Density	cg14878147	-5.47794	6.359E-07	0.00891	0.4826	7.59E-06	5.09E-06
Job Density	cg14980188	-5.98813	8.222E-08	0.0025	0.0624	1.265E-10	4.48E-06
Job Density	cg15259572	4.83513	7.779E-06	0.04274	1	-7.944E-06	4.91E-06
Job Density	cg15375883	5.56902	4.578E-07	0.00748	0.3475	-3.562E-07	6.58E-06
Job Density	cg15535372	-5.23764	1.631E-06	0.01769	1	-1.842E-06	5.65E-06
Job Density	cg15683687	-5.40869	8.355E-07	0.01107	0.6341	8.145E-07	5.07E-06
Job Density	cg15739985	-7.59276	1.026E-10	3.9E-05	8E-05	1.055E-08	1.61E-06
Job Density	cg16088676	-4.95511	4.837E-06	0.03136	1	-2.876E-06	4.43E-06
Job Density	cg16191174	5.15054	2.286E-06	0.02254	1	4.386E-06	6.64E-06
Job Density	cg16243359	-5.93504	1.02E-07	0.00282	0.0774	-6.145E-06	6.22E-06
Job Density	cg16415405	5.00883	3.942E-06	0.03022	1	-9.874E-06	8.4E-06
Job Density	cg16609534	-4.95084	4.916E-06	0.03136	1	-5.582E-07	3.72E-07
Job Density	cg16655424	-4.89632	6.046E-06	0.03616	1	3.875E-06	7.23E-06
Job Density	cg16800724	-5.75496	2.109E-07	0.00433	0.16	-2.793E-06	3.5E-06
Job Density	cg17153205	-5.53617	5.385E-07	0.00817	0.4087	-2.6E-06	1.42E-06
Job Density	cg17158083	5.37634	9.488E-07	0.0118	0.7201	-6.586E-06	4.85E-06
Job Density	cg17230578	-4.94142	5.096E-06	0.03196	1	-4.705E-06	3.65E-06
Job Density	cg17275345	-5.61415	3.704E-07	0.00654	0.2811	-2.216E-07	3.82E-07
Job Density	cg17606115	-5.21959	1.75E-06	0.01851	1	-5.707E-06	5.82E-06
Job Density	cg17964532	6.21774	3.22E-08	0.00136	0.0244	3.118E-07	9.85E-07
Job Density	cg17967224	4.8979	6.01E-06	0.03616	1	4.321E-07	4.35E-06
Job Density	cg18043283	-4.99895	4.189E-06	0.03057	1	6.765E-06	5.56E-06
Job Density	cg18169916	4.959	4.766E-06	0.03118	1	3.156E-06	8.25E-06
Job Density	cg18330856	5.56079	4.73E-07	0.00748	0.3589	1.045E-06	1.04E-06
Job Density	cg18420846	-5.39804	8.713E-07	0.01121	0.6612	3.998E-06	6.17E-06
Job Density	cg18575346	-5.19115	1.954E-06	0.02004	1	-4.93E-06	5.64E-06
Job Density	cg18658674	-4.82822	7.819E-06	0.04274	1	-4.688E-07	5.18E-07
Job Density	cg19478500	4.90131	5.933E-06	0.03616	1	-3.687E-06	5.86E-06
Job Density	cg19601293	-6.8614	2.233E-09	0.00024	0.0017	-2.54E-06	6E-06
Job Density	cg19834028	-5.28596	1.351E-06	0.01554	1	1.15E-07	3.47E-06
Job Density	cg20426096	-4.8665	6.768E-06	0.03833	1	1.144E-06	1.13E-06
Job Density	cg20576936	-4.98042	4.393E-06	0.03109	1	-1.712E-07	4.07E-07
Job Density	cg20827314	-5.1147	2.626E-06	0.02372	1	-1.189E-07	6.15E-07
Job Density	cg20920163	4.78886	9.064E-06	0.04844	1	-3.881E-07	3.53E-07
Job Density	cg21653365	-6.3282	2.045E-08	0.00097	0.0155	1.334E-06	1.45E-06
Job Density	cg21799270	5.6759	2.895E-07	0.00549	0.2197	-4.467E-06	5.53E-06
Job Density	cg21882990	-4.94228	5.079E-06	0.03196	1	2.345E-06	7.71E-06
Job Density	cg21889322	-5.09656	2.815E-06	0.02514	1	-1.298E-06	9.55E-07
Job Density	cg21900997	-5.29067	1.327E-06	0.01549	1	2.176E-08	1.06E-07
Job Density	cg22327802	-4.86803	6.729E-06	0.03833	1	-1.437E-06	5.19E-06
Job Density	cg22501690	-5.72627	2.366E-07	0.0046	0.1796	7.404E-07	3.5E-06
Job Density	cg22512068	-5.16174	2.19E-06	0.02211	1	-3.994E-06	4.95E-06
Job Density	cg22576658	5.14502	2.336E-06	0.0227	1	-3.218E-07	1.63E-06
Job Density	cg22680075	-5.30279	1.266E-06	0.01501	0.9605	-9.243E-06	6.27E-06
Job Density	cg22865728	6.56992	7.525E-09	0.00058	0.0057	-6.089E-06	6.79E-06
Job Density	cg23123972	-6.68432	4.676E-09	0.00044	0.0035	-2.657E-07	2.1E-06
Job Density	cg23682641	-5.21868	1.756E-06	0.01851	1	-2.327E-07	3.41E-07
Job Density	cg23787267	-4.9753	4.48E-06	0.03109	1	-1.596E-06	1.01E-06
Job Density	cg24100360	-5.62735	3.514E-07	0.00635	0.2667	-5.329E-06	4.22E-06
Job Density	cg24505395	5.15887	2.214E-06	0.02211	1	-1.443E-08	1.78E-06
Job Density	cg24624256	-5.02707	3.676E-06	0.02937	1	7.938E-07	7.79E-06
Job Density	cg25132484	-5.25003	1.555E-06	0.0171	1	-2.234E-06	6.83E-06
Job Density	cg25366155	-5.13242	2.452E-06	0.0227	1	-2.01E-07	3.18E-07
Job Density	cg25839853	-4.97889	4.419E-06	0.03109	1	1.073E-06	6.79E-07
Job Density	cg25994418	-4.98421	4.33E-06	0.03109	1	1.062E-06	6E-06
Job Density	cg26049092	-5.41307	8.46E-07	0.01107	0.6421	-4.68E-06	4.88E-06
Job Density	cg26259171	4.82426	7.936E-06	0.04294	1	-3.179E-07	4.66E-07
Job Density	cg26349395	-6.10334	5.143E-08	0.00163	0.039	9.761E-08	4.02E-07
Job Density	cg26487088	-7.02001	1.148E-09	0.00024	0.0009	2.149E-06	1.49E-06
Job Density	cg26873031	-4.97237	4.53E-06	0.03109	1	-2.697E-07	1.76E-07
Job Density	cg27007625	-6.42874	1.351E-08	0.00079	0.0102	-5.005E-06	4.3E-06
Job Density	cg27338512	-5.79333	1.807E-07	0.00392	0.1372	-4.044E-06	4.91E-06
Job Density	cg27438841	4.95995	4.749E-06	0.03118	1	-1.457E-05	1.09E-05

Sensitivity Analysis Cutpoints and Significance

Exposure	CPG.Labels	Outliers?	Cutoff	Still Significant?	P.Value
College	cg04734977	No		Yes	
College	cg09254001	No		Yes	
College	cg15196042	No		Yes	
College	cg20226051	No		Yes	
College	cg22544350	Yes	< 0.6	Yes	p = 0.000096
Job Density	cg00038239	Yes	> 0.7	No	
Job Density	cg00042994	Yes	> 0.6	No	
Job Density	cg00052865	Yes	> 0.7	No	
Job Density	cg00341089	Yes	> 0.6	No	
Job Density	cg00443451	Yes	> 0.65	No	
Job Density	cg00548173	Yes	> 0.4	No	
Job Density	cg00657582	Yes	< 0.4	No	
Job Density	cg00730549	No		Yes	
Job Density	cg00773475	Yes	> 0.7	No	
Job Density	cg00851060	No		Yes	
Job Density	cg00950813	No		Yes	
Job Density	cg01154248	Yes	> 0.6	No	
Job Density	cg01359967	Yes	> 0.5	No	
Job Density	cg01504472	Yes	> 0.65	No	
Job Density	cg01571625	Yes	< 0.3	No	
Job Density	cg02352612	Yes	> 0.5	No	
Job Density	cg02449575	No		Yes	
Job Density	cg02531277	Yes	> 0.5	No	p = 0.052
Job Density	cg02631718	Yes	> 0.75	No	
Job Density	cg02847472	Yes	> 0.6	No	
Job Density	cg02911248	Yes	> 0.4	No	
Job Density	cg03115690	No		Yes	
Job Density	cg03195060	Yes	> 0.5	No	
Job Density	cg03637703	Yes	> 0.7	No	
Job Density	cg03654391	Yes	> 0.4	No	
Job Density	cg03699958	Yes	< 0.4	No	
Job Density	cg03936955	Yes	< 0.3	No	
Job Density	cg04302567	Yes	< 0.25	No	
Job Density	cg04432267	Yes	> 0.6	No	
Job Density	cg04837991	Yes	> 0.6	No	
Job Density	cg05069807	Yes	> 0.75	No	
Job Density	cg05181301	Yes	> 0.5	No	
Job Density	cg05268278	Yes	> 0.5	No	
Job Density	cg05271910	Yes	> 0.5	No	
Job Density	cg05342467	Yes	> 0.5	No	p = 0.40
Job Density	cg05409915	Yes	> 0.5	No	
Job Density	cg06014763	Yes	> 0.6	No	
Job Density	cg06334667	Yes	> 0.6	No	
Job Density	cg06520003	No		Yes	
Job Density	cg06823517	Yes	> 0.6	No	
Job Density	cg07141484	No		Yes	
Job Density	cg07379028	Yes	< 0.4	No	
Job Density	cg07422416	No		Yes	
Job Density	cg07657131	Yes	< 0.2	No	
Job Density	cg07684879	Yes	> 0.6	No	
Job Density	cg07946827	Yes	> 0.3	No	
Job Density	cg07994487	No		Yes	
Job Density	cg08027369	Yes	< 0.2	No	
Job Density	cg08147226	Yes	> 0.70	No	
Job Density	cg08214329	No		Yes	
Job Density	cg08429721	Yes	< 0.4	No	
Job Density	cg08550205	Yes	> 0.60	No	
Job Density	cg08554114	Yes	> 0.70	No	
Job Density	cg08595995	Yes	> 0.60	No	
Job Density	cg09178970	No		Yes	
Job Density	cg09384811	Yes	< 0.4	No	
Job Density	cg09807821	Yes	> 0.60	No	
Job Density	cg09866303	No		Yes	
Job Density	cg09920043	Yes	> 0.75	No	
Job Density	cg10319073	Yes	> 0.60	No	
Job Density	cg10695356	Yes	< 0.35	No	
Job Density	cg11230447	Yes	> 0.4	No	
Job Density	cg11275750	Yes	> 0.60	No	
Job Density	cg11295761	Yes	> 0.60	No	
Job Density	cg11601519	Yes	> 0.70	No	
Job Density	cg11920325	Yes	< 0.20	No	p = 0.13
Job Density	cg12312131	Yes	< 0.5	No	
Job Density	cg12535551	Yes	> 0.6	No	
Job Density	cg13249914	Yes	> 0.55	No	
Job Density	cg13256476	Yes	> 0.5	No	
Job Density	cg13625295	Yes	> 0.5	No	
Job Density	cg13665866	Yes	< 0.2	No	
Job Density	cg13774948	Yes	< 0.14	No	
Job Density	cg13833988	Yes	> 0.6	No	
Job Density	cg13927040	Yes	> 0.5	No	
Job Density	cg14536353	Yes	> 0.75	No	
Job Density	cg14645721	Yes	> 0.5	No	
Job Density	cg14838356	No		Yes	
Job Density	cg14864022	Yes	> 0.5	No	
Job Density	cg14878147	Yes	> 0.5	No	
Job Density	cg14980188	Yes	> 0.4	No	p = 0.29
Job Density	cg15259572	Yes	< 0.6	No	
Job Density	cg15375883	No		Yes	
Job Density	cg15535372	Yes	> 0.6	No	
Job Density	cg15683687	Yes	> 0.6	No	
Job Density	cg15739985	Yes	> 0.5	No	
Job Density	cg16088676	No		Yes	
Job Density	cg16191174	Yes	< 0.8	No	
Job Density	cg16243359	Yes	> 0.7	No	
Job Density	cg16415405	Yes	< 0.5	No	p = 0.73
Job Density	cg16609534	Yes	> 0.6	Yes	p = 0.0029
Job Density	cg16655424	Yes	> 0.7	No	
Job Density	cg16800724	Yes	> 0.6	No	
Job Density	cg17153205	Yes	> 0.7	No	
Job Density	cg17158083	Yes	< 0.18	No	p = 0.33
Job Density	cg17230578	Yes	> 0.65	No	
Job Density	cg17275345	Yes	> 0.6	No	
Job Density	cg17606115	No		Yes	
Job Density	cg17964532	Yes	< 0.4	No	
Job Density	cg17967224	Yes	< 0.3	No	
Job Density	cg18043283	Yes	> 0.6	No	
Job Density	cg18169916	Yes	< 0.2	No	
Job Density	cg18330856	Yes	< 0.3	No	
Job Density	cg18420846	Yes	> 0.6	No	
Job Density	cg18575346	Yes	> 0.6	No	
Job Density	cg18658674	No		Yes	
Job Density	cg19478500	Yes	< 0.5	No	
Job Density	cg19601293	Yes	> 0.65	No	p = 0.12
Job Density	cg19834028	Yes	> 0.6	No	
Job Density	cg20426096	Yes	> 0.5	No	
Job Density	cg20576936	No		Yes	
Job Density	cg20827314	Yes	> 0.5	No	
Job Density	cg20920163	Yes	< 0.4	No	
Job Density	cg21653365	Yes	> 0.65	No	
Job Density	cg21799270	Yes	< 0.5	No	
Job Density	cg21882990	Yes	> 0.4	No	
Job Density	cg21889322	Yes	> 0.6	No	
Job Density	cg21900997	No		Yes	
Job Density	cg22327802	Yes	> 0.55	No	
Job Density	cg22501690	Yes	> 0.6	No	
Job Density	cg22512068	Yes	> 0.7	No	
Job Density	cg22576658	Yes	< 0.15	No	
Job Density	cg22680075	Yes	> 0.65	No	
Job Density	cg22865728	Yes	< 0.7	No	p = 0.45
Job Density	cg23123972	Yes	> 0.4	No	
Job Density	cg23682641	Yes	> 0.65	No	
Job Density	cg23787267	Yes	> 0.5	No	
Job Density	cg24100360	Yes	> 0.5	No	
Job Density	cg24505395	Yes	< 0.3	No	
Job Density	cg24624256	Yes	> 0.6	No	
Job Density	cg25132484	Yes	> 0.6	No	
Job Density	cg25366155	Yes	> 0.65	No	p = 0.62
Job Density	cg25839853	Yes	> 0.6	No	
Job Density	cg25994418	No		Yes	
Job Density	cg26049092	Yes	> 0.5	No	
Job Density	cg26259171	Yes	< 0.5	No	
Job Density	cg26349395	Yes	> 0.75	No	
Job Density	cg26487088	Yes	> 0.55	No	
Job Density	cg26873031	Yes	> 0.5	No	
Job Density	cg27007625	Yes	> 0.6	No	
Job Density	cg27338512	Yes	> 0.5	No	
Job Density	cg27438841	Yes	< 0.25	No	

Post-Sensitivity Analysis Remaining CpGs

Exposure	CPG.Labels	Outliers?	Cutoff	Still Significant?	P.value
College	cg04734977	No		Yes	
College	cg09254001	No		Yes	
College	cg15196042	No		Yes	
College	cg20226051	No		Yes	
College	cg22544350	Yes	< 0.6	Yes	p = 0.000096
Job Density	cg00730549	No		Yes	
Job Density	cg00851060	No		Yes	
Job Density	cg00950813	No		Yes	
Job Density	cg02449575	No		Yes	
Job Density	cg03115690	No		Yes	
Job Density	cg06520003	No		Yes	
Job Density	cg07141484	No		Yes	
Job Density	cg07422416	No		Yes	
Job Density	cg07994487	No		Yes	
Job Density	cg08214329	No		Yes	
Job Density	cg09178970	No		Yes	
Job Density	cg09866303	No		Yes	
Job Density	cg14838356	No		Yes	
Job Density	cg15375883	No		Yes	
Job Density	cg16088676	No		Yes	
Job Density	cg16609534	Yes	> 0.6	Yes	p = 0.0029
Job Density	cg17606115	No		Yes	
Job Density	cg18658674	No		Yes	
Job Density	cg20576936	No		Yes	
Job Density	cg21900997	No		Yes	
Job Density	cg25994418	No		Yes	

Reference Gene Information

Exposure	CPG.Labels	T.statistic	FDR	Reference Gene 1	Reference Gene 2	Methylation	Reference Gene 1 Additional Study Findings	Reference Gene 2 Additional Study Findings
College	cg04734977	-5.774159989	0.03764121	ZNF680		Decreased	Nothing Found	
College	cg09254001	-5.716322402	0.03764121	IKBIP	APAF1	Decreased	IKIP, located next to APAF1 gene locus, regulated by p53. Proapoptotic function	Methylation plays an important role in the regulation of APAF1 in breast cancer
College	cg15196042	-5.682002916	0.03764121	LOC100129716	ARRDC3	Decreased		ARRDC3 suppresses breast cancer progression by negatively regulating integrin beta4
College	cg20226051	-5.69306936	0.03764121	MTF1		Decreased	Inhibition of MTF1 induces the expression of tumor suppressor factor KLF4	
College	cg22544350	-5.87179349	0.03764121	KDM5A	CCDC77	Decreased	KDM5A, a histone demethylase, can increase proliferation, metastasis, and drug resistance of breast cancer	May play a role in the protein-protein interaction pathway of the TNF-induced NF-kB signal transduction pathway
Job Density	cg00730549	-4.993920705	0.03057076	TNRC18		Decreased	May interact with Ras oncogene	
Job Density	cg00851060	-4.860108118	0.03897728			Decreased		
Job Density	cg00950813	-5.204878183	0.01926161	ZNF282		Decreased	SUMOylation of ZNF282 positively regulates co-activator activity and enhances estrogen stimulated breast cancer growth	
Job Density	cg02449575	-5.339826138	0.01340216	SPTLC2		Decreased		
Job Density	cg03115690	-5.066195063	0.02698114			Decreased		
Job Density	cg06520003	4.999475594	0.03057076	ACSF2		Increased		
Job Density	cg07141484	-4.895146632	0.03616419	TLDC2		Decreased	Nothing Found	
Job Density	cg07422416	4.822847067	0.04294266	MFHAS1		Increased		
Job Density	cg07994487	-5.047444855	0.02774616	IFT140	TMEM204	Decreased		
Job Density	cg08214329	-5.053127803	0.02744327	IFT140	TMEM204	Decreased	Interflagellar Transport	Regulates VEGF receptor signalling pathway
Job Density	cg09178970	-4.878572358	0.03775013	VPS37B		Decreased		
Job Density	cg09866303	-5.067394175	0.02698114	RREB1		Decreased		
Job Density	cg14838356	-5.421696094	0.01075848	AGO2		Decreased		
Job Density	cg15375883	5.569023018	0.007478	ST3GAL4		Increased	High expression associated with gastric cancer	Low expression associated with cervical cancer
Job Density	cg16088676	-4.955112716	0.03135577			Decreased		
Job Density	cg16609534	-4.950844056	0.03135577	AFAP1		Decreased	No significant associations found between expression of APAF1 in tumor and normal tissue. Downregulated in Ki-67 negative tumor samples	
Job Density	cg17606115	-5.219590486	0.01851064	GNAI2		Decreased	GNAI2 a critical regulator of oncogenesis in ovarian cancer	May play an oncosuppressive role in breast cancer
Job Density	cg18658674	-4.828215317	0.04273983			Decreased		
Job Density	cg20576936	-4.980419233	0.0310881	ZNF627		Decreased		
Job Density	cg21900997	-5.290668184	0.0154925	SCMH1		Decreased		
Job Density	cg25994418	-4.984207664	0.0310881	PLCG1		Decreased		

Interaction Analysis

Exposure	CPG.Labels	P.value	FDR	Bonferroni	Reference Genes
College	cg04734977	7.89E-01	1	1	ZNF680
College	cg09254001	8.36E-01	1	1	IKBIP; APAF1
College	cg15196042	5.85E-01	9.51E-01	1	LOC100129716; ARRDC3
College	cg20226051	7.37E-01	1	1	MTF1
College	cg22544350	2.67E-02	0.2315882	0.6947646	KDM5A; CCDC77
Job Density	cg00730549	1.26E-02	6.54E-02	3.27E-01	TNRC18
Job Density	cg00851060	2.12E-01	1	1	
Job Density	cg00950813	3.17E-02	2.75E-01	8.24E-01	ZNF282
Job Density	cg02449575	2.42E-02	2.10E-01	6.29E-01	SPTLC2
Job Density	cg03115690	9.47E-01	1.00E+00	1.00E+00	
Job Density	cg06520003	6.83E-02	5.92E-01	1.00E+00	ACSF2
Job Density	cg07141484	1.43E-01	6.71E-01	1.00E+00	TLDC2
Job Density	cg07422416	9.79E-01	1.00E+00	1.00E+00	MFHAS1
Job Density	cg07994487	3.15E-01	1.00E+00	1.00E+00	IFT140; TMEM204
Job Density	cg08214329	3.21E-01	1.00E+00	1.00E+00	IFT140; TMEM204
Job Density	cg09178970	3.99E-01	9.42E-01	1.00E+00	VPS37B
Job Density	cg09866303	7.01E-01	3.35E-01	1.00E+00	RREB1
Job Density	cg14838356	1.41E-01	6.20E-01	1.00E+00	AGO2
Job Density	cg15375883	6.78E-01	1.00E+00	1.00E+00	ST3GAL4
Job Density	cg16088676	2.47E-01	1.00E+00	1.00E+00	
Job Density	cg16609534	3.71E-01	1.00E+00	1.00E+00	AFAP1
Job Density	cg17606115	4.28E-01	1.00E+00	1.00E+00	GNAI2
Job Density	cg18658674	6.25E-01	1.00E+00	1.00E+00	
Job Density	cg20576936	8.86E-01	1.00E+00	1.00E+00	ZNF627
Job Density	cg21900997	9.45E-02	6.05E-01	1.00E+00	SCMH1
Job Density	cg25994418	2.25E-01	5.32E-01	1.00E+00	PLCG1

Hazard Analyses

		Age					Age, Race					Age, Race, Stage, Subtype				
Exposure	CPG.Labels	HR	95% CI	Pr (> |z|)	FDR	Bon.	HR	95% CI	Pr (> |z|)	FDR	Bon.	HR	95% CI	Pr (> |z|)	FDR	Bon.
College	cg04734977	0.9539	0.656, 1.387	0.805	1	1	0.9542	0.6526, 1.395	0.809	1	1	0.8441	0.5239, 1.360	0.4862	1	1
College	cg09254001	0.9681	0.5496, 1.705	0.911	1	1	0.9633	0.5450, 1.703	0.898	1	1	0.7928	0.3790, 1.658	0.5374	1	1
College	cg15196042	1.577	0.9643, 2.579	0.0695	1	1	1.5839	0.9653, 2.599	0.0687	1	1	1.969	1.0027, 3.866	0.0491	0.5404	1
College	cg20226051	1.082	0.7103, 1.648	0.714	1	1	1.0721	0.7025, 1.636	0.747	1	1	1.117	0.6250, 1.998	0.7079	1	1
College	cg22544350	0.9678	0.9028, 1.038	0.357	1	1	0.967	0.9016, 1.037	0.348	1	1	0.9246	0.8435, 1.013	0.0941	1	1
Job Density	cg00730549	0.9405	0.875, 1.011	0.961	1	1	0.9401	0.8743, 1.011	0.0951	1	1	0.9388	0.8571, 1.028	0.174	1	1
Job Density	cg00851060	0.959	0.921, 0.9986	0.0424	1	1	0.9565	0.9178, 0.9968	0.0348	0.90354	0.9035	0.9781	0.9253, 1.034	0.4338	1	1
Job Density	cg00950813	0.9596	0.9297, 0.9904	0.0105	0.27187	0.27187	0.9546	0.9179, 0.9928	0.0202	0.52532	0.5253	0.9542	0.9079, 1.003	0.0648	1	1
Job Density	cg02449575	0.9649	0.8989, 1.036	0.322	1	1	0.9651	0.8982, 1.037	0.332	1	1	0.9482	0.8656, 1.039	0.252	1	1
Job Density	cg03115690	0.9308	0.8760, 0.9891	0.0206	0.53515	0.53515	0.93	0.8748, 0.9887	0.0202	0.52413	0.5241	0.9697	0.8954, 1.050	0.449	1	1
Job Density	cg06520003	1.017	0.9356, 1.106	0.691	1	1	1.0212	0.9395, 1.110	0.622	1	1	0.9818	0.8993, 1.072	0.6811	1	1
Job Density	cg07141484	0.9123	0.8499, 0.9794	0.0112	0.29137	0.29137	0.9099	0.8466, 0.9778	0.0102	0.26461	0.2646	0.9115	0.8404, 0.9886	0.0253	0.6579	0.65785
Job Density	cg07422416	1.004	0.9655, 1.044	0.849	1	1	1.0043	0.966, 1.044	0.83	1	1	1.001	0.9541, 1.051	0.9581	1	1
Job Density	cg07994487	0.9434	0.9077, 0.9804	0.00302	0.07856	0.07856	0.9425	0.9064, 0.9801	0.003	0.078	0.078	0.9518	0.9083, 0.9974	0.0386	1	1
Job Density	cg08214329	0.9233	0.8819, 0.9667	0.000657	0.01707	0.01707	0.9215	0.8793, 0.9656	0.000618	0.01607	0.0161	0.926	0.8732, 0.9819	0.0102	0.2657	0.26569
Job Density	cg09178970	0.964	0.7485, 1.241	0.776	1	1	0.9682	0.7527, 1.245	0.801	1	1	1.098	0.8105, 1.487	0.5464	1	1
Job Density	cg09866303	0.9737	0.9303, 1.019	0.251	1	1	0.9737	0.9305, 1.019	0.249	1	1	0.9707	0.9211, 1.023	0.2678	1	1
Job Density	cg14838356	0.9756	0.9419, 1.010	0.168	1	1	0.9748	0.9410, 1.01	0.157	1	1	0.9689	0.9295, 1.010	0.137	1	1
Job Density	cg15375883	1.196	0.9909, 1.444	0.0622	1	1	1.1934	0.9875, 1.442	0.0673	1	1	1.273	1.0420, 1.555	0.0181	0.4713	0.47135
Job Density	cg16088676	0.9325	0.8900, 0.9771	0.00335	0.08719	0.08719	0.9291	0.8863, 0.9738	0.00218	0.05677	0.0568	0.943	0.8932, 0.9956	0.0342	0.8889	0.88886
Job Density	cg16609534	0.8917	0.8032, 0.9899	0.0315	0.81943	0.81943	0.8885	0.8010, 0.9854	0.0252	0.65646	0.6565	0.8819	0.7866, 0.9887	0.0312	0.8118	0.8118
Job Density	cg17606115	0.8841	0.7967, 0.9813	0.0207	0.53706	0.53706	0.8833	0.7953, 0.9811	0.0205	0.53405	0.534	0.8899	0.7889, 1.004	0.0579	1	1
Job Density	cg18658674	0.9668	0.9285, 1.007	0.102	1	1	0.9669	0.9287, 1.007	0.101	1	1	0.9819	0.9351, 1.031	0.463	1	1
Job Density	cg20576936	0.9846	0.9325, 1.040	0.575	1	1	0.9848	0.9321, 1.041	0.587	1	1	0.9593	0.8972, 1.026	0.2239	1	1
Job Density	cg21900997	0.9084	0.8193, 1.007	0.0683	1	1	0.9068	0.8095, 1.016	0.0909	1	1	0.8896	0.7798, 1.015	0.0817	1	1
Job Density	cg25994418	1.001	0.9553, 1.048	0.977	1	1	1.0006	0.9548, 1.049	0.979	1	1	0.9788	0.9275, 1.033	0.4344	1	1

Correlations with Other Neighborhood-Level Factors

Exposure 1	Exposure 2	Correlation	P.value
Job Density	Job Density	1	
Job Density	Population Density	0.35	6.00E-04
Job Density	College	0.14	0.1958
Job Density	Rent	0.26	0.0128
Job Density	Poverty	-0.04	0.7181
Job Density	Income	0.16	0.1322
Job Density	Nonwhite	-0.17	0.1139
Job Density	Single Parent	-0.16	0.1173
Job Density	Job Growth	0.1	0.3595
College	College	1	
College	Population Density	0.3	0.0042
College	Job Density	0.14	0.1958
College	Rent	-0.05	0.6445
College	Poverty	0.16	0.1304
College	Income	-0.14	0.1896
College	Nonwhite	0.24	0.0202
College	Single Parent	0.35	7.00E-04
College	Job Growth	0	0.9636