

**THE INFLUENCE OF SOCIAL AND PSYCHOLOGICAL FACTORS ON THE
RELATIONSHIP BETWEEN BODY COMPOSITION AND COLON CANCER
OUTCOMES**

by

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Abstract

The current five-year survival rate for colorectal cancer in Canada is 65%, which is influenced by well-established factors (e.g., age, cancer stage). There is also consistent observational research that higher body mass or social factors (e.g., living alone) can negatively impact survival. This thesis project examined the association between body composition at diagnosis and relapse-free survival (RFS) at three years post-diagnosis, and how these relationships may be influenced by social or psychological factors at diagnosis in individuals with colon cancer. **Methods:** A cohort of individuals treated for stage III colon cancer at BC Cancer from 2012 to 2015 with clinical and demographic data available was created. CT scans of the third lumbar vertebra at diagnosis were analyzed to determine skeletal muscle index (SMI) (muscle cross-sectional area normalized for height), sarcopenia (using published SMI cut-off points), skeletal muscle density (SMD) (average attenuation of muscle), and skeletal muscle gauge (SMG) (SMI multiplied by SMD). Social and psychological factors were obtained at diagnosis and included social isolation, patient-reported concerns, and symptoms of anxiety and depression from BC Cancer's Psychosocial Screen for Cancer-Revised, and community size and neighbourhood income based on individuals' postal codes. Multivariable logistic regression models were used to examine: 1) The associations of SMI, SMD, SMG, and sarcopenia with RFS; 2) How social and psychological factors (selected using variable visualization and univariable regression) influenced the relationships. **Results:** Individuals were a median age of 62.0 years and 51.1% were male. Individuals with a lower SMD (OR= 0.97, 95% CI= 0.95,0.997), lower SMG (for a 100-unit change, OR= 0.93, 95% CI= 0.88,0.98), or sarcopenia (OR= 1.80, 95% CI= 1.06,3.10) had greater odds of having a relapse. This association was

influenced by social isolation; for any given SMD, SMG, or sarcopenia status, individuals with one or more markers of social isolation had approximately two times greater odds of having a relapse than individuals without markers of social isolation. **Conclusion:** Consistent with the literature, sarcopenia was associated with RFS, as was SMD and SMG, measures for which there is less evidence surrounding their relationship with long-term outcomes. Social isolation appeared to influence these relationships.

Lay Summary

Colorectal cancer (CRC) is the third most common cancer in Canada, making it important to study factors that influence CRC survival. This thesis project explored the influence of body composition (e.g., muscle) and social factors (e.g., support, community size) on cancer relapse. In a group of individuals treated at BC Cancer, the amount and quality of muscle were gathered from clinical scans already collected as part of individuals' cancer diagnoses and treatments. A BC Cancer questionnaire called the Psychosocial Screen for Cancer-Revised and census data were used to determine social factors. The amount and quality of an individual's muscle at diagnosis were shown to impact CRC relapse. Additionally, individuals with one or more markers of social isolation at diagnosis were approximately two times more likely to have a relapse. This project provides insight into how future research, supportive care, and rehabilitation interventions should be developed.

Preface

I, Hannah Kathleen Schulte, worked in collaboration with my supervisor (Dr. Kristin Campbell), thesis committee members (Drs. Howard Lim, Jackie Whittaker), and study co-investigators (Drs. Cheryl Ho, Colin Mar) to identify and design this thesis project. The cohort of colon cancer patients was compiled by the Gastrointestinal Cancer Outcomes Unit, which was primarily the work of Rekha Manhas Diocee and Caroline Speers. The Psychosocial Screen for Cancer-Revised data was obtained from analysts involved in the Data Access Requests process at BC Cancer. However, I created and submitted the needed requests for both sets of data. Additionally, I was not involved in conducting routine clinical care computerized tomography (CT) scans but was responsible for retrieving scans from BC Cancer's system (with guidance from Dr. Colin Mar and Christine Lam), as well as all subsequent analysis. I obtained CT scans and retrieved information from individuals' BC Cancer medical records. I completed all data cleaning, analysis, and interpretation, with insight from other members of the research team (Drs. Kristin Campbell, Howard Lim, Jackie Whittaker). Sections of this thesis may be submitted for publication as a manuscript in a peer-reviewed journal. This thesis project received approval from The University of British Columbia – BC Cancer Research Ethics Board (H20-03499).

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List of Symbols

β – Beta value/regression coefficient

= – Equals

< – Less than

\leq – Less than or equal to

n – Sample size

% – Percent

\pm – Plus or minus

p – p-value

r – Correlation coefficient

R^2 – R-squared value/coefficient of determination

List of Abbreviations

BIA – Bioelectrical impedance analysis

BMI – Body mass index

CAIS – Cancer Agency Information System

CI – Confidence interval

cm – Centimeters

Cook's D – Cook's distance

CPC – Canadian Problem Checklist

CRC – Colorectal cancer

CT – Computerized tomography

DAR – Data access request

DFS – Disease-free survival

DICOM – Digital Imaging and Communications in Medicine

DW – Durbin-Watson

DXA – Dual-energy X-ray absorptiometry

EORTC QLQ – European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire

EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer Quality of

Life Questionnaire-Core 30

EWGSOP – European Working Group on Sarcopenia in Older People

GICOU – Gastrointestinal Cancer Outcomes Unit

HU – Hounsfield units

HADS – Hospital Anxiety and Depression Scale

HR – Hazard ratio

ID – Identification

IMAT – Intramuscular adipose tissue

is – In situ

kg – Kilograms

L3 – Third lumbar vertebra

max – Maximum

M – Metastases

m – Meters

min – Minimum

MRE – Mean relative error

MRI – Magnetic resonance imaging

N – Nodes

OaSIS – Outcomes and Surveillance Integration System

OR – Odds ratio

OS – Overall survival

PACS – Picture Archiving and Communication System

PCCF – Postal Code Conversion File

PCCF+ – Postal Code Conversion File Plus

PHSA – Provincial Health Services Authority

PSSCAN – Psychosocial Screen for Cancer

PSSCAN-R – Psychosocial Screen for Cancer-Revised

QOL – Quality of life

RCT – Randomized controlled trial

RFS – Relapse-free survival

RR – Relative risk

SAT – Subcutaneous adipose tissue

SD – Standard deviation

SE – Standard error

SEE – Standard error of the estimate

SMI – Skeletal muscle index

SMD – Skeletal muscle density

SMG – Skeletal muscle gauge

SOU – Surveillance & Outcomes Unit

SR – Systematic review

T – Tumour

v – Versus

VAT – Visceral adipose tissue

VIF – Variance inflation factor

5FU – Fluorouracil

Glossary

agency_id – A number assigned to each individual treated at BC Cancer

CAPOX – A chemotherapy regimen consisting of capecitabine and oxaliplatin

FOLFOX – A chemotherapy regimen consisting of fluorouracil, folinic acid (leucovorin), and oxaliplatin

site_num – A number that identifies the specific cancer diagnosis in study (i.e., for individuals with more than one cancer, this allows for differentiation)

TNM staging system – A cancer staging system that is based off tumour size and extent, spread to nearby lymph nodes, and cancer metastases

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To my parents: Schulte, Mark and Dania. Thank you for always believing in me.

Chapter 1: Introduction

1.1 Cancer statistics

In 2020, there were an estimated 225,800 new cancer cases and 83,300 cancer-related deaths in Canada.¹ Cancer was responsible for approximately 30% of all deaths in Canada, making it the leading cause of death in the country. Further, colorectal cancer (CRC) was projected to remain as the third most commonly diagnosed cancer type in 2020.² An estimated 26,900 Canadians were diagnosed with CRC and 9,700 died from CRC in 2020, accounting for 12% of cancer diagnoses and 12% of cancer deaths.

1.2 CRC characteristics, location, staging, and treatment

Cancer is defined as a group of cells (i.e., a malignant tumour) that can grow into nearby tissues and spread to distant parts of the body.³ Cancer can be classified according to the type of tissue in which it originated (i.e., histological type) and the location in the body where the cancer first developed (i.e., primary site).⁴ For example, carcinoma begins in the cells that cover or line organs.⁴⁻⁷ Specifically, adenocarcinoma is a type of carcinoma that develops in gland cells such as the intestine.⁴⁻⁷ Adenocarcinoma is the most common type of CRC.⁷

Specific to primary site, CRC derives from cells in the colon or rectum.⁶ The colon and rectum are components of the large intestine, which also contains the cecum and anus.^{8,9} Colon cancers includes those of the ascending colon, hepatic flexure (i.e., curve between the ascending and transverse colon), transverse colon, splenic flexure (i.e., curve between the transverse and descending colon), descending colon, sigmoid colon, and rectosigmoid junction (i.e., separates the sigmoid colon and rectum).⁹ Additionally, if cancer develops in the cecum, it is treated as a colon cancer.⁸ Rectal cancers are those that exist in the rectum, typically after the rectosigmoid

junction and before the anus.^{8,9} Of note, cancers of the rectosigmoid junction can be classified as either colon or rectal cancer.¹⁰ Colon and rectal cancers are often group together because there is no clear boundary between them.⁶ Finally, anal cancers are distinct from CRC.⁸ This thesis will focus solely on individuals who were diagnosed with colon cancer.

Cancer stage refers to the extent of cancer in the body.¹¹ There are five stages of CRC, which are largely classified based on the TNM staging system.¹¹⁻¹³ Tumour (T) refers to the size and extent of the tumour.¹¹ Nodes (N) refers to nodal invasion or the number of lymph nodes that have cancer. Metastasis (M) refers to the spread of cancer to distant parts of the body. Within each category (i.e., T, N, or M), subcategories exist to provide further information.¹¹ For example, colon cancer can be classified as T0 (i.e., tumour cannot be found), TX (i.e., tumour cannot be measured), Tis (in situ), T1, T2, T3, or T4, depending on the characteristics of the tumour. Based on the T, N, and M values assigned, individuals are described as stage 0 (i.e., in situ), I, II, III, or IV.^{11,13} The work in this thesis will focus exclusively on individuals with stage III colon cancer, as defined by the American Joint Committee on Cancer 7th Edition TNM Staging System and captured by the BC Cancer Data Quality & Registry.¹⁴ Stage III includes various combinations of T and N values but only those without metastases (i.e., M0).¹⁴

Cancer treatments are prescribed based on a variety of factors, such as tumour location, cancer stage, and individual age, comorbidities, and preferences for care.¹⁵⁻¹⁷ Treatment for colon cancer often consists of surgery and adjuvant chemotherapy.^{15,16} Adjuvant refers to treatment administered after surgery, whereas neoadjuvant refers to treatment administered before surgery.¹⁸ In contrast, treatment for rectal cancer often involves radiation and chemotherapy, administered before or after surgery.^{19,20} Chemotherapy regimens often consist of several drugs. Capecitabine, fluorouracil (5FU), folinic acid (leucovorin), and oxaliplatin are

commonly used in different combinations to treat colon cancer.^{15–18,21} For example, a combination of 5FU, leucovorin, and oxaliplatin is commonly known as FOLFOX. CAPOX is a combination of capecitabine and oxaliplatin. Both of these commonly used chemotherapy protocols are administered in specific doses and durations,^{17,18} with three and six month protocols being most prominent.²¹ At BC Cancer, FOLFOX is delivered every two weeks for 12 cycles (i.e., six months) or six cycles (i.e., three months). CAPOX is delivered every three weeks for eight cycles (i.e., six months) or four cycles (i.e., approximately three months).²¹ Previous research suggests that six months of oxaliplatin-based treatment is most effective for individuals with a high risk of recurrence, whereas three or six months of treatment may be administered to individuals with a low risk of recurrence.^{22,23} In individuals with a low risk of recurrence, three months of treatment may be selected to reduce the likelihood of adverse events (i.e., peripheral sensory neurotoxicity) occurring with no corresponding significant change in disease-free survival (DFS).²² Treatment decisions are based on individual and physician values and preferences, tumour characteristics, comorbidities, and a host of other factors.²³ The cohort in this project all received oxaliplatin-based chemotherapy (i.e., FOLFOX and CAPOX).

1.3 CRC outcomes

Key cancer outcomes include cancer-related mortality or cancer-specific survival, overall survival (OS), DFS, relapse-free survival (RFS) (also named recurrence-free survival), as well as hospitalization outcomes and measures of morbidity. OS refers to those who have not died from any cause, whereas cancer-specific mortality and survival only use deaths identified as being due to a specified cancer.²⁴ DFS is the duration of time after primary treatment that an individual survives without any events of disease recurrence (local or metastatic) and is often used

interchangeably with RFS.^{25,26} However, it should be noted that the definition of DFS can also include death from any cause as part of the endpoint. For studies of colon cancer outcomes, time elapsed is commonly calculated from surgery to relevant endpoints, for all outcomes listed above. However, researchers also perform calculations that are study context dependent, such as starting from individuals' cancer diagnoses, study enrollment, or other relevant time points. Despite different definitions used in the literature to date, the relationships between outcomes are relatively consistent. For instance, DFS at two or three years has been shown to be highly correlated with OS at five years in individuals with stage III colon cancer, suggesting that DFS at two or three years is a relevant survival outcome.²⁷⁻²⁹

Lastly, it is well-established that these mortality and morbidity outcomes are influenced by age, sex, the location of cancer in the body, cancer stage, and treatment type.^{1,2,30-33} However, there has more recently been an appreciation that additional factors may also play a role, including body composition at the time of diagnosis, as well as social and psychological factors. Body composition refers to the amount of fat and fat-free mass an individual has.³⁴ Fat-free mass consists of skeletal and non-skeletal muscle, organs, connective tissue, and bone.³⁴ This thesis project will focus on skeletal muscle mass and density at the time of diagnosis, which has been shown to be associated with cancer-specific mortality, OS, DFS, measures of morbidity, and other key outcomes.^{24,35-37} Of note, the results for skeletal mass muscle and DFS are quite consistent, but the association between markers of muscle density or quality and DFS are inconclusive. Social factors that have been associated with CRC outcomes include educational attainment and income level.^{30,38} Lastly, common psychological factors have also been associated with CRC outcomes, including individual experience with the cancer care system and sleep problems, but less is known about anxiety and depression.^{39,40} This project will investigate

numerous social and psychological factors, which are outlined in further detail in later sections of this thesis.

There are several pathways by which a poorer body composition (i.e., reduced muscle mass or quality) may negatively influence CRC outcomes, including: 1) Physiologic and metabolic pathways (e.g., local and systemic inflammation and insulin resistance); 2) Worse short-term CRC outcomes (e.g., increased surgical complications and chemotherapy-related toxicities, dose reductions, and premature discontinuation); 3) Higher rates of frailty and functional impairments³⁶; 4) Behavioural factors (e.g., lower levels of physical activity due to fatigue).⁴¹ Social and psychological factors may also influence cancer outcomes through potential pathways such as disparities in CRC screening practices, differential access to health care, and the presence/absence of informal caregiving.^{38,42-44} Lastly, to the best of my knowledge, social and psychological factors have not been explored in relation to body composition in individuals with CRC. However, these factors have been associated with body composition in other populations via the following pathways: 1) Availability to healthy meals (e.g., grocery shopping, assistance cooking); 2) Walkability of individuals' living environments; 3) Access to recreational facilities; 4) Metabolic pathways (e.g., long-term deprivation of social contacts may result in chronic stress).^{45,46}

1.4 Purpose

The purpose of this study was to explore the factors that influence the relationship between skeletal muscle measures (i.e., mass and density) and RFS in individuals who were diagnosed with stage III colon cancer and treated with oxaliplatin-based chemotherapy. This thesis intended to contribute to the field of research surrounding the relationship between body

composition and colon cancer outcomes, as well as provide a greater understanding of how the relationship between the two is influenced by social and psychological factors. To the best of my understanding, there is currently no other research that examines the influence of social and psychological factors on the relationship between skeletal muscle and colon cancer outcomes. Research in this area is needed to add a potentially overlooked aspect of the growing body of knowledge surrounding the influences of skeletal muscle and colon cancer outcomes. Our team accessed a unique cohort of individuals where additional social and psychological data was available, in addition to body composition and clinical data.

Ultimately, the goal of this project was to provide foundational knowledge to assist with the development and testing of targeted supportive care and rehabilitation interventions to improve colon cancer outcomes. It is essential to identify the factors that influence the relationship between skeletal muscle and colon cancer outcomes; this affords researchers the knowledge needed to devise interventions and programming that consider important social and psychological factors and have the most optimal chances of improving outcomes.

Chapter 2: Background

2.1 Body composition in individuals with CRC

This section will focus on the background information related to body composition by exploring: 1) How body composition is measured; 2) Definitions of body composition parameters; 3) The use of computerized tomography (CT) scans specific to individuals with CRC; 3) The influence of body composition on CRC outcomes; 4) The ability of interventions to modify body composition parameters in individuals with CRC.

2.1.1 Measuring body composition

There are a variety of measures used to decipher body composition, which vary in terms of the amount of technology and equipment required. One of the most commonly employed measures of body composition is body mass index (BMI).^{34,47,48} BMI is a value derived from self-reported or measured weight and height (kilograms (kg)/meters (m)²). BMI is inexpensive and easy to employ. However, research suggests that BMI alone is a poor surrogate for body composition.^{41,49,50} BMI does not portray the distribution of adipose tissue throughout the body, nor does it differentiate between adipose and muscle tissue, which have different densities.^{41,50} Additionally, in a retrospective cohort study of 3,408 individuals with stage I-III CRC, a BMI in the overweight range of 25 to <30kg/m² at diagnosis was associated with the lowest risk of mortality, across all BMI ranges.⁵⁰ The apparent survival advantage among those with a BMI in the overweight range is known as the “obesity paradox.”^{41,49} It is hypothesized to be explained by the observation that individuals with higher BMIs also have higher levels of protective muscle to counter the negative catabolic effects of the malignancy and subsequent cancer treatments. Other anthropometric techniques to measure body composition have also been used, including

circumferences (e.g., waist or hip circumference) and skinfold thicknesses.³⁴ However, these measures do not quantify the components of human body composition directly and only provide a surrogate measure of body composition.⁵¹

Bioelectric impedance analysis (BIA) uses impedance to electrical flow to quantify fat-free mass and indirectly determine fat mass (i.e., fat-free mass subtracted from total body mass).^{34,51} BIA is inexpensive, portable, easy to operate, and poses no radiation or other risk to the individual. However, there are disadvantages associated with this modality: 1) The reliability of the measurement is influenced by external factors, such as the electrodes, operator, subject's hydration status, and environmental conditions (e.g., ambient temperature, due to its influence on systemic blood flow); 2) Population-specific equations are required (i.e., different equations are required, depending on age, ethnicity, etc.)⁵²; 3) There is limited applicability for those with a BMI >34kg/m² due to BIA underestimating fat mass.³⁴ The concerns regarding the validity of BIA to determine body composition variables have limited its translation into use in clinical care.^{34,51,52}

Imaging is the most commonly employed body composition measure in the clinical setting.^{34,53} Dual-energy X-ray absorptiometry (DXA) uses high- and low-energy X-rays to scan the entire body and differentiate between bone mineral, lean soft tissue mass, and fat mass.^{34,51,54} DXA provides accurate and precise regional body composition measures.³⁴ Additionally, it is quick and safe to employ in most situations. However, DXA has certain limitations: 1) DXA does not provide information on specific body composition compartments within lean and fat tissues; 2) The measurements can be influenced by tissue thickness and lean tissue hydration; 3) Differences in measurements are observed depending on the manufacturer and software version being used.³⁴ To gain more specific information on the various components of body composition,

magnetic resonance imaging (MRI) and CT scans can be used. MRI uses a strong magnetic field and the body's magnetic properties to produce a series of detailed cross-sectional images of the organs and other internal body structures.^{34,51,55} CT scans use the attenuation of X-rays to produce a series of cross-sectional images, where a single slice can act as a proxy to estimate total visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), intramuscular adipose tissue (IMAT), and skeletal muscle.^{34,51,53} Potential disadvantages of MRI and CT scans include a high cost and degree of specialization, as well as the inability to accommodate larger subjects due to the size of the scanner.³⁴ Additionally, MRI poses little risk, while CT scans result in a large degree of radiation exposure to the individual.³⁴ However, MRI and CT scans provide highly accurate measures of body composition at the tissue-organ level and are readily available if imaging is obtained as part of clinical care.³⁴

2.1.2 Defining muscle mass, muscle quality, and sarcopenia

Muscle quality and mass can be measured in a variety of ways in free-living humans. Quantification of muscle quality can include “aspects of anatomic structure, chemical compositions and metabolic and mechanical performance.”⁵⁶ For skeletal muscle, muscle quality is not uniformly defined across the literature.⁵⁶ Imaging techniques, such as CT and MRI, can be used to quantify composition of the muscle, which can be defined as quality, while another definition of quality is ratio of strength to muscle mass for various extremities.^{36,57}

A common proxy of muscle quality is quantified using skeletal muscle density (SMD). SMD is a measure of IMAT infiltration in skeletal muscle, with a low SMD corresponding to a high amount of IMAT (also known as myosteatorsis) and thus a poorer muscle quality.³⁶ Skeletal muscle index (SMI) is a common proxy measure of skeletal muscle mass, calculated as skeletal

muscle area normalized for height (centimeters (cm)²/m²).³⁵ SMD and SMI are the basis for calculating other body composition variables, such as skeletal muscle gauge (SMG). SMG integrates both muscle quality (i.e., density) and quantity (i.e., mass) into a single variable and is derived by multiplying SMD by SMI.⁵⁸

Sarcopenia is another commonly used term to define body composition based on skeletal muscle measures. However, one large gap in the literature is the lack of a consistent definition for sarcopenia; it is operationalized in several different ways. In many instances, sarcopenia is defined solely by the loss of skeletal muscle mass.^{34,59} In contrast, the European Working Group on Sarcopenia in Older People (EWGSOP) includes a functional component in its definition of sarcopenia, namely sarcopenia is “a syndrome characterised by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death.”⁶⁰ This lack of consensus makes sarcopenia difficult to assess for research purposes.

To address the component of muscle strength used in the EWGSOP definition of sarcopenia, a variety of outcome measures have been employed throughout the literature.⁶⁰ Two of the most commonly used measures are grip strength (can be measured via a dynamometer) and chair stand tests, which measure the number of times an individual can rise from a chair in a defined period of time.⁶⁰ Numerous performance measures has also been used as a proxy for muscle strength, including gait speed, Timed-Up and Go tests, and 400- and 600-m walk tests.⁶⁰ Gait speed measures usual walking speed over a defined distance, often four meters. Timed-Up and Go assessments measure the time needed for an individual to rise from a chair, walk around a marker, turn around, walk back, and sit down. Lastly, 400- and 600-m walk tests evaluate both

walking ability and endurance by instructing individuals to complete a certain number of laps (of a predetermined distance) as fast as possible.

In clinical populations, imaging can be used to objectively measure skeletal muscle mass and quality (i.e., density).^{34,53} However, functional assessments are not readily performed as part of routine clinical practice. Therefore, the definition of sarcopenia that only includes the loss of skeletal muscle mass is most common when studying clinical populations, including individuals with cancer.^{34,53} SMI, as calculated as skeletal muscle area normalized for height, can be obtained from routinely performed CT imaging and has been used to determine if an individual has sarcopenia or not.⁶¹ Sex-specific SMI cut-off points are commonly used, due to differences in total regional skeletal muscle mass between men and women.⁴⁹ Adjusting sex-specific cut-off points for BMI is another method commonly used in recent literature⁴⁹, allowing individuals to be classified as having sarcopenic obesity (i.e., low muscle mass and high adiposity).^{62,63} In a 2017 retrospective cohort study of 3,262 individuals with early stage (I-III) CRC, Caan et al. used optimal stratification to determine sex- and BMI-specific cut-off points for sarcopenia.⁴⁹ These results are displayed in Table 2.1.

Table 2.1 Sarcopenia sex- and BMI- specific SMI cut-off points for individuals with early stage (I-III) CRC

	SMI value*	
	Men (cm ² /m ²)	Women (cm ² /m ²)
BMI <30kg/m²	52.3	38.6
BMI >30kg/m²	54.3	46.6

From cut-off points established by Caan et al. (2017).⁴⁹

Abbreviations: BMI, body mass index; cm, centimeters; CRC, colorectal cancer; kg, kilograms; m, meters, SMI, skeletal muscle index.

Legend: * The listed values represent SMI, as calculated using skeletal muscle area (cm²) and height (m²).

2.1.3 Using CT imaging to measure body composition parameters specific to individuals with CRC

As outlined above, MRI and CT scans provide highly accurate and detailed measures of body composition. Specific to individuals with CRC, abdominal CT scans are a part of regular care for diagnosis, treatment response, and follow-up.⁵³ Therefore, CT-based body composition can be conducted with little increase in healthcare costs and no extra radiation exposure for a patient, outside of the exposure posed by routine clinical scans. As a result, CT scans pose a unique opportunity to study outcomes in individuals with CRC; Prado denotes CT scans as a “hidden treasure in body composition research in oncology.”⁵³

While abdominal CT scans depict thoracic vertebrae, lumbar vertebra, and sacral vertebra, the third lumbar vertebra (L3) slice has been established as a strong predictor of whole body composition, especially for measures of skeletal muscle. A cross-sectional study of 123 healthy men and 205 healthy women first found that skeletal muscle area five centimeters above the fourth to fifth lumbar vertebrae was most strongly correlated with skeletal muscle volume, as measured by whole body MRI ($r= 0.924$). Subsequently, skeletal muscle area five centimeters above the fourth to fifth lumbar vertebrae was found to accurately predict whole body skeletal muscle volume ($R^2= 0.854$).⁶⁴ Specific to cancer populations, Mourtzakis et al. studied a cohort of 51 individuals with locally advanced or non-small cell lung cancer or CRC and reported that the fat and fat-free tissue measured by CT at L3 related significantly to the whole body fat and fat-free tissues measured by DXA. Fat tissue at L3 predicted whole body fat mass ($r= 0.881$, $p< 0.001$, standard error of the estimate (SEE)= 0.80 kg, mean relative error (MRE)= 3.49 ± 2.31 kg). Fat-free tissue at L3 accurately depicted whole body fat-free tissue ($r= 0.83$, $p< 0.001$, SEE= 1.2kg, MRE= 5.23 ± 3.45 kg). Finally, the skeletal muscle measured by CT at L3 (divided

by height²) also related significantly to appendicular skeletal muscle mass (divided by height²) as measured by DXA ($r=0.89$, $p< 0.001$, $SEE= 0.10\text{kg/m}^2$, $MRE= 0.45 \pm 0.33\text{kg/m}^2$).⁵⁴

Once L3 has been landmarked, commercially available imaging software, such as SliceOMatic V5.0 (Tomovision, Montreal, Canada) can be used to perform analysis. The software differentiates between tissue types using Hounsfield units (HU).^{34,53,54} HU represent the relative attenuation coefficient (i.e., the density) of tissues, using water as a reference. Tissues with lower densities than water (i.e., fat) have a negative HU and tissues with higher densities than water (i.e., muscle) have a positive HU. Tissues have defined HU ranges to allow for their identification in a cross-sectional image. The ranges outlined in Table 2.2 are widely accepted.⁵⁴ Further, tissue differentiation can be performed via manual (i.e., researcher-performed) or automated (i.e., software-performed) means. A previous project in the Clinical Exercise Physiology Lab has shown an automated module (Voronoi Health Analytics ABACS L3 Module) to be reliable and valid for analyzing the L3 slice of CT scans in individuals with colon cancer.⁶⁵ The research team calculated inter-class correlation values for manual tissue segmentation done by a trained analyst, as compared to that done by the automated module. High levels of relative agreement were found. Inter-class correlation values were 0.981 (95% confidence interval (CI)= 0.873,0.994, $p< 0.01$), 0.710 (95% CI= 0.320,0.874, $p< 0.01$), 0.997 (95% CI= 0.993,0.999, $p< 0.01$) and 0.992 (95% CI= 0.978,0.997, $p< 0.01$) and 0.992 (95% CI= 0.982,0.996, $p< 0.01$) for muscle, IMAT, VAT, SAT, and muscle attenuation (i.e., density), respectively. Agreement between manual and automated tissue segmentation was also found to be strong for muscle, VAT, and SAT surface areas, with only one or two outliers beyond the 95% limits of agreement in the Bland-Altman plots developed. Agreement was also high for IMAT, with only one outlier beyond the 95% limits of agreement. However, agreement tended to

be higher for smaller IMAT values and lower for high IMAT values, indicating potential bias. Finally, agreement for muscle attenuation was also relatively strong, with three limits beyond the 95% limits of agreement and a similar bias as observed in IMAT.⁶⁵

After L3 is landmarked and analyzed using HU parameters (manually or via software automation), the number of pixels identified for each tissue is multiplied by the surface area of the individual tissue. The resulting muscle and adipose tissue surface areas can be used to calculate further body composition variables, such as SMI and sarcopenia. Additionally, the average attenuation of muscle (i.e., SMD), IMAT, VAT, and SAT can be determined by the automated module (Voronoi Health Analytics ABACS L3 Module).

Table 2.2 Hounsfield Unit parameters for distinguishing tissues in SliceOMatic V5.0 (Tomovision, Montreal, Canada)

	Lower Limit (HU)	Upper Limit (HU)
Muscle	-29	+150
IMAT	-190	-30
VAT	-150	-50
SAT	-190	-30

From HU parameters determined by Mourtzakis et al. (2008)⁵⁴

Abbreviations: HU, Hounsfield units.

2.1.4 The influence of body composition on CRC outcomes

The most recent systematic review (SR) and meta-analysis exploring the impact of sarcopenia on CRC outcomes was published by Sun et al. in 2018 and used the L3 slice of a preoperative CT scan to calculate SMI and diagnose sarcopenia based on body composition only. The review included 12 prospective and retrospective studies, with 5337 individuals with non-metastatic CRC in total. Individuals with CRC who were sarcopenic at diagnosis were more likely to have a higher incidence of postoperative complications, such as longer hospital stays (weighted mean difference= 1.29, 95% CI= 0.50,2.08, p< 0.01) and postoperative morbidity

(odds ratio (OR)= 1.70, 95% CI= 1.07,2.70, $p < 0.01$), infection (OR= 2.21, 95% CI= 1.50,3.25, $p < 0.01$), and 30-day mortality (OR= 3.45, 95% CI= 1.69,7.02, $p < 0.01$). Sarcopenia at diagnosis was also associated with lower OS (hazard ratio (HR)= 1.63, 95% CI= 1.24,2.14, $p < 0.01$), cancer-specific survival (HR= 1.62, 95% CI = 1.16,2.27, $p < 0.01$), and DFS (HR= 1.95, 95% CI= 1.36,2.80, $p < 0.01$) using a time-to-event analysis and HRs in individuals with non-metastatic CRC.⁶⁶

Malietzis et al. examined the prevalence of sarcopenia and visceral obesity and the impact of visceral obesity on CRC outcomes, in addition to solely focusing on the impact of sarcopenia on outcomes.³⁵ The 2015 SR contained 20 prospective and retrospective cohort studies. Only studies with CT-based measured of body composition were included, with 13 studies using L3, two studies using the fourth to fifth lumbar vertebrae level,^{67,68} and one study using three-dimensional reconstruction to calculate visceral fat volume.²⁵ The approach used to classify sarcopenia differed across studies and included SMI cut-off values or total psoas area. The approach to the classification of visceral obesity also varied, defined by measuring visceral fat area, visceral fat area/subcutaneous fat area, or visceral fat volume. The number of individuals with CRC that were classified as sarcopenic ranged from 16% to 71% across studies, with a range of 18% to 62% of individuals being classified as viscerally obese. Next, due to the high study heterogeneity in approaches to measuring body composition, no quantitative data analysis was conducted. The results of the individual studies were highlighted through a narrative review. Both visceral obesity and sarcopenia were associated with an increased number of postoperative complications, such as infection and other major complications and a higher 30-day mortality rate. Additionally, lean body mass (as extrapolated from abdominal muscle area in L3 CT slices) and sarcopenia acted as prognostic factors for developing severe chemotherapy-

related toxicity. Lastly, individuals determined to be sarcopenic appeared to have lower DFS and OS. Individuals with visceral obesity were observed to have lower DFS, OS, and RFS.³⁵

Next, in a 2020 SR, Lee et al. focused on skeletal muscle quality, versus skeletal muscle mass, in individuals with stage I-IV CRC. Lee et al. included five to 12 studies (dependent on the outcome being available) that examined SMD at L3, with the exception of one study that used the fourth lumbar vertebra and psoas muscle. Individuals were classified as having myosteatorosis (i.e., low SMD or high adiposity of skeletal muscle) or not (i.e., high SMI or low adiposity of skeletal muscle) using sex-specific SMD cut-off points (except one study that only used sex-specific SMD cut-off points). Individuals with myosteatorosis had an increase in overall (OR= 1.55, 95% CI= 1.23,1.96, $p < 0.00001$) and CRC-specific mortality (OR= 1.69, 95% CI= 1.43,2.00, $p < 0.00001$). There was no evidence of an association between myosteatorosis and DFS (HR= 1.00, 95% CI= 0.95,1.05, $p = 0.88$).³⁷ However, previous research in individuals with stage I-III CRC reported an association between myosteatorosis and worse DFS (HR= 1.68, 95% CI= 1.14,2.47), using different sex- and BMI-specific SMD cut-off points.⁶⁹

Finally, SMG as a combined measure of muscle mass and quality is not as well-established in the cancer literature. However, in a retrospective cohort study of older adults with cancer, both SMD and SMG were associated with physical function impairments. For example, higher SMD and SMG values were associated with less limitations in activities of daily living (relative risk (RR)= 0.84, 95% CI= 0.67,0.90 and RR= 0.91, 95% CI= 0.87,0.96, respectively) and a shorter Timed-Up and Go (RR= 0.83, 95% CI= 0.75,0.92 and RR= 0.92, 95% CI= 0.88,0.96, respectively).⁵⁸ Related to cancer outcomes, a prospective cohort study of individuals with gastric cancer found that a low SMG combined with low grip strength was most predictive of postoperative complications, as compared to SMI, SMD, or grip strength or SMG alone.⁷⁰

Next, a cohort study of individuals with metastatic breast cancer receiving taxane based chemotherapy showed significant associations between SMG and treatment toxicity ($p= 0.04$), hospitalization ($p= 0.01$), and time to treatment failure (i.e., time between treatment initiation and premature discontinuation due to disease progression or toxicity) ($p= 0.03$). Additionally, borderline significant associations were found between SMG and OS ($p= 0.07$).⁷¹ Most recently, Park et al. reported that a low SMG (as defined by sex-specific SMG cut-off points) was associated with poorer OS in individuals with stage I-IV CRC (OR= 1.79, 95% CI= 1.07,3.00, $p= 0.025$).⁷² To the best of my understanding, this was the first study to investigate the association of SMG and survival in individuals with CRC and further research surrounding SMG in the CRC population is warranted.

2.1.5 Modifying body composition variables in individuals with CRC

This section summarizes the available literature on interventions that focused on body composition and outcomes in individuals with CRC. Interventions can be delivered at many time points throughout the cancer trajectory: 1) Before treatment (i.e., prehabilitation); 2) During treatment; 3) After treatment completion.

Firstly, Gillis et al. performed a pooled analysis of two randomized controlled trials (RCTs) that studied a prehabilitation intervention that initiated four weeks before colorectal cancer surgery, in comparison to an identical intervention that initiated after individuals' colorectal surgeries. The intervention included: 1) A personalized nutrition intervention; 2) Anxiety-reducing components involving deep breathing and relaxation exercises performed twice weekly; 3) A combination of home-based and supervised aerobic and resistance training for 50 minutes at least three days per week. As measured by BIA, individuals in the

prehabilitative group had more absolute and relative lean body mass compared to the rehabilitative group, at both four (prehabilitative group had 1.22kg (standard error (SE)= 0.49) more absolute lean body mass than rehabilitative group, $p= 0.013$; prehabilitative group had 1.33% (SE= 0.52%) more relative lean body mass than rehabilitative group, $p= 0.011$) and eight (+1.55kg (SE= 0.54), $p= 0.004$; +1.30% (SE= 0.57%), $p= 0.042$) weeks post-surgery. Additionally, prehabilitated individuals had less absolute and relative fat mass at four weeks post-surgery (prehabilitative group had 0.91kg (SE=0.39kg) less absolute in fat mass than rehabilitative group, $p= 0.018$; prehabilitative group had 0.99% (SE= 0.42%) less relative fat mass than rehabilitative group, $p=0.024$)

Second, a pilot controlled trial by Shim et al. studied the effects of exercise during adjuvant CRC chemotherapy on treatment completion and toxicity and body composition. The intervention consisted of 50 minutes of home-based exercise three times per week, consisting of 10 minutes of warm-up core stretching, 30 minutes of aerobic and anaerobic exercise, and 10 minutes of wrap-up core stretching. Muscle to fat ratios were determined using SAT and muscle area at the L3 level of a CT scan. The reduction in muscle to fat ratios was significantly greater in the control group than in the exercise group ($p= 0.047$). Muscle to fat ratios decreased during adjuvant treatment in the control group (0.92 versus 0.81, $p= 0.039$), while remaining the relatively constant in the exercise group (0.98 versus 0.97, $p= 0.742$). Notably, compared to the control group, the exercise group had less grade three or four nausea symptoms (71% versus 32%, $p= 0.0018$) and grade three or four neurotoxicity symptoms (50% versus 16%, $p= 0.052$). Of note, the grading was from zero to four based on commonly used treatment-related toxicity guidelines.

In terms of post-treatment interventions, Gao et al. conducted an SR to investigate the effects of exercise on psychosocial outcomes, physical function, body composition, and other outcomes in individuals with CRC who were complete primary cancer treatment (i.e., surgery, chemotherapy, or radiotherapy). Specific to body composition, two studies reported that high intensity exercise increased lean mass and decreased fat mass, with a moderate exercise program showing no change. However, three studies found no significant differences in lean mass and a meta-analysis including BMI (six studies), body fat percentage (four studies), and waist circumference (three studies) found insignificant changes with a moderate aerobic intervention compared to usual care.

To conclude, to the best of my knowledge, no studies have further investigated the relationship between exercise- and nutrition-based interventions and outcomes in individuals with CRC. However, this research is currently underway. First, Caan et al. aim to examine the influence of resistance training (shown to improve muscle mass) on chemotherapy completion and toxicity in individuals with non-metastatic colon cancer receiving adjuvant treatment (NCT03291951).⁷³ Second, the Canadian Cancer Trials Group Colon Health and Life-Long Exercise Change Trial is investigating the effect of an aerobic exercise intervention on DFS in individuals with high-risk stage II or III colon cancer who completed adjuvant chemotherapy two to six months prior to trial enrollment (NCT00819208).⁷⁴ Preliminary feasibility results showed a significant difference in self-reported physical activity between the group receiving exercise and the group receiving health education materials. Additionally, individuals receiving an exercise program showed improvements in many areas of physical function, including the six-minute walk test ($p < 0.001$) and eight-foot Timed-Up and Go ($p = 0.004$).⁷⁵

2.1.6 Summary of body composition section

In summary, many body composition variables can be derived from the various modalities that exist. CT scans provide a unique avenue to examining the relationship between body composition and outcomes in individuals with CRC.⁵³ Specifically, research suggests that muscle mass at L3 is the best proxy for whole body muscle volume. Therefore, there is a growing body of evidence surrounding the important effect of body composition, including skeletal muscle mass and density at the level of L3, on CRC outcomes.^{24,35-37} As a result, there are an increasing number of exercise- and nutrition-based interventions being developed to target and modify body composition variables in individuals with CRC, based on the premise that this will subsequently improve outcomes.⁷⁶⁻⁷⁸ Research regarding the factors that may influence the link between an improved body composition (e.g., increased skeletal muscle mass or density) and better CRC outcomes (e.g., RFS) is warranted.

2.2 Social and psychological factors relevant to individuals with CRC

This section will focus on the background information related social and psychological factors: 1) Defining social and psychological factors; 2) Outlining the tools used to measure social and psychological factors; 3) Examining the influence of social and psychological factors on cancer outcomes.

2.2.1 Defining social and psychological factors

There is an array of factors that influence health outcomes, from individual-level variables to larger societal-level variables.^{79,80} Historically, health was perceived solely as a biological construct.⁷⁹ Therefore, disease was the result of biochemical, physiological, and other

biological processes, while any other potential contributors were neglected. The biopsychosocial model arose when researchers found the previous approach to be very limited in terms of its ability to explain health-related phenomenon.⁷⁹ The biopsychosocial model attributes health to a combination of biological, psychological, and social factors, and it views physical and mental health in unison. Previously, the biomedical approach viewed physical and mental health as independent from each other. The biopsychosocial model, along with additional models that have been developed, such as social ecological paradigms, provide useful lenses with which to view the variables that impact health outcomes in various populations. Social factors are “concerned with social structure and social processes that impinge on the individual.”⁸¹ Social factors encompass an individual’s social connections and interactions, to population-level factors like income, educational attainment, and access to services.^{79,80} Psychological factors are defined as “individual-level processes and meanings that influence mental states.”⁸¹ Some examples of psychological factors include coping and distress.^{79,80}

Social and psychological factors as considerations in the determination of an individual’s quality of life (QOL). There are several definitions for QOL, with one example being “an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social, and emotional well-being together with the extent of personal development and purposeful activity, all weighted by a personal set of values.”⁸² Health-related QOL includes the aspects of QOL that are “related to or affected by the presence of disease or treatment.”⁸³ Therefore, health-related QOL is important to measure in individuals with chronic (i.e., long-term) conditions such as cancer.⁸⁴ However, there are various tools to measure health-related QOL, as the aspects of QOL that are most impacted by poor health differ depending on the disease or condition of interest.⁸⁵

2.2.2 Measuring social and psychological factors

Social and psychological factors are often collected by means of patient-reported outcomes, namely self-reported using standardized surveys and questionnaires. For example, the Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire that is commonly used to assess psychological factors and evaluates how the individual has felt in the past week, with seven items related to depression and seven items related to anxiety.⁸⁶ The HADS is a simple yet reliable tool for use in medical practice and has been validated in a variety of settings, including various community settings and primary care medical practice.⁸⁶ However, this tool only assesses for anxiety and depression, where other measures assess for broader aspects of an individual's QOL and other facets of the cancer journey.^{87,88}

There are also instruments specific for use in individuals with a cancer diagnosis, such as the commonly used European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQs).⁸⁹ The EORTC QLQs have been developed to assess social, psychological, and other factors associated with health-related QOL in individuals with cancer. There are EORTC QLQs focused on specific groups within the cancer population, including those with bone metastases, breast cancer, and palliative cancer, as well as the EORTC QLQ-Core 30 (EORTC QLQ-C30), which has been widely validated for use in individuals with any cancer type.⁸⁸ Overall, there are many challenges associated with the collection of social and psychological factors via surveys and questionnaires, including: 1) There is no agreement on the best tool to use; 2) Many tools have a large number of questions that can take too long for an individual to complete as part of routine screening; 3) Copyright protection and fees may make many validated tools inaccessible.^{87,90}

To overcome these challenges, BC Cancer researchers and clinicians developed a measurement tool to capture both social and psychological factors that may impact individuals' cancer care and outcomes, as well as a tool that is accessible and feasible to administer in a clinical setting.^{87,90} The resulting tool assesses for psychosocial distress in individuals with cancer and is called the Psychosocial Screen for Cancer (PSSCAN).⁸⁷ The PSSCAN was introduced at BC Cancer in 2005⁸⁷ and revised in 2014.⁹⁰ The Psychosocial Screen for Cancer-Revised (PSSCAN-R) can be found in Appendix A. The PSSCAN-R is a 21-item instrument made up of three sections:

1. Part A: A five-item social support checklist pertaining to living alone, contact with family and friends and other markers of support or potential isolation. The checklist was created by BC Cancer, based on a scale used in the Epidemiological Study of the Elderly.⁸⁷
2. Part B: The six-domain Canadian Problem Checklist (CPC). The following domains are addressed by the CPC: 1) Emotional concerns; 2) Informational concerns; 3) Practical concerns; 4) Spiritual struggles; 5) Social/family concerns; 6) Physical Concerns. Within each domain, individuals are instructed to mark items that have been a concern to them in the previous week. For example, the social/family concerns domain contains the following items: 1) Feeling like a burden to others; 2) Worrying about family/friends; 3) Feeling alone. The Canadian Partnership Against Cancer created the CPC. Specifically, a Screening for Distress Toolkit Working Group created the CPC in an effort to promote person-centered care and address the many challenges faced by individuals with cancer. The Canadian Partnership Against Cancer recognizes screening for distress as “the 6th vital sign” and the Working Group was created to establish the tools needed to screen for distress.⁹¹

3. Part C: A 10-item symptoms of depression and anxiety scale, each with a five-point Likert-type scale. Individuals' responses range from zero ("not at all") to four ("very much"). Within the larger scale, there are five items pertaining to anxiety and five items that address depression. This scale was created by BC Cancer and validated against the HADS. As outlined above, the HADS is a valid and widely recognized screening tool.^{87,90}

Individuals complete the PSSCAN-R during one of their first visits at BC Cancer (i.e., around the time of diagnosis).⁸⁷ The PSSCAN-R is endorsed as an effective clinical tool by the clinicians and researchers who work with it. The PSSCAN-R is endorsed for the following reasons: 1) It was developed in the clinical context that it is being used and subsequently includes a scope of domains shown to be important to individuals with cancer; 2) It is brief and simple for individuals to complete as part of routine clinical care visits; 3) It is inexpensive to administer; 4) It measures both negative and positive aspects of individuals' health-related QOL. Of note, the PSSCAN was also developed and validated against widely accepted tools.^{87,90} Therefore, the domains included were important to individuals with cancer, while still being psychometrically sound. However, since its revision in 2014, the PSSCAN-R has not been revalidated. The exception is for Part C (i.e., symptoms of anxiety and depression) alone, which was included in the first version of the PSSCAN and has been validated against the HADS.^{87,90}

In addition to patient-reported surveys and questionnaires, social factors can also be gathered using objective population-level data like census data.^{43,92,93} For example, the Postal Code Conversion File (PCCF) has been developed by Statistics Canada, and it is annually updated based on postal code data from Canada Post Corporation, health region boundaries, documentation regarding geographic attributes, and other administrative files. The PCCF affords researchers the ability to study variables such as neighborhood income, community size, and

immigrant terciles (i.e., defined by the immigrant and non-permanent resident population in Canada).⁹²

2.2.3 The influence of social and psychological factors on CRC outcomes

There are a range of social and psychological factors that have been linked to CRC outcomes. For example, in a retrospective cohort study of 35,661 CRC individuals in Denmark by Degett et al. reported that one year survival after acute colorectal surgery was reduced in individuals who had a fewer years of formal education (i.e., the mandatory seven or nine years or primary school only) (HR= 1.18, 95% CI= 1.03,1.36), lower income (i.e., the lowest of five income quintiles, taking into account median age- and sex-adjusted income in Denmark) (HR= 1.16, 95% CI= 1.01,1.34), or lived alone (HR= 1.25, 95% CI= 1.13,1.38).³⁸ In a cross-sectional study of 770 individuals with CRC also in Denmark, loss of a life partner, either through divorce, separation, or death, was also associated with higher all-cause mortality (RR= 1.4, 95% CI= 1.1,1.8).⁹⁴

Community size or rurality, another social factor, has been linked to CRC outcomes.^{42,43,95} In a retrospective cohort study of 6163 individuals in Alberta with stage II-III CRC, rurality was assessed based on distance to the nearest tertiary cancer centre. Hines et al. reported that individuals from urban, rural, and suburban communities had median OS of 104, 94, and 83 months, respectively, or significant differences in OS ($p < 0.001$). Additionally, in direct comparisons of suburban and rural communities with urban communities, individuals from suburban (HR= 1.60, 95% CI= 1.24,2.08, $p < 0.001$) and rural Alberta (HR= 1.24, 95% CI= 1.02,1.50, $p = 0.042$) had worse OS than individuals from urban communities.

Social support has also been identified as a key social factor found to be strongly associated with cancer outcomes. A 2020 retrospective study of 1,431 postmenopausal women, who were all previously enrolled the large Women’s Health Initiative Trial in the United States, examined pre-diagnosis social support in relation to CRC outcomes.⁴⁴ Social support was measured using the overall score from nine items on the Medical Outcomes Survey. The survey looks at an individual’s perceived availability of specific types of support, including emotional support, affection, tangible support (i.e., “rides to appointments”), informational support, and positive interaction (i.e., “someone to have fun with”). Women were categorized as having low, moderate, and high perceived support. Those with low (HR= 1.52, 95% CI= 1.23,1.88, p< 0.001) and moderate (HR= 1.21, 95% CI= 0.98,1.50, p< 0.001) perceived social support before diagnosis had higher overall mortality, compared to those with high perceived social support (p< 0.001). The same trend was found with CRC-specific mortality, which was higher for those with low (HR= 1.42, 95% CI= 1.07,1.88, p= 0.007) and moderate (HR= 1.28, 95% CI= 0.96,1.70, p< 0.01) perceived social support, as compared to high perceived social support. Investigating each specific domain, lower overall mortality was associated with higher emotional support (HR= 0.94, 95% CI = 0.90,0.98), tangible support (HR= 0.95, 95% CI= 0.91,0.99), informational support (HR= 0.94, 95% CI= 0.90,0.98), and positive interaction (HR= 0.93, 95% CI= 0.89,0.97). No association was found for affection (HR= 0.99, 95% CI= 0.92,1.08). The same trend was found for CRC-specific mortality.⁴⁴ Lastly, furthering identifying the importance of emotional support, a 2018 retrospective observational study of 692 individuals with stage II-III CRC treated at BC Cancer by Hsu et al. reported that a lack of emotional support at diagnosis was associated with worse OS (HR= 4.36, p= 0.0003) and CRC-specific survival (HR= 1.92, p= 0.02).⁹⁶

The level of social integration is another aspect of social support that captures the relationships of individuals who have CRC with a spouse or intimate partner, club ties, religious ties, and other affiliations. In the retrospective observational of 1,431 postmenopausal women with CRC from the Women's Health Initiative Trial outlined above, high social integration was associated with lower overall mortality ($p= 0.02$), but not CRC-specific mortality ($p= 0.25$).⁴⁴ However, a 2018 prospective cohort study of 896 women with stage I-III CRC in the United States found that a higher social integration before diagnosis was related to lower overall (HR= 0.65, 95% CI= 0.46,0.92) and CRC-specific mortality (HR= 0.63, 95% CI= 0.38,1.06). Specifically, having more intimate ties to family and friends was associated with lower overall mortality (HR= 0.61, 95% CI= 0.42,0.88) and CRC-specific mortality (HR= 0.59, 95% CI= 0.34,1.03). Social integration and the presence of intimate ties were also assessed after diagnosis in the same study, with this analysis yielding similar results. High social integration after diagnosis, as compared to low levels of social integration, was associated with lower overall mortality (HR= 0.57, 95% CI= 0.37,0.88, $p= 0.03$) and CRC-specific mortality (HR= 0.53, 95% CI= 0.25,1.15, $p= 0.19$).⁹⁷

Other patient-reported factors that have an influence on CRC outcomes include physical factors (e.g., fatigue and sleep problems). In the retrospective observational study of 692 individuals with stage II-III CRC by Hsu et al., outlined previously, higher physical fatigue was associated with higher OS (HR= 1.99, $p< 0.0001$) and CRC-specific survival (HR= 1.63, $p= 0.03$).⁹⁶ Innominato et al. examined patient-reported sleep problems, as measured by the EORTC QLQ-C30 questionnaire, in a post-hoc analysis from a phase III trial on 361 chemo-naïve individuals with metastatic CRC. Individuals who reported any sleep problems in the EORTC QLQ-C30 (e.g., “during the past week, have you had trouble sleeping?”) were compared to those

who reported no sleep problems. Individuals with sleep problems at baseline were associated with a higher risk of overall mortality, (HR= 1.39, p= 0.0034), CRC progression (HR= 1.44, p= 0.0009), and a poorer treatment response (RR= 0.58, p= 0.011).⁴⁰

Finally, individuals' experiences with service quality at their cancer centre may also impact survival outcomes. This has been measured by self-report of perception of service quality, such as the ease of the registration process (e.g., operations and services) and a "whole person" approach to patient care (e.g., multidisciplinary patient care team). A 2013 prospective observational study of 702 individuals with CRC in the United States administered a questionnaire containing a series of service quality items, as well as one question to gauge how satisfied individuals with CRC were with their overall experience. Each item was measured on a seven-point Likert-type scale, and then dichotomized into two categories: 1) Completely satisfied (a score of seven); 2) Not completely satisfied (a score of one to six). Individuals who were satisfied overall had a median survival of 23.1 months, compared to individuals who were not completely satisfied overall with a median survival of 18.8 months (p= 0.04). Univariate Cox analysis found six service quality items that were significantly associated with OS, namely: 1) "Timeliness with which care was delivered" (p= 0.002); 2) "The ease with which care was delivered" (p= 0.004); 3) "Team explaining treatment options" (p= 0.04); 4) "Team calling you by name" (p= 0.04); 5) "Team's 'whole person' approach to patient care" (p= 0.04); and 6) "The treating medical oncologist" (p= 0.01).³⁹

2.2.4 Summary of social and psychological factors section

Social and psychological factors can be measured via numerous self-report surveys and questionnaires or derived from population-level data. Self-report measures can be targeted

towards the entirety of the population or certain subgroups within the population, with the PSSCAN-R being specifically designed to understand the needs of individuals with cancer. There are varying degrees of evidence regarding the influence of social and psychological factors on CRC outcomes. The most evidence is surrounding income, educational attainment, living alone, community size, and social support. The least evidence is regarding the informational and spiritual concerns listed on the CPC and larger PSSCAN-R. Finally, to the best of my knowledge, there is no evidence regarding these factors with respect to the relationship between body composition and CRC outcomes, resulting in this thesis project.

Chapter 3: Study Aims and Hypotheses

The specific aims of the project are as follows:

1. To examine the association between body composition measures of skeletal muscle at diagnosis and RFS at three years post-diagnosis in individuals with stage III colon cancer who received oxaliplatin-based treatment, considering the influence of age and sex.
 - a. Body composition measures of skeletal muscle include: 1) SMI; 2) SMD; 3) SMG; 4) Sarcopenia status.
2. To explore how various social and psychological factors influence the above relationships.
 - a. Social factors include: 1) Social isolation; 2) Neighborhood income; 3) Community size
 - b. Psychological factors include: 1) Patient-reported concerns (i.e., emotional concerns, informational concerns, practical concerns, spiritual struggles, social/family concerns, and physical concerns); 2) Symptoms of anxiety and depression.

The hypotheses are that:

1. Body composition measures of skeletal muscle at diagnosis will be associated with RFS at three years post-diagnosis in individuals with stage III colon cancer who received oxaliplatin-based treatment. Specifically, individuals with a lower SMI, SMD, or SMG, or individuals with sarcopenia will have poorer RFS (i.e., will experience relapse). Individuals with a higher SMI, SMD, or SMG, or individuals without sarcopenia, will have higher RFS (i.e., will not experience relapse).

2. Social (i.e., social isolation, neighborhood income after tax, and community size) and psychosocial (i.e., patient-reported concerns and symptoms of anxiety and depression) factors may influence the relationship between body composition measures of skeletal muscle at diagnosis and three-year RFS in individuals with stage III colon cancer who received oxaliplatin-based treatment.

Chapter 4: Methods

4.1 Study design

This was a retrospective cohort study and chart review. The BC Cancer Gastrointestinal Cancer Outcomes Unit (GICOU) created a cohort of individuals who were diagnosed with stage III colon cancer between 2010 and 2016 across all BC Cancer sites. After the cohort was created by the GICOU, data linkages were performed with additional data sources at BC Cancer, namely the Surveillance and Outcomes Unit (SOU), the Pharmacy database, the Outcomes and Surveillance Integration System (OaSIS), the Cancer Agency Information System (CAIS) (i.e., individuals' electronic medical records), and Radiology. Data that was obtained from each source and who retrieved the data is outlined in Table 4.1.

To link data from all sources, individuals' BC Cancer identification numbers (`agency_id`) and other variables were used. `Agency_id` was retained for the cohort created by the GICOU and used to request data from the SOU, Pharmacy database, and OaSIS. The candidate (HS) also used `agency_id` to retrieve information from CAIS and Radiology. Once data from all sources was linked, each individual was assigned a random study identification (ID) to de-identify data prior to analysis. Lastly, additional variables used to link data are as follows: 1) The SOU used site number (`site_num`) to identify the correct cancer diagnosis; 2) The dates of diagnosis and relapse (if applicable) were used to request the Pharmacy data associated with individuals' colon cancer diagnoses; 3) The diagnosis date was used to select both the appropriate measurements from CAIS and CT scans from Radiology.

Table 4.1 Outline of variables obtained from each data source

Data source	Variables obtained	How were the variables obtained?
GICOU	<ul style="list-style-type: none"> • Site_num (i.e., starting from one, site_num identifies the specific cancer diagnosis) • Diagnosis date • Age at diagnosis • Sex • BC Cancer location at admit • Cancer site (e.g., ascending colon, cecum) • Cancer stage (i.e., T and N staging variables) • Histology (e.g., adenocarcinoma) • RFS 	Compiled by the GICOU (RMD) after request submitted by the research team (HS, KC, and HL)
SOU	<ul style="list-style-type: none"> • Neighborhood income (as determined from individual postal code) • Community size (as determined from individual postal code) 	Via a DAR application
Pharmacy database	<ul style="list-style-type: none"> • Drugs in chemotherapy regimen 	Via a DAR application
OaSIS	<ul style="list-style-type: none"> • PSSCAN-R 	Via a DAR application
Radiology	<ul style="list-style-type: none"> • CT scan (from as close to diagnosis as possible) 	Retrieved by the candidate (HS)
CAIS	<ul style="list-style-type: none"> • Height (from as close to diagnosis as possible) • Weight (from as close to diagnosis as possible) 	Retrieved by the candidate (HS)

Abbreviations: CAIS, Cancer Agency Information System; CT, computer tomography; DAR, Data access request; GICOU, Gastrointestinal Cancer Outcomes Unit; N, nodes; OaSIS, Outcomes and Surveillance Integration System; PSSCAN-R, Psychosocial Screen for Cancer-Revised; site_num, site number; T, tumour; SOU, Surveillance Outcomes Unit.

4.2 Study participants

4.2.1 GICOU cohort

As outlined above, the GICOU created the initial cohort of individuals with colon cancer.

Specific inclusion criteria for this request included:

1. Individuals diagnosed with stage III colon cancer via pathology (i.e., classified during surgery) between 2010 and 2016
2. Individuals referred to BC Cancer with a new disease
3. Individuals who were BC residents at diagnosis

The exclusion criteria were:

1. Individuals with unknown pathological stage (i.e., missing T or N staging variables) or only an overall clinical stage assigned (i.e., via imaging and tests)
2. Individuals diagnosed with metastatic cancer
3. Individuals who received neoadjuvant treatment
4. Gastrointestinal stromal tumour and neuroendocrine tumour histology cases
5. Individuals with a previous or synchronous GI cancer (including all invasive and in-site GI cancers)
6. Individuals with a previous or synchronous invasive cancer of any site

Further, Pharmacy data was requested for the cohort created by the GICOU to provide one additional inclusion criterion, as follows: Individuals with stage III colon cancer who received oxaliplatin-based primary treatment (i.e., FOLFOX and CAPOX). Pharmacy data was sorted, and the above inclusion criterion implemented by the GICOU.

4.2.2 Final study cohort

The following additional criteria was employed by the candidate (HS) to create a final cohort for data analysis:

1. At least one baseline CT scan
2. Completed at least Part A or Part C of the PSSCAN-R measure
3. CT scans with an L3 image accessible via the Philips iSite Picture Archiving and Communication System (PACS) in Radiology
4. CT scans of sufficient enough quality as to allow for accurate measurements of the tissue area
5. No radiation therapy as to differentiate between cancers in the rectosigmoid junction (i.e., individuals with cancer in the rectosigmoid junction can be classified as having rectal or colon cancer, so these individuals were subsequently included in the GICOU cohort. However, if an individual received radiation therapy, this is more characteristic of rectal cancer.)

4.3 Ethical considerations

This study was performed in accordance with the ethical standards laid out in the 1964 Declaration of Helsinki. Ethical approval was obtained from The University of British Columbia – BC Cancer Research Ethics Board (H20-03499). There was no direct contact with individuals in the study cohort, so it was classified as a minimal risk application. Due to the retrospective and observational nature of this study, informed consent from participants was not required. All identifiable data was stored on the Provincial Health Services Authority (PHSA) network H drive, which is password-protected and encrypted. Once data sets were linked, agency_ids were

removed, and each individual was assigned a random study ID. De-identified data was subsequently transferred to the Clinical Exercise Physiology Lab drive at the University of British Columbia, also password-protected and encrypted, for analysis. The master list linking agency_id to random study ID was retained on the PHSA network H drive, for reference. Lastly, de-identified CT scans were also securely transferred to the Clinical Exercise Physiology Lab, for analysis in the automated software (Voronoi Health Analytics ABACS L3 Module).

4.4 Outcome measures and variables

4.4.1 Clinical and demographic variables

Demographic variables, including age at diagnosis, sex, and BC Cancer location were obtained from the GICOU. We obtained height and weight from the date closest to individuals' diagnoses and the CT scans being used by reviewing individuals' BC Cancer medical records. Height and weight are typically retrieved at the first oncologist consultation (i.e., after surgery, when assessing for adjuvant chemotherapy). However, the order of priority for the height and weight measurements retrieved is outlined below:

1. If height and/or weight available from before both surgery and chemotherapy (i.e., closest the individual's diagnosis date and the CT scan being used), retrieve these measurements.
2. If height and/or weight available from the initial oncologist consultation at BC Cancer (i.e., after surgery, when assessing for chemotherapy), retrieve these measurements.

We used height and weight to calculate BMI and aid in the calculation of SMI. If height and weight could not be abstracted, individuals were still included in the cohort but only reported for analyses where these measurements were not required (i.e., analyses involving SMD). Other clinical variables, namely, diagnosis date, site_num, cancer site (e.g., ascending colon, cecum),

cancer stage (T and N staging variables), and histology (e.g., adenocarcinoma) were obtained from the GICOU. Data regarding individuals' chemotherapy regimens was obtained from the Pharmacy database.

4.4.2 Body composition measures of skeletal muscle

We determined body composition for individuals in the cohort via abdominal CT scans, which we obtained from Radiology at BC Cancer. CT scans were acquired via the following workflow:

1. In the PACS, select the agency_id and appropriate CT scan to be used.
2. Within the CT scan, select the axial series to be anonymized for export.
3. Using all available series and planes (e.g., the sagittal plane, coronal plane, and other axial series), landmark the image corresponding to L3 in the selected axial series.
4. Label the scan with each individual's random cohort ID. All other identifying information will be removed at this stage.
5. Export the selected series to a third party application (i.e., GearView) to allow the Digital Imaging and Communications in Medicine (DICOM) file (i.e., the type of file containing the CT scan) to be transferred to the PHSA H drive.
6. Transfer the CT scan from the PHSA H drive to a Universal Serial Bus or portable hard drive for transport to the University of British Columbia Clinical Exercise Physiology Lab. Steps 1 to 5 will be performed onsite at BC Cancer.
7. Import the DICOM file to SliceOMatic V5.0 (Tomovision, Montreal, Canada) at the Clinical Exercise Physiology Lab for analysis.

For Step 1 above, we selected CT scans from as close to diagnosis as possible. Specific rules implemented surrounding when CT scans could be performed for inclusion in this study are outlined in Table 4.2. Next, further specifics in terms of the appropriate axial series to use in Step 2 are displayed in Table 4.3. Both the protocols in Table 4.2 and Table 4.3 were employed to ensure consistency among individuals and CT scans. Finally, to further explain Step 3, CT scans consist of multiple series. The automated software (Voronoi Health Analytics ABACS L3 Module) requires an axial L3 image to determine body composition parameters. The parameters surrounding the steps taken to landmark each L3 image are displayed in Table 4.4.

After landmarking L3, the candidate (HS) analyzed the L3 slice of CT scans using the automated software (Voronoi Health Analytics ABACS L3 Module). The HU parameters presented in Table 2.2 were used, to provide estimates of the cross-sectional areas of skeletal muscle, IMAT, VAT, and SAT. Our body composition variables of interest were as follows: 1) SMD; 2) SMI; 3) SMG; 4) Sarcopenia. SMD was derived from the automated software's (Voronoi Health Analytics ABACS L3 Module) estimate of the average HU of skeletal muscle from the L3 CT slice. SMD was a continuous variable. Next, we calculated SMI based on the skeletal muscle cross-sectional area in the L3 slice of the CT scan obtained from the automated software (Voronoi Health Analytics ABACS L3 Module), with the height obtained from individuals' BC Cancer medical records. SMI was a continuous variable. Thirdly, SMG was calculated as SMI multiplied by SMD and was a continuous variable. Finally, SMI, sex, and BMI were used to classify individuals according to the sarcopenia cut-off points outlined in Table 2.1 Sarcopenia was a dichotomous (i.e., yes/no) variable.

Table 4.2 Rules surrounding the timing of CT scans in individuals' cancer trajectories

If a scan available on the diagnosis date...	Select this scan
If scans only available from before and after the diagnosis date...	Select the scan from before <ul style="list-style-type: none">• This is assuming it is within six months of the diagnosis date.• If more than six months prior to the diagnosis date, the scan from after was used (to be closest to the diagnosis date).
If multiple scans from before the diagnosis date...	Select the scan taken latest or closest to the diagnosis date
If scans only available from after the diagnosis date, but there were multiple scans...	Select the scan take earliest or closest to the diagnosis date <ul style="list-style-type: none">• Ideally, the scan was from before any treatment (i.e., surgery or chemotherapy).• However, images from after surgery and before chemotherapy were acceptable in cases where this was the only scan available.• Scans from after both surgery and the start of chemotherapy were acceptable if within two weeks of the chemotherapy start date.

Abbreviations: CT, computerized tomography.

Table 4.3 Protocols determining the appropriate axial series to be used

If only 1 series with an L3 image...	Select this series
If scans with and without contrast-enhancement	Took the scan without contrast
If multiple series with an L3 image, due to the use of contrast (i.e., there are scans from immediately after the use of contrast, the arterial phase, the venous phase, etc.)...	Select the venous phase series <ul style="list-style-type: none"> • In other cases, only the venous phase is collected. Therefore, we always selected the venous phase (even when there were multiple options) to ensure consistency between images.
If there are scans labelled with “l30f” and “b30f”...	Select the “b30f” series <ul style="list-style-type: none"> • “b30f” is focused on resolving soft tissue (e.g., muscle)
If there are CT scans of different thicknesses	Select the thinner slice <ul style="list-style-type: none"> • Slice thickness is inversely related to resolution (i.e., took the higher resolution scans)
If there are regular and reconstructed series with an L3 image...	Use the regular image <ul style="list-style-type: none"> • In some cases, there were scans labelled with “recon2.” This refers to a different image reconstruction from the same CT scan. We used the non-reconstructed image for consistency.

Abbreviations: CT, computerized tomography; L3, third lumbar vertebra.

Table 4.4 Rules applied to landmark the L3 slice of the selected axial series

If a thoracic series (i.e., the CT scan involved the chest) was available...	Identify the first thoracic vertebra via a rib attachment, count from the first thoracic vertebra to the twelfth thoracic vertebra, then from the first lumbar vertebra to L3 <ul style="list-style-type: none"> • This is to allow for the most accurate identification of L3 (e.g., in case there are rudimentary ribs on the first lumbar vertebra or other anomalies)
If the first thoracic vertebra is not available (i.e., the scan begins at a lower point than that)...	Identify the twelfth thoracic vertebra by the last rib attachment, then count from the first lumbar vertebra to L3

Abbreviations: CT, computerized tomography; L3, third lumbar vertebra.

4.4.3 Social and psychological factors

The PSSCAN-R (a patient-reported outcome measure) data is stored in the OaSIS at BC Cancer. To be included in analyses, individuals must have completed at least one of Part A or C of the PSSCAN-R (i.e., blank responses in Part B are permitted, so this section was assumed to be complete for entries in which individuals completed at least one other PSSCAN-R section that require a response). If one section of various PSSCAN-R entries was incomplete, individuals were included in all analyses other than those requiring the specific variable(s) from that section. The PSSCAN-R entries from closest to individuals' diagnoses were used, including entries from up to six months following individuals' diagnoses dates. Variables related to individuals' postal codes at diagnosis (an objective outcome measure) were obtained from the SOU. Descriptions of social factors are below:

- Social isolation: This is Part A of the PSSCAN-R (Appendix A). The five-item social isolation checklist was used to create a dichotomous (i.e., yes/no) variable. Low social support was defined as individuals with one or more markers of social isolation and high social support was defined as individuals with no markers of social isolation.
- Neighbourhood income: This was determined by neighborhood income of listed residence, rather than individual income data, using individuals' postal codes and the Postal Code Conversion File Plus (PCCF+) Version 7D.⁹² Quintiles were formed based on other the incomes reported for neighbourhoods in the area (i.e., one or more adjacent municipalities). Neighbourhood income from both before and after tax was obtained. The SOU has access to this file, in order to perform analysis and supply specific variables of interest. Income was a categorical variable, with the categories as follows: 1) Lowest

quintile and medium-low quintile; 2) Middle quintile; 3) Medium-high and highest quintile.

- Community size: This was also determined using individuals' postal codes and the PCCF+ Version 7D. Community size was a categorical variable, with three categories as follows: 1) 1,500,000 individuals and upwards; 2) 10,000-1,500,000 individuals; 3) below 10,000 individuals.

Descriptions of psychological factors are below:

- Patient-reported concerns: The CPC is Part B of the PSSCAN-R. Each of the six CPC domains created a single dichotomous (i.e., yes/no) variable. For example, the presence of social/family concerns was defined as individuals with one or more checkmarks for any of the items in this domain and the absence of social/family concerns was defined as individuals without checkmarks under this domain. The same was done with the other five items.
- Symptoms of anxiety and depression: Part C of the PSSCAN-R is the 10-item depression and anxiety scale. Individuals received an overall anxiety score and a separate overall depression score. There were three possible categories for both anxiety and depression. For example, in regard to anxiety, the three categories were as follows: 1) No symptoms of anxiety (i.e., a score of zero to seven); 2) Subclinical symptoms of anxiety (i.e., a score of eight to 11); 3) Clinical symptoms of anxiety (i.e., a score of 11 to 20). Depression was scored in the same manner as anxiety.

4.4.4 Cancer outcome

RFS was obtained for three years post-diagnosis from the GICOU. This was a dichotomous (i.e., yes/no) outcome. RFS was calculated from diagnosis to the occurrence of the first type of relapse (i.e., local, regional, or distant). Individuals were not included in analyses if they experienced death due to other causes within three years of their diagnosis, developed a subsequent CRC within three years of their first colon cancer diagnosis, or did not have follow-up data available at three years.

4.5 Data management

A summary of all exposure variables and type of exposure variables used in the formal analysis are defined in Table 4.5. Covariables are displayed in Table 4.6, and the outcome variable is displayed in Table 4.7. If possible, all dichotomous variables were coded so that zero represented the absence of a trait (e.g., no relapse, no emotional concerns) and one represented presence of the trait (e.g., relapse, emotional concerns). The reference group for sex was female and the reference group for community size was communities with a population $\geq 1,500,000$. Neighbourhood income was coded using the lowest or medium-low quintiles for reference.

Table 4.5 Exposure variable definitions and types of variables

Variable name	Variable code	Variable type	Variable units or categorization
Skeletal muscle index	SMI	continuous	cm ² /m ²
Skeletal muscle density	SMD	continuous	HU (Hounsfield units)
Skeletal muscle gauge	SMG	continuous	cm ² xHU/m ² *
Sarcopenia status†	sarco	0	no
		1	yes

Legend: * In multivariable logistic regression modelling, one unit represented 100 cm²xHU/m² due to a potential large range in values after multiplying SMI by SMD, an approach that has previously been employed⁹⁸; † Sarcopenia was defined by using sex- and BMI-specific SMI cut-off points previously established by Caan et al.⁶¹

Table 4.6 Covariable definitions and types of variables

	Variable name	Variable code	Variable type	Variable units or categorization
Demographic covariables	Age	age	continuous	years
	Sex	sex	0	female
			1	male
Social covariables	Social isolation (Part A of PSSCAN-R)	iso	0	no
			1	yes, if a checkmark to any of the following questions: <ol style="list-style-type: none"> 1. Do you live alone? 2. When needed, can you count on anyone to help with daily tasks such as grocery shopping, cooking, giving you a ride? 3. Do you have regular contact with friends or relatives? 4. Have you lost your life partner in the last few years? 5. Can you count on anyone for emotional support?
	Community size (from PCCF+ Version 7D)	Csize	0	1,500,000 individuals and upwards
			1	10,000-1,500,000 individuals
			2	Below 10,000 individuals
	Neighbourhood income quintile (from PCCF+ Version 7D)	QABTIPPE (before tax) or QAATIPPE (after tax)	0	Lowest and medium-low quintiles
			1	Middle quintile
			2	Medium-high and highest quintiles

	Variable name	Variable code	Variable type	Variable units or categorization
Psychological covariables	Emotional concerns (from CPC)	CPC_emotion	0	no
			1	yes, if any of the following items a concern in the week prior to PSSCAN-R completion: <ul style="list-style-type: none"> • Fear/worries • Sadness • Frustration/anger • Changes in appearance • Intimacy/sexuality • Coping • Change in sense of self
	Informational concerns (from CPC)	CPC_info	0	
			1	yes, if any of the following items a concern in the week prior to PSSCAN-R completion: <ul style="list-style-type: none"> • Understanding my illness/treatment • Talking with the health care team • Making treatment decisions • Knowing about available resources • Quitting smoking
	Physical concerns (from CPC)	CPC_physical	0	
			1	yes, if any of the following items a concern in the week prior to PSSCAN-R completion: <ul style="list-style-type: none"> • Concentration/Memory • Sleep • Weight

	Variable name	Variable code	Variable type	Variable units or categorization
Psychological covariables	Social/family concerns (from CPC)	CPC_social	0	
			1	yes, if any of the following items a concern in the week prior to PSSCAN-R completion: <ul style="list-style-type: none"> • Feeling a burden to others • Worry about family/friends • Feeling alone • Relationship difficulties
	Spiritual struggles (from CPC)	CPC_spiritual	0	
			1	yes, if any of the following items a concern in the week prior to PSSCAN-R completion: <ul style="list-style-type: none"> • Meaning/Purpose of life • Faith
	Practical concerns (from CPC)	CPC_practical	0	
			1	yes, if any of the following items a concern in the week prior to PSSCAN-R completion: <ul style="list-style-type: none"> • Work/School • Finances • Getting to & from appointments • Accommodation • Child/family/elder care
	Symptoms of anxiety (Part C of PSSCAN-R)	anx	0	no symptoms of anxiety, if a score of 0-7
			1	subclinical symptoms of anxiety, if a score of 8-11
			2	clinical symptoms of anxiety, if a score of 11-20

	Variable name	Variable code	Variable type	Variable units or categorization
Psychological covariables	Symptoms of depression (Part C of PSSCAN-R)	dep	0	no symptoms of depression, if a score of 0-7
			1	subclinical symptoms of depression, if a score of 8-11)
			2	clinical symptoms of depression, if a score of 11-20

Abbreviations: CPC, Canadian Problem Checklist; PSSCAN-R, Psychosocial Screen for Cancer-Revised.

Table 4.7 Outcome variable definition and type of variable

Variable name	Variable code	Variable type	Variable units or categorization
Relapse-free survival	RFS	0	experienced RFS (i.e., no relapse)
		1	did not experience RFS (i.e., had a relapse within 3 years of diagnosis)

4.6 Data analysis

RStudio (RStudio Team (2019). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL <http://www.rstudio.com/>) was used for data analysis. The distribution of exposure variables (i.e., SMI, SMD, SMG, and sarcopenia status), covariables (i.e., age, sex, social, and psychological variables), and the outcome variable (i.e., RFS), as well as the relationships within covariables (to assess for possible collinearity) and between exposure variables, covariables, and the outcome variable were visualized using histograms (distribution of continuous variables), bar graphs (distribution and relationships between dichotomous and/or categorical variables), and scatter plots, box plots, and density plots (relationships between continuous and dichotomous or categorical variables). Individual and baseline characteristics were described using mean (standard deviation (SD)) and median (minimum and maximum values) for continuous variables as applicable (based on distribution), and number (%) for categorical and dichotomous variables. *Post hoc* Independent t-tests and Fisher's exact tests were conducted to examine potential selection bias caused by excluding individuals who were missing data (i.e., no PSSCAN-R entry, missing RFS data, or no CT scan of sufficient quality/in relevant time period) for age (i.e., a continuous variable) and sex (i.e., a dichotomous variable), respectively.

The association between each of the four body composition measures of skeletal muscle (i.e., SMI, SMD, SMG, and sarcopenia status) and RFS, accounting for the influence of age at diagnosis and sex, was assessed using unique multivariable logistic regression models (i.e., the primary models). For each model, a backwards selection process, starting with full models (i.e., body composition variable, age, sex, and RFS) and sequentially eliminating covariables (age and sex) with non-significant p-values, was used to identify the most parsimonious model.

Confounding was assessed by observing if the size and/or direction of the regression coefficient of each body composition measure of skeletal muscle changed upon removal of the covariable. If confounding was detected, the variable was included in the final model regardless of significance. Statistical significance was set at $p \leq 0.05$.

Candidate social and psychological covariables for inclusion in the exploratory multivariable logistic regression models were selected based on past evidence that these covariables influence skeletal muscle body composition or RFS and/or univariable associations (linear or logistic regression as appropriate, with $p \leq 0.50$) between covariables that demonstrated a potential visual relationship with either the body composition measures of skeletal muscle or RFS. Age and sex were selected a priori based on substantive evidence from previous research that these covariables influence either the body composition measures of skeletal muscle or RFS.^{32,33,99} No previous research assessing the influence of social and psychological covariables on body composition measures of skeletal muscle was identified. A backwards selection process, as described above, was conducted to create final exploratory models for each body composition measure of skeletal muscle.

Model diagnostics were checked for all of the multivariable logistic regression models. The assumptions of logistic regression are¹⁰⁰:

1. Independence of observations: The observations should not be related to each other in any way.
2. Multicollinearity among independent variables: In multivariate models (i.e., not needed in univariate models), the independent variables should not be highly correlated with one another.

3. Influential observations: In models with one or more continuous variables present, there should be no influential observations (i.e., when removed, the observation would largely change the predicted regression coefficients).
4. Linearity: In models with one or more continuous variables present, there should be a linear association between the independent variable and the logit of the dependent variable.

The corresponding tests used to check these assumptions are outlined in Appendix E.

Chapter 5: Results

5.1 Study cohort numbers

Between 2010 and 2016, 1125 individuals met the GICOU eligibility criteria. After additional exclusions by the candidate (HS), 376 individuals remained. The progression of individual numbers is displayed in Appendix C, from the preliminary GICOU cohort to the final number of individuals included in all analyses.

5.2 Variable visualization

Visualization of variable distribution and relationships is shown in Appendix D. SMI, SMD, and age (i.e., the continuous outcomes included logistic regression analyses) all deviated from normality. Of note, one individual was included in visualization in error at this stage (i.e., did not receive oxaliplatin-based primary treatment/received oxaliplatin-based treatment after relapse) but then was excluded before calculation of cohort characteristics and the development of logistic regression models.

Based on variable distribution, a decision was made to recode two variables. First, community size was recategorized from three to two groups: 1,500,000 individuals and upwards; below 1,500,000 individuals due to small number of individuals in living in communities below 10,000 individuals. Second, the entirety of the CPC (i.e., measure of patient-reported concerns) was dichotomized to two groups: no concerns; one or more concerns on any section of the CPC based on potential collinearity problem between domains. The modified variables were visualized as previously described.

5.3 Individual characteristics

Individual demographic and medical characteristics are presented in Table 5.1. The number of individuals in each row varies to represent the total number of individuals with available data. Individuals were a median age of 62.0 years and 51.1% were male. There was no difference between individuals who were included in the study analyses and individuals who were excluded due to missing data (i.e. no PSSCAN-R entry, missing RFS data, or no CT scan of sufficient quality/in a relevant time period) for age ($p= 0.60$) or sex ($p= 0.25$). The median BMI was 26.1 kg/m^2 . The highest number of individuals were admitted at diagnosis to the Vancouver location of BC Cancer (33.5%), followed by the Abbotsford (17.8%) and Vancouver Island (17.3%) locations. The greatest number of individuals presented with cancer of the sigmoid colon (26.4%), and the majority were classified as having adenocarcinoma (98.4%). The most common T and N staging variables were T3 (54.0%) and N1a (29.5%), and the majority of individuals received FOLFOX chemotherapy (64.0%).

Baseline body composition variables are displayed in Table 5.2. The median times from diagnosis to CT scan acquisition, CT scan acquisition to the collection of height/weight, and CT scan acquisition to the start of chemotherapy were three days, 56 days, and 77 days, respectively. Hence, the primary order of events was: 1) diagnosis; 2) CT scan acquisition; 3) collection of height/weight (i.e., oncologist consultation after surgery and before chemotherapy); 4) start of chemotherapy. The median SMI, SMD, and SMG values were $46.1 \text{ cm}^2/\text{m}^2$, 38.9 HU, and $1747.9 \text{ cm}^2 \times \text{HU}/\text{m}^2$, respectively, and 44.0% of individuals had sarcopenia. Of note, our research team identified CT scans with no ribs on the twelfth thoracic vertebra, ribs on the first lumbar vertebra, sacralization (i.e., the last lumbar vertebra fused with the sacrum), six lumbar vertebra,

and other less frequent anomalies. These CT scans were still retrieved and subsequently analyzed with assistance of the project Radiologist (CM) for L3 landmarking.

Baseline social and psychological variables are presented in Table 5.3. The median time from diagnosis to PSSCAN-R screening was 65 days. The prevalence of indicating any patient-reported concern was between 13.1% corresponding to spiritual struggles and 66.2% representing informational concerns. Most individuals did not have symptoms of anxiety (6.3%) or depression (3.3%). Only 22.0% of individuals had one or more markers of social isolation. The majority of individuals were from communities of 1,500,000 individuals and upwards (57.0%), and the greatest number of individuals were from the medium-high- or highest-income quintile neighborhoods after tax (44.7%).

Table 5.1 Demographic and medical characteristics of the study cohort

Characteristic	Total	No relapse	Relapse
	n=376	n=280	n=96
	median (min,max)	median (min,max)	median (min,max)
Age at diagnosis (years)	62.0 (24,84)	62.0 (32,84)	62.0 (24,83)
BMI (kg/m ²)	26.1 (17.1,54.2)	26.1 (17.1,54.2)	26.0 (18.8,44.8)
	n (%)	n (%)	n (%)
Sex			
Female	184 (48.9)	136 (48.6)	48 (50.0)
Male	192 (51.1)	144 (51.4)	48 (50.0)
Location at admit			
Vancouver	126 (33.5)	90 (32.1)	36 (37.5)
Vancouver Island	65 (17.3)	46 (16.4)	19 (19.8)
Fraser Valley	79 (21.1)	64 (22.9)	15 (15.6)
Kamloops	1 (0.3)	0	1 (1.0)
Southern Interior	25 (6.7)	19 (6.8)	6 (6.3)
Abbotsford Centre	67 (17.8)	51 (18.2)	16 (16.7)
North	11 (2.9)	8 (2.9)	3 (3.1)
Penticton	1 (0.3)	1 (0.4)	0
Nanaimo	1 (0.3)	1 (0.4)	0
Cancer site			
Cecum	67 (17.8)	49 (17.5)	18 (18.8)
Ascending colon	50 (13.3)	32 (11.4)	18 (18.8)
Hepatic flexure	15 (4.0)	8 (2.9)	7 (7.3)
Transverse colon	24 (6.4)	21 (7.5)	3 (3.1)
Splenic flexure	14 (3.7)	12 (4.3)	2 (2.1)
Descending colon	23 (6.1)	18 (6.4)	5 (5.2)
Sigmoid colon	137 (36.4)	105 (37.5)	32 (33.3)
Rectosigmoid junction	44 (11.7)	33 (11.8)	11 (11.5)
Colon, not otherwise specified	1 (0.3)	1 (0.4)	0
Colon, overlapping lesion	1 (0.3)	1 (0.4)	0
Histology			
Adenocarcinoma	370 (98.4)	277 (98.9)	93 (96.9)
Medullary carcinoma, not otherwise specified	1 (0.3)	1 (0.4)	0
Signet ring cell carcinoma	5 (1.3)	2 (0.7)	3 (3.1)

Characteristic	Total	No relapse	Relapse
	n=376	n=280	n=96
	n (%)	n (%)	n (%)
T staging variable			
1	21 (5.6)	21 (7.5)	0
2	37 (9.8)	36 (12.9)	1 (1.0)
3	224 (59.6)	176 (62.9)	48 (50.0)
4a	82 (21.8)	41 (14.6)	41 (42.7)
4b	12 (3.2)	6 (2.1)	6 (6.3)
N staging variable			
1a	111 (29.5)	98 (35.0)	13 (13.5)
1b	107 (28.5)	81 (28.9)	26 (27.1)
1c	17 (4.5)	13 (4.6)	4 (4.2)
2a	83 (22.1)	56 (20.0)	27 (28.1)
2b	58 (15.4)	32 (11.4)	26 (27.1)
Chemotherapy regimen			
FOLFOX	229 (64.0)	172 (61.4)	57 (59.4)
CAPOX	126 (35.2)	92 (32.9)	34 (35.4)
Mixed or Indeterminate*	21 (5.9)	16 (5.7)	5 (5.2)

Abbreviations: BMI, body mass index; max, maximum; min, minimum; N, nodes; n, sample size; T, tumour.

Legend: * Indicating patients that switched chemotherapy regimens (e.g., due to adverse side effects) or received multiple combinations of drugs due to extenuating circumstances.

Table 5.2 Baseline body composition variables as measured by L3 abdominal CT slice

Variable	Total n=376	No relapse n=280	Relapse n=96
	mean (SD) median (min,max)	mean (SD) median (min,max)	mean (SD) median (min,max)
Time from diagnosis date to CT scan (days)*	3.0 (-133**,190)	7.0 (-133,190)	0 (-98,119)
Time from CT scan to chemotherapy start date (days)	77.0 (-12,251)	78.0 (-4,251)	74.0 (-12,190)
Time from CT scan to BMI measurements (days)	56.0 (-135,312)†	57.0 (-135,224)††	51.0 (-13,312)‡
SMI (cm ² /m ²)	46.1 (18.9,75.3)†	46.1 (18.9,75.3)††	45.9 (30.2,70.1)‡
SMD (HU)	38.9 (7.4,64.1)	39.0 (7.4,64.1)	37.4 (12.0,58.8)
SMG (cm ² xHU/m ²)	1804.5 (609.3)†	1837.8 (588.4)††	1709.23 (660.39)‡
	n (%)	n (%)	n (%)
Sarcopenia	124 (44.0)†	84 (40.2)††	40 (54.8)‡

Abbreviations: CT, computer tomography; max, maximum; min, minimum; n, sample size; SD, standard deviation; SMD, skeletal muscle density; SMG, skeletal muscle gauge; SMI, skeletal muscle index.

Legend: * Variables related to time were not visualized. However, both median and mean were calculated and all time-related variables appeared to be skewed; ** Some CT scans were conducted before individuals' diagnoses dates; † n= 282; †† n= 209; ‡ n= 73.

Table 5.3 Baseline social and psychological outcome measures

Variable	Total n=358	No relapse n=265	Relapse n=93
	median (min, max)	median (min,max)	median (min,max)
Time from diagnosis date to PSSCAN-R screening (days)	65.0 (7, 172)	68.0 (7, 172)	54.0 (16, 165)
	n (%)	n (%)	n (%)
Social isolation	76 (22.0)*	47 (18.5)†	29 (31.9)‡
Concerns from the CPC			
Emotional concerns	224 (62.6)	166 (62.6)	58 (62.4)
Informational concerns	237 (66.2)	176 (66.4)	61 (65.6)
Physical concerns	153 (42.7)	114 (43.0)	39 (41.9)
Social/family concerns	130 (36.3)	97 (36.6)	33 (35.5)
Spiritual struggles	47 (13.1)	33 (12.5)	14 (15.1)
Practical concerns	120 (33.5)	88 (33.2)	32 (34.4)
Symptoms of anxiety	21 (6.3)**	16 (6.4)††	5 (5.8)‡‡
Symptoms of depression	11 (3.3)**	7 (2.8)††	4 (4.7)‡‡
Community size			
1,500,000 individuals and upwards	204 (57.0)	156 (58.9)	48 (51.6)
10,000 to 1,499,999 individuals	127 (35.47)	92 (34.72)	35 (37.63)
Below 10,000 individuals	27 (7.54)	17 (6.42)	10 (10.75)
Neighbourhood income quintile after tax			
Lowest and medium-low quintiles	129 (36.0)	93 (35.1)	36 (38.7)
Middle quintile	69 (19.3)	49 (18.5)	20 (21.5)
Medium-high and highest quintiles	160 (44.7)	123 (46.4)	37 (39.8)

Abbreviations: CPC, Canadian Problem Checklist; max, maximum; min, minimum; n, sample size; PSSCAN-R, Psychosocial Screen for Cancer-Revised;

Legend: * n= 345; ** n= 336; † n= 254; †† n= 250; ‡ n= 91; ‡‡ n= 86.

5.4 Logistic regression modelling

5.4.1 Multivariable logistic regression models for body composition measures of skeletal muscle and RFS

After the backwards selection process (Appendix D), there was no evidence of an association between SMI and RFS (OR= 1.00, 95% CI= 0.97,1.02, p= 0.78) (Table 5.4). The odds of having a relapse were lower for each one unit ($100 \text{ cm}^2 \times \text{HU}/\text{m}^2$) increase in SMG (i.e., a better SMG) (OR=0.93, 95% CI= 0.88,0.98, p= 0.01). This association was influenced by sex; for any given SMG value, males had 1.97 times greater odds of having a relapse than females (OR= 1.97, 95% CI=1.03,3.81, p= 0.04) (Table 5.4). Age was left in the model due to potential confounding (Appendix D). For each one unit (one HU) increase in SMD (i.e., a better SMD), the odds of having a relapse were lower (OR= 0.97, 95% CI= 0.95,0.997, p= 0.01) (Table 5.4). Of note, the 95% CIs for both SMG and SMD were only marginally less than one (i.e., marginally significant). Individuals with sarcopenia had 1.80 times greater odds of having a relapse than individuals without sarcopenia (OR= 1.80, 95% CI= 1.06,3.10, p= 0.03) (Table 5.4). Neither of the associations between SMD and RFS or sarcopenia and RFS were influenced by age at diagnosis or sex, so these covariables were removed from the final models. For example, for any given SMD value, males and females had largely equivalent odds of having a relapse. Assumptions were checked and met for all models (Appendix E) and individual numbers included in each analysis can be found in Appendix B.

Table 5.4 The odds of RFS for various body composition measures of skeletal muscle, considering the influence of age and sex

Model	SMI, SMD, SMG, or sarcopenia		Age at diagnosis		Male (v. female)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
SMI and RFS	1.00 (0.97,1.02)	0.78	-	-	-	-
SMD and RFS	0.97 (0.95,0.997)*	0.03	-	-	-	-
SMG† and RFS	0.93 (0.88,0.98)*	0.01	0.98 (0.96,1.01)	0.23	1.97 (1.03,3.81)*	0.04
Sarcopenia†† and RFS	1.80 (1.06,3.10)*	0.03	-	-	-	-

Abbreviations: CI, confidence interval; OR, odds ratio; SMD, skeletal muscle density; SMG, skeletal muscle gauge, SMI, skeletal muscle index; v, versus.

Legend: * $p \leq 0.05$; † One unit represented $100 \text{ cm}^2 \times \text{HbU/m}^2$; †† No sarcopenia was used as the reference (not applicable for SMI, SMD, and SMG, which were continuous exposures).

5.4.2 Univariable models to investigate covariables for exploratory multivariable logistic regression models

Based on variable visualization, univariable associations were created with the candidate covariables, including: 1) community size (dichotomous after modification); 2) neighbourhood income after tax (three categories); 3) social isolation (dichotomous); 4) patient-reported concerns (dichotomous after modification). Three social covariables, community size, neighbourhood income after tax, and social isolation subsequently met the p-value threshold ($p \leq 0.50$) for inclusion in the exploratory multivariate logistic regression models created for each body composition parameter (Table 5.5 and Table 5.6). This was supported by evidence from previous research, in which the social and psychological factors most reported to influence CRC outcomes are community size, income, social isolation (often captured by means of living alone, regular contact with family and friends, etc.), and educational attainment (not available in this study cohort).^{38,42,50} Some patient-reported concerns (e.g., informational concerns) are shown to

be associated with CRC outcomes in other research, but there is less evidence regarding these factors.³⁹

Table 5.5 Univariable associations between RFS and community size, neighborhood income after tax, patient-reported concerns, or social isolation

	Community size of <1,500,000 (v. ≥1,500,000)		Middle income quintile after tax (v. medium-low and lowest quintile)		Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)		Social isolation (v. no isolation)		Patient-reported concerns (v. no concerns)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
RFS	1.34 (0.83,2.19)*	0.22	1.05 (0.55,2.00)	0.87	0.78 (0.46,1.33)*	0.35	2.06 (1.19,3.54)*	0.01	1.15 (0.62,2.23)*	0.67

Abbreviations: CI, confidence interval; OR, odds ratio; RFS, relapse-free survival; v, versus.

Legend: * $p \leq 0.50$.

Table 5.6 Univariable associations between body composition measures of skeletal muscle and community size or neighbourhood income after tax

	Community size of <1,500,000 (v. ≥1,500,000)		Middle income quintile after tax (v. medium-low and lowest quintile)		Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
SMI	-	-	1.64* (-1.61,4.89)	0.32	-2.81* (-5.42,-0.19)	0.04
SMD	-3.35* (-5.34,-1.37)	< 0.01	-	-	-	-
SMG†	-2.01* (-3.46,-0.55)	0.01	0.53 (-1.51,2.58)	0.61	-0.55 (-2.19,1.10)	0.52

Abbreviations: β , beta value/regression coefficient; CI, confidence interval; OR, odds ratio; SMD, skeletal muscle density; SMG, skeletal muscle gauge; SMI, skeletal muscle index; v, versus.

Legend: * $p \leq 0.50$; † One unit represented 100 cm²xHU/m².

Note: All univariable associations (regardless of significance) are presented. Dashes represent those pairs of variables for which univariable regression analysis was not conducted (i.e., no visual evidence of a relationship).

5.4.3 Multivariable logistic regression models to explore the influence of social and psychological factors

There was no evidence that community size or neighbourhood income after tax influenced the relationships between body composition measures of skeletal muscle and RFS. Therefore, these variables were removed from all of the exploratory multivariable logistic regression models represented in Table 5.7. There was no evidence of an association between SMI and RFS after adding social covariables (in addition to age and sex) (Table 5.7) and performing the backwards selection process (OR= 1.00, 95% CI= 0.97,1.03, p= 0.87) (Appendix D). The odds of having a relapse were lower for each one unit (one HU) increase in SMD (i.e., a better SMD) (OR= 0.97, 95% CI= 0.95,0.997, p= 0.03), an association which was influenced by social isolation; for any given SMD value, individuals with one or more markers of social isolation had approximately two times greater odds of having a relapse than individuals without markers of social isolation (OR= 2.04, 95% CI= 1.17,3.52, p= 0.01) (Table 5.7).

For each one unit ($100 \text{ cm}^2 \times \text{HU}/\text{m}^2$) increase in SMG (i.e., a better SMG), the odds of having a relapse were lower (OR= 0.93, 95% CI= 0.87,0.99, p= 0.02) (Table 5.7). This association was influenced by both social isolation and sex. For any given SMG value, males or individuals with one or more markers of social isolation had approximately two times greater odds of having a relapse than female individuals (OR= 2.02, 95% CI= 1.02,4.06, p= 0.04) or individuals without markers of social isolation (OR= 2.09, 95% CI= 1.11,3.89, p= 0.02), respectively (Table 5.7). Age was left in the model as a potential confounder (Appendix D).

Individuals with sarcopenia had 1.81 times greater odds of having a relapse than individuals without sarcopenia (OR= 1.81, 95% CI= 1.03,3.20, p= 0.04) (Table 5.7). This association was also modified by social isolation; for any given sarcopenia status (i.e., yes/no),

individuals with one or more markers of social isolation had almost two times greater odds of having a relapse than individuals without markers of social isolation (OR= 1.98, 95% CI= 1.06,3.76, p= 0.04) (Table 5.7). All model assumptions were met (Appendix E) and the number of individuals in each analysis can be found in Appendix B.

Table 5.7 The odds of RFS for various body composition measures of skeletal muscle, considering the additional influence of social factors

Model	SMI, SMD, SMG [†] , or Sarcopenia ^{††}		Age at diagnosis		Sex (v. male)		Social isolation (v. no markers)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
SMI and RFS	1.00 (0.97,1.03)	0.87	-	-	-	-	2.01 (1.08,3.71)*	0.03
SMD and RFS	0.97 (0.94,0.998)*	0.03	-	-	-	-	2.04 (1.17,3.52)*	0.01
SMG and RFS	0.93 (0.87,0.99)*	0.02	0.98 (0.95, 1.01)	0.14	2.02 (1.02, 4.06)*	0.04	2.09 (1.11,3.89)*	0.02
Sarcopenia and RFS	1.82 (1.03,3.20)*	0.04	-	-	-	-	1.98 (1.06,3.67)*	0.03

Abbreviations: CI, confidence interval; OR, odds ratio; SMD, skeletal muscle density; SMG, skeletal muscle gauge, SMI, skeletal muscle index; v, versus.

Legend: * $p \leq 0.05$; [†] One unit represented 100 cm²xHU/m²; ^{††} No sarcopenia was used as the reference (not applicable for SMI, SMD, and SMG, which were continuous exposures).

Chapter 6: Discussion

The findings from this retrospective cohort study and chart review contribute to the growing body of knowledge on the prognostic impact of body composition measures of skeletal muscle in individuals with colon cancer, specifically those that influence RFS. SMD, SMG, and sarcopenia at diagnosis were all associated with RFS at three years post-diagnosis. The findings also suggest that social isolation at diagnosis may influence the relationship between body composition measures of skeletal muscle and RFS, while community size and neighbourhood income were not found to be influential. These findings are essential considerations for the development of further studies and eventual targeted supportive care and rehabilitation interventions to improve colon cancer outcomes.

6.1 The association between body composition measures of skeletal muscle and RFS, considering the influence of age and sex

The primary objective of the study was to examine the relationship between skeletal muscle and RFS at three years post-diagnosis in individuals with stage III colon cancer. In this thesis project, there were 376 individuals with SMD available and 282 with height and weight available, allowing analyses involving SMI, SMG, and sarcopenia to be conducted. Two continuous variables, namely SMD and SMG, displayed evidence of an association with RFS. The odds of having a relapse were lower for each one unit increase in both SMD (for one HU, OR=0.97, 95% CI= 0.95,0.997, p= 0.03) and SMG (for 100 cm²xHU/m², OR= 0.93, 95% CI= 0.88,0.98, p= 0.01), in the final (i.e., most parsimonious) models developed. While these findings suggest that the impact of SMD and SMG on the odds of relapse may be small, the large range in values (i.e., the range of SMG values was 295.9 cm²xHU/m² to 3546.5 cm²xHU/m²) suggest that

even a minimal change may be meaningful and could be suggestive of a protective effect of increasing SMD and SMG values. However, with 95% CIs only marginally lower than one (i.e., the marker of a significant association), the associations found may be a consequence of the specific individuals in this study cohort and should be investigated in future studies involving body composition and cancer outcomes.

SMD is a measure of fat infiltration in muscle and is a proxy for muscle quality. The results of this thesis project (OR=0.97, 95% CI= 0.95,0.997, p= 0.03) are consistent with previous research by van Baar et al. and Kroenke et al., in which individuals with early-stage (stage I-III) CRC who had lower SMD values at diagnosis (measured at the L3 level) also had poorer overall and CRC-specific mortality compared to those with higher SMD's.^{69,101} van Baar et al. reported that the risk of overall mortality was decreased by a factor of 0.02 with a one unit (one HU) increase in SMD (HR= 0.98, 95% CI= 0.96,0.99).⁶⁹ Both van Baar et al. and Kroenke et al. also investigated poor muscle quality at diagnosis using SMD cut-off points, termed myosteatorsis. Using sex- and BMI-specific SMD cut-off points, van Baar et al. reported those individuals categorized with a "low" SMD had poorer DFS than individuals with "normal" SMD (HR= 1.68, 95% CI= 1.14,2.47). These results related to DFS are contrary to a recent SR by Lee et al.³⁷ Lee et al. included between five and 12 studies (dependent on the outcome of interest being available) that calculated myosteatorsis at the L3 level (except one study that used L4 and the psoas muscle) for individuals with stage I-IV CRC using sex- and BMI-specific SMD cut-off points proposed by Martin et al.¹⁰² (except one study that used only sex-specific SMD cut-off points).³⁷ Lee et al. displayed that individual's with myosteatorsis had a significant increase in overall (OR= 1.55, 95% CI= 1.23,1.96, p< 0.00001 in 10 studies) and CRC-specific mortality (OR= 1.69, 95% CI= 1.43,2.00, p< 0.00001 in five studies). However, Lee et al. reported no

effect of myosteatosis on DFS (HR= 1.00, 95% CI= 0.95,1.05, p= 0.88) in seven studies, not inclusive of the van Baar et al. study.³⁷ Two potential rational for this contradiction include: 1) Myosteatosis may be an indication of an individuals' fragility but not the aggressiveness of their cancer³⁷; 2) The cut-off points derived by Martin et al.¹⁰² are inappropriate for use for individuals with early stage CRC due to their creation in a mixed cancer population and in individuals with poor prognoses.⁶⁹ This supports the use of appropriate cut-off points derived for the specific population in study,^{69,101} or the investigation of SMD as a continuous outcome in the absence of such cut-off points (as done in this thesis project). This thesis project contributes to the body of literature regarding the influence of muscle quality in individuals with colon cancer by suggesting that poorer SMD may be indicative of lower RFS (a comparable outcome to DFS).

SMG is a newer variable that is now gaining attention as another way to examine the impact of body composition on clinical outcomes. It is viewed as a proxy of skeletal muscle function. SMG is associated with physical function impairments and limitations in daily living in older adults with cancer. In a sample of 185 older adults with mixed cancer types, higher SMG values were associated with significant decreases in risk of impairment. Impairment was characterized as prolonged time to complete Timed-Up and Go test or impaired independent activities of daily living such as difficulty climbing one flight of stairs, walking one block, and bending, kneeling, or stooping.⁵⁸ For each 100 cm²xHU/m² increase in SMG, an individual's risk of having a prolonged TUG decreased by 8% after controlling for sex (RR= 0.92, 95% CI= 0.88,0.96, p< 0.01). A limited number of studies to date have examined the association between SMG and longer-term cancer outcomes, with only one study conducted in individuals with colon cancer.^{72,103,104} Park et al. derived optimal sex-specific SMG cut-off points (measured at the L3 level) in individuals with stage I-IV colon cancer and subsequently identified SMG at diagnosis

as an independent prognostic factor of OS (OR= 1.79, 95% CI= 1.07,3.00, p= 0.025).⁷² Although further research in larger cohorts is needed, the results of this thesis project (for 100 cm²xHU/m², OR= 0.93, 95% CI= 0.88,0.98, p= 0.01) contribute to the emerging field of knowledge regarding the influence of SMG on survival outcomes in individuals with colon cancer. Additionally, to the best of my knowledge, the influence of SMG on RFS specifically (i.e., versus OS) has not been previously reported.

SMI is a measure of muscle mass and is a proxy for muscle quantity. The results from this thesis study did not suggest an association between SMI and RFS (OR= 1.00, 95% CI= 0.97,1.02, p= 0.78) in individuals with stage III colon cancer. However, when the study cohort was examined using a dichotomous variable for sarcopenia, defined via sex- and BMI-specific SMI cut-off points established by Caan et al.,⁴⁹ 44% of individuals were categorized as being sarcopenic at diagnosis. This range is consistent with the findings of Caan et al., who reported that 42% of individuals in their cohort of 3,262 individuals with early-stage (stage I-III) CRC were sarcopenic at baseline using the same sex- and BMI-specific SMI cut-off points employed in this study cohort.⁴⁹ In this thesis project, individuals categorized as sarcopenic at diagnosis had almost twice the odds of having a relapse (OR= 1.80, 95% CI= 1.06,3.10, p= 0.03) than individuals who were not categorized as sarcopenic. These results are consistent with a recent SR by Sun et al. of 12 studies including 5337 individuals, where individuals who were sarcopenic at baseline (as defined by SMI at the L3 level) had poorer DFS (HR= 1.70, 95% CI= 1.24,2.32, p< 0.01),²⁴ as well as the cohort study developed by Caan et al. which reported sarcopenic patients had a 27% higher risk of overall mortality than those who were not sarcopenic (adjusted HR= 1.27, 95% CI= 1.09,1.48).⁴⁹

The relationships reported above were not influenced by age or sex, with the exception of the model developed for SMG, in which males had almost two times greater odds of having a relapse (OR= 1.97, 95% CI= 1.03,3.81, p= 0.04). However, sex was not influential in the models developed for SMI, SMG, or sarcopenia. This suggests that sex may be an important covariable for future studies but makes it difficult to form conclusion about its impact on RFS in this study cohort. Age was not significant but was left in the final model developed for SMG due to potential confounding (OR= 0.98, 95% CI= 0.96,1.01). Post hoc Independent t-tests and Fisher's exact tests were not significant for either age (p= 0.60) or sex (p= 0.25), respectively. This finding indicates that the removal of age and sex from models was not due to selection bias caused by excluding individuals who were missing data (i.e., no PSSCAN-R entry, missing RFS data, or no CT scan of sufficient quality/in relevant time period).

Individuals were a median age of 62.0 years and 51.1% were male. These distributions were comparable to the cohort study developed by Caan et al., which included individuals with stage I-III CRC who received surgical resection (i.e., did not focus exclusively on stage III or individuals with a specific chemotherapy regimen, as was done in this thesis project). The mean age of individuals in the Caan et al. cohort was 62.6 years and 50.1% of individuals were male. Caan et al. adjusted for age and sex in survival analyses but did not indicate the significance of these variables. Also, of note, older individuals were excluded in the analyses by Caan et al.⁶¹ due to missing CT scans, CT scans of insufficient quality, or missing weight measurements. Additionally, while an older age is consistently associated with poorer survival,³³ there is potential that the study cohort in this thesis project was also skewed to contain a younger demographic due to the inclusion of only individuals who received oxaliplatin-based therapies which may have influenced this finding. Compared to younger individuals, older adults (i.e., 70-

75 years and above) do not as often receive oxaliplatin-based treatment due to a lack of evidence surrounding its additional long-term benefits, as compared to a single-agent oral treatment option.¹⁰⁵ The median age of the study cohort at diagnosis was 62 years versus an average age at diagnosis of 68 in men and 72 in women (calculated by the American Cancer Society).¹⁰⁶

There is now consistent research to suggest that establishing the presence/absence of sarcopenia at diagnosis in individuals with colon cancer using routine CT scans is of clinical importance.²⁴ Interventions to test the potential of supportive care and rehabilitation interventions post-diagnosis to positively impact longer-term survival outcomes are needed. The cohort study reported in this thesis project also adds new knowledge to the growing fields of research regarding new skeletal muscle measures, namely SMD and SMG. These results will inform further research examining the impact of both skeletal muscle mass and quality on survival in individuals with colon cancer.

6.2 Exploring the potential influence of social and psychological factors on the relationship between body composition measures of skeletal muscle and RFS

This thesis project also aimed to extend what is known in the literature surrounding the impact of body composition measures of skeletal muscle on RFS by exploring if any relationships were also influenced by social and psychological factors. This project was possible due to the unique data set available at BC Cancer that captures social and psychological variables and the use of the PCCF+ Version 7D. In exploratory multivariable logistic regression analyses, social isolation at diagnosis influenced the associations of SMD, SMG, and sarcopenia at diagnosis with RFS at three years post-diagnosis. There was no evidence that community size or neighbourhood income after tax influenced the observed associations.

Social isolation is captured in Part A of the PSSCAN-R (Appendix A) and has previously been shown to influence CRC outcomes. For example, factors such as living alone and loss of a life partner are markers of social isolation and both have previously been reported to influence colon cancer outcomes.^{38,94} Additionally, Hsu et al investigated variables from the PSSCAN-R and found that a lack of emotional support (i.e., the last of five questions on the social isolation checklist), when studied individually, was associated with worse OS (HR= 4.36, $p < 0.01$) and CRC-specific survival (HR= 1.92, $p = 0.02$).⁹⁶

The findings from this thesis project that social isolation may impact RFS are not surprising considering previous literature. However, to the best of my knowledge, this is the first study related to body composition in individuals with colon cancer that has investigated the influence of social and psychological factors. The findings display that those individuals with one or more markers of social isolation have approximately two times greater odds of having a relapse than individuals without markers of social isolation, for any given value of SMI, SMD, SMG, or sarcopenia (i.e., yes/no). In turn, the findings suggest that social isolation may be an important covariable to consider in further research aiming to predict the odds of RFS and an essential target of future supportive care interventions, in addition to interventions that may aim to address the body composition measures of skeletal muscle that were found to have an association with RFS.

There was no evidence that community size influenced the relationship between body composition measures of skeletal muscle and RFS. That is inconsistent with evidence from previous research. In a cohort study of 6163 individuals, Bosma et al. reported that individuals in suburban (HR= 1.60, 95% CI= 1.24,2.08, $p < 0.001$) and rural Alberta (HR= 1.24, 95% CI= 1.02,1.50, $p = 0.042$), as defined by distance to tertiary cancer centres, had poorer OS.⁴² Other

results, using proxies for rurality such as residential address and population-level data, suggest similar findings.^{43,95} Socioeconomic factors (e.g., income level, private insurance) are also reported to be associated with colon cancer outcomes.^{38,107,108} The lack of findings in this thesis project could be due to differences in healthcare availability across various communities (i.e., the referenced studies are in Alberta, but also Australia, the United States, and Denmark), the effect of the small sample size and a limited statistical power (i.e., the 95% CIs for neighbourhood income after tax are large), or both.

There are additional variables captured on the PSSCAN-R that are shown to influence CRC outcomes. For example, informational concerns (e.g., understanding my illness/treatment, making treatment decisions) is one domain measured on Part B of the PSSCAN-R (i.e., the CPC) (Appendix A). In previous literature, Gupta et al. reported a significant association between various service quality items and OS. Specifically, patient-reported satisfaction with the explanation of their treatment options was associated with OS (HR= 0.39, 95% CI= 0.60,0.99, p= 0.04).³⁹ However, in a cohort of this size, it was not possible to investigate all available variables (i.e., would lead to overparameterization of models). However, variables such as informational concerns may be of interest in future exploration of studies of body composition and cancer outcomes.

Lastly, there are other social and psychological factors that are shown to influence outcomes in individuals with CRC but are not captured in the PSSCAN-R, including smoking behaviour and alcohol before diagnosis and educational level.^{38,109} Therefore, this thesis project was unable to examine their potential relationship with body composition and their influence on RFS in individuals with colon cancer.

6.3 Strengths and limitations

The main strength of this retrospective cohort study and chart review was its novel data set, consisting not only of clinical, demographic variables, and body composition parameters, but also social and psychological variables that are not often available at other cancer centres. Additionally, the characteristics of the study cohort were representative of a large population of individuals with colon cancer in British Columbia. For example, there were relatively equal numbers of males and females, with slightly more males as expected by observing the numbers of males and females diagnosed with CRC.² Next, the majority (57.0%) of individuals were from community sizes of 1,500,000 individuals and upwards. In British Columbia, this is indicative of an individual being from the Metro Vancouver area, as all other community sizes are smaller than this threshold.¹¹⁰ This distribution is consistent with the pattern of British Columbia population. According to the Government of British Columbia's population estimates, 53.8% of individuals reside in the Metro Vancouver area.¹¹⁰ Next, all neighbourhood income quintiles after tax appear to be represented, with 44.7% of individuals from the highest two income quintiles and 36.0% from the lowest two income quintiles (i.e., a relatively equal distribution).

There are also several limitations associated with this thesis project. First, provided the number of relationships and variables of interest, the sample size was small. Thus, the analyses are not properly powered and are exploratory in nature. This should be considered in the interpretation of all variables and outlined relationships.

Second, although the study cohort was representative of the general population of individuals with colon cancer in British Columbia in some regards, it was not representative in other areas. First, the study cohort included individuals with stage III colon cancer who received oxaliplatin-based treatment. This decision was justified as it controlled for numerous factors that

could have influenced the relationships of interest. However, it does limit the generalizability to this specific population and comparison of our findings to the literature, which has commonly included individuals with stage I-III cancer in analysis of body composition and outcomes. The oxaliplatin-based treatment criterion may have also led to the cohort being unintentionally representative of younger individuals compared to the mean age of those diagnosed with colon cancer. The results of this thesis project cannot be generalized to individuals from outside this collection of characteristics.

Next, at the stage of data collection, another limitation was anomalies on CT scans. Irregularities on CT scans included those with no ribs on the twelfth thoracic vertebra, ribs on the first lumbar vertebra, sacralization (i.e., last lumbar vertebra fused with the sacrum), six lumbar vertebra, and other less frequent irregularities. This could have led to inconsistencies in the landmarking of L3 and subsequent differences in the estimates of skeletal muscle area (cm²) and density (HU) by the automated software (Voronoi Health Analytics ABACS L3 Module), which was designed to provide estimates from only the L3 level. In addition, height and weight were not available for 94 individuals who otherwise had all available data, contributing to the previously outlined small sample size. When possible, additional data abstraction of paper charts may be warranted to obtain this data. This suggests the need going forward for height and weight data to be recorded and easily accessible to researchers to continue advancing the field of body composition and cancer outcomes.

6.4 Future directions

The outlined limitations should be addressed in the development of further studies. Several future directions can be pursued with the GICOU-created study cohort used for this

thesis project. This thesis project only investigated individuals diagnosed between 2012 and 2015 with PSSCAN-R data available due to time restraints associated with a Master of Science degree. However, the total GICOU-created cohort consists of 1126 individuals who were diagnosed with stage III colon cancer between 2010 and 2016 and received oxaliplatin-based treatment. Due to factors such as radiation therapy, missing data, and the quality of available CT scans, not all individuals will be included in future analyses. However, this potentially larger sample size provides the opportunity to better understand the relationships between skeletal muscle, RFS, and postal code-related variables (i.e., community size and neighbourhood income after tax), which are available for all individuals regardless of the presence/absence of PSSCAN-R data. PSSCAN-R data is available for an additional 160 individuals diagnosed with colon cancer in 2010, 2011, and 2016 (majority of the additional PSSCAN-R data available from 2016), potentially providing increased power for analyses involving social and psychological variables from the PSSCAN-R. Additionally, this data could allow for more meaningful analyses with variables such as symptoms of anxiety and depression, for which there was not a sufficient sample size to observe any relationships or include in logistic regression models.

Second, this thesis project focused on CT scans from diagnosis. However, the relationship between a potential change in body composition (e.g., diagnosis to post-chemotherapy) and RFS is of interest, as variation in skeletal muscle during chemotherapy is a potentially modifiable target for future supportive care and rehabilitation interventions. The change in body composition could be measured using the baseline CT scans retrieved for this thesis project and an additional follow-up CT scan conducted three to six months later.

Next, software for three-dimensional segmentation has recently become available for use in body composition research.¹¹¹ In individuals with colon cancer, this will allow for

visualization and measurements of the chest, abdomen, and pelvis, instead of focusing solely on the L3 level of a CT scan. Future research in this cohort could investigate how the extended measurements obtained from this software influence outcomes such as RFS in individuals with colon cancer, and how these relationships compare with those obtained using the L3 level of CT scans. In the long-term, three-dimensional segmentation could provide increased information regarding body composition parameters and allow for highly efficient and accurate measurements in larger cohort sizes, for the purpose of both research and the development of rehabilitation interventions.¹¹¹

Lastly, this field of research is largely based on the notion that if a changing body composition influences outcomes, it is important to target body composition measures through resistance training, nutritional programming, and exercise interventions.⁷⁶⁻⁷⁸ However, further research is needed to elucidate the factors that influence skeletal muscle density (i.e., not solely mass)⁶⁹ and the impact of rehabilitation interventions on longer-term outcomes. To the best of my knowledge, there are no published RCTs of rehabilitation intervention in individuals with colon cancer and survival outcomes. However, there is an on-going multi-centre, international RCT examining the influence of aerobic exercise on DFS in individuals with stage II-III colon cancer who have a high risk of recurrence (NCT00819208).⁷⁴ There are reported improvements in physical function (e.g., 6-minute walk test, eight-foot Timed-Up and Go) in the first 100 individuals receiving the aerobic exercise intervention, but no survival outcomes have been reported yet.⁷⁵ There is also one on-going RCT investigating the influence of resistance training on chemotherapy-related dose limiting toxicities and dose reductions in individuals receiving chemotherapy for colon cancer that will also examine change on body composition and physical function (NCT03291951).⁷³

6.5 Impact

This thesis project provides further evidence regarding the association between sarcopenia at diagnosis and RFS at three years post-diagnosis, as well as novel information on the potential relationship of SMD and SMG at diagnosis with RFS. If the latter relationships are confirmed by larger studies, this suggests that both muscle quantity and quality are important predictors of RFS in individuals with colon cancer and potential targets of further research and rehabilitation programming.

Next, to the best of my understanding, this was the first study to explore the influence of social and psychological factors on the relationship between body composition and RFS, a potentially overlooked area in the growing body of knowledge surrounding body composition and outcomes in individual with colon cancer. Social isolation at diagnosis was found to be influential, while community size and neighbourhood income were not, providing direction for which factors to include/not include in further, appropriately powered research regarding these relationships. Additionally, these findings highlight the importance of rehabilitation and supportive care programming for individuals with social isolation at diagnosis, in addition to those with poorer muscle quantity and quality at diagnosis.

Chapter 7: Conclusion

In conclusion, there is strong and consistent evidence across the literature to demonstrate that sarcopenia at diagnosis influences outcomes, such as RFS at three years post-diagnosis, in individuals with colon cancer. There are also emerging bodies of knowledge regarding the association of measures of muscle quality (i.e., SMD and SMG) and outcomes in individuals with cancer, with this thesis project contributing novel evidence to suggest that both SMD and SMG at diagnosis may influence RFS at three years post-diagnosis for individuals with colon cancer. Social isolation at diagnosis appeared to influence the associations between body composition measures of skeletal muscle at diagnosis and RFS at three years post-diagnosis. Therefore, social isolation could be an important prognostic factor to consider in further studies investigating colon cancer outcomes. Larger, appropriately powered studies are needed to further elucidate relationships between social and psychological variables, body composition, and outcomes to provide evidence that will inform future supportive cancer care and rehabilitation programming for individuals with colon cancer aimed at improving RFS.

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Appendices

Appendix A The Psychosocial Screen for Cancer-Revised (PSSCAN-R)



PSSCAN-R Psychological Screening

Please answer the following questions to help us learn more about your well being. A serious illness can affect the quality of your life in many ways. We may contact you to offer our counselling services based on the information you provide to us, or contact you regarding opportunities to participate in research.

Part A:

Please respond to each question with "Yes" or "No" by making a circle around the appropriate answer. There are no right or wrong answers.

- | | | |
|---|----|-----|
| 1. Do you live alone? | No | Yes |
| 2. When you need help, can you count on anyone to help with daily tasks such as grocery shopping, cooking, giving you a ride? | No | Yes |
| 3. Do you have regular contact with friends or relatives? | No | Yes |
| 4. Have you lost your life partner within the last few years? | No | Yes |
| 5. Can you count on anyone to provide you with emotional support? | No | Yes |

Part B:

Please check all of the following items that have been of concern or a problem for you in the past week including today.*

<p>6. Emotional:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Fears/Worries <input type="checkbox"/> Sadness <input type="checkbox"/> Frustration/Anger <input type="checkbox"/> Changes in appearance <input type="checkbox"/> Intimacy/Sexuality <input type="checkbox"/> Coping <input type="checkbox"/> Change in sense of self 	<p>7. Informational:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Understanding my illness/treatment <input type="checkbox"/> Talking with the health care team <input type="checkbox"/> Making treatment decisions <input type="checkbox"/> Knowing about available resources <input type="checkbox"/> Quitting smoking
<p>8. Practical:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Work/School <input type="checkbox"/> Finances <input type="checkbox"/> Getting to & from appointments <input type="checkbox"/> Accommodation <input type="checkbox"/> Child/family/elder care 	<p>9. Spiritual:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Meaning/Purpose of life <input type="checkbox"/> Faith
<p>10. Social/Family:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Feeling a burden to others <input type="checkbox"/> Worry about family/friends <input type="checkbox"/> Feeling alone <input type="checkbox"/> Relationship difficulties 	<p>11. Physical:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Concentration/Memory <input type="checkbox"/> Sleep <input type="checkbox"/> Weight

Other concerns, please specify: _____

* Canadian Problem Checklist developed by the Canadian Partnership Against Cancer, August 2010.



Provincial Health Services Authority

Part C: Please place an 'X' in the box that best describes what you have experienced.

	Not at all	A little bit	Moderately	Quite a bit	Very much
12. During the past week I have felt my heart race and I tremble.					
13. During the past week I have felt that I cannot control anything.					
14. During the past week I have lost interest in things I usually cared for or enjoyed.					
15. During the past week I have felt nervous and shaky inside.					
16. During the past week I have felt tense and cannot relax.					
17. During the past week my thoughts are repetitive and full of scary things.					
18. During the past week I have felt restless and find it difficult to sit still.					
19. I have recently thought about taking my life. NOTE: If you have, a member of your health care team will talk with you today to see what support they can offer.					
20. In the past year, I have had 2 weeks or during which I felt sad, blue or depressed.					
21. I have had 2 years or more in my life when I felt depressed or sad most days even if I felt okay sometimes.					

Thank you for taking the time to respond to this form.

If you or your family is currently struggling with the stress of your diagnosis, information and support is available on our website: www.bccancer.bc.ca/health-info/coping-with-cancer or by calling:
BC Cancer Patient & Family Counselling Departments

Abbotsford	604.851.4733
Kelowna	250.712.3963
Prince George	250.645.7330
Surrey	604.930.4000
Vancouver	604.877.6000 x 672194
Victoria	250.519.5525

Patient and Family Counselling Documentation:

D = _____ A = _____

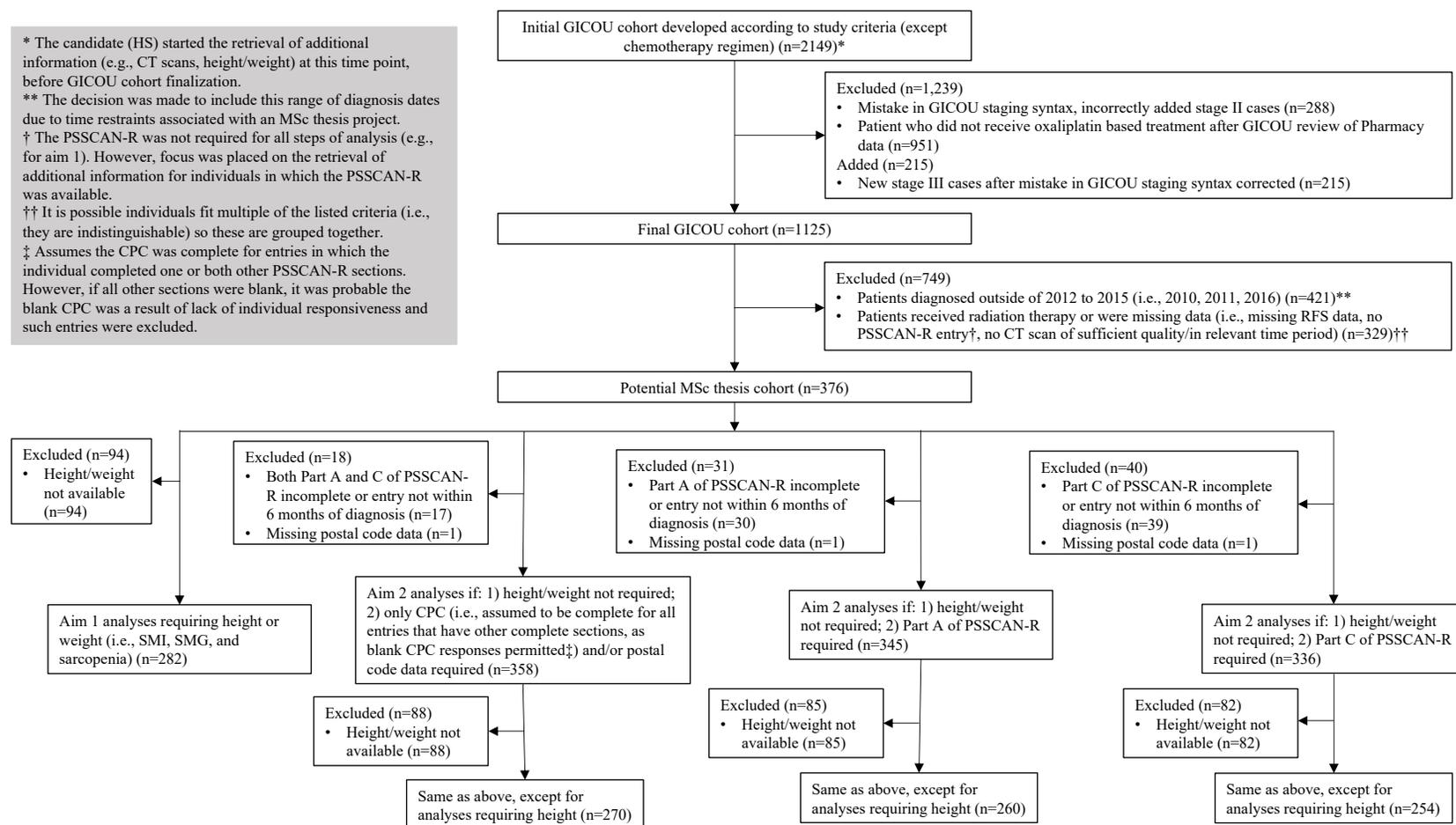
Comments: _____

Reviewed by: _____

Date: _____

Appendix B Flow diagram of individual numbers throughout this thesis project

* The candidate (HS) started the retrieval of additional information (e.g., CT scans, height/weight) at this time point, before GICOU cohort finalization.
 ** The decision was made to include this range of diagnosis dates due to time restraints associated with an MSc thesis project.
 † The PSSCAN-R was not required for all steps of analysis (e.g., for aim 1). However, focus was placed on the retrieval of additional information for individuals in which the PSSCAN-R was available.
 †† It is possible individuals fit multiple of the listed criteria (i.e., they are indistinguishable) so these are grouped together.
 ‡ Assumes the CPC was complete for entries in which the individual completed one or both other PSSCAN-R sections. However, if all other sections were blank, it was probable the blank CPC was a result of lack of individual responsiveness and such entries were excluded.



Abbreviations: CPC; Canadian Problem Checklist; CT, computer tomography; GICOU, Gastrointestinal Cancer Outcomes Unit; PSSCAN-R, Psychosocial Screen for Cancer-Revised; SMG, skeletal muscle gauge; SMI, skeletal muscle index.

Appendix C Variable visualization tables and graphs

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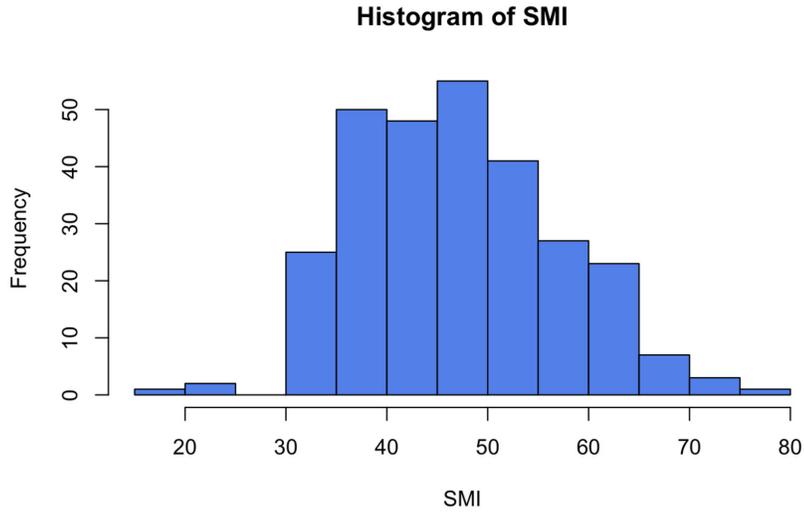
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Variable distribution

SMI distribution



Mean: 47.06457

Median: 46.03126

Kurtosis: 2.660618

Skewness: 0.2632633

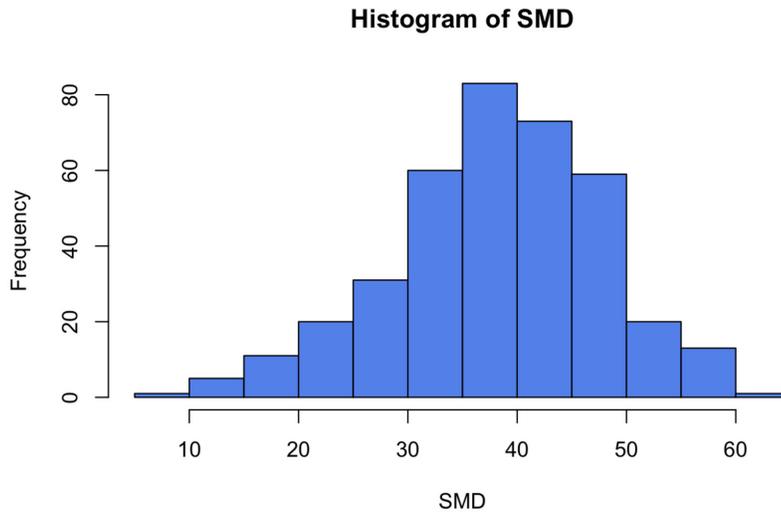
Shapiro-Wilk normality test:

data: inclusion_criteria_c\$SMI

W = 0.98607, p-value = 0.007659

Notes: Histogram is fairly normally distributed but appears to have a right skew. The mean and median are close, a sign of normality. Additionally, both kurtosis and skewness appear to be alright. Skewness is a very small number (mean and median are close together) and kurtosis is a value close to 3 (in R, this is what you are looking for). However, the p-value of the Shapiro-Wilk test is less than 0.05, indicating a deviation from normality.

SMD distribution



Mean: 38.3087

Median: 38.92

Kurtosis: 3.080663

Skewness: -0.332592

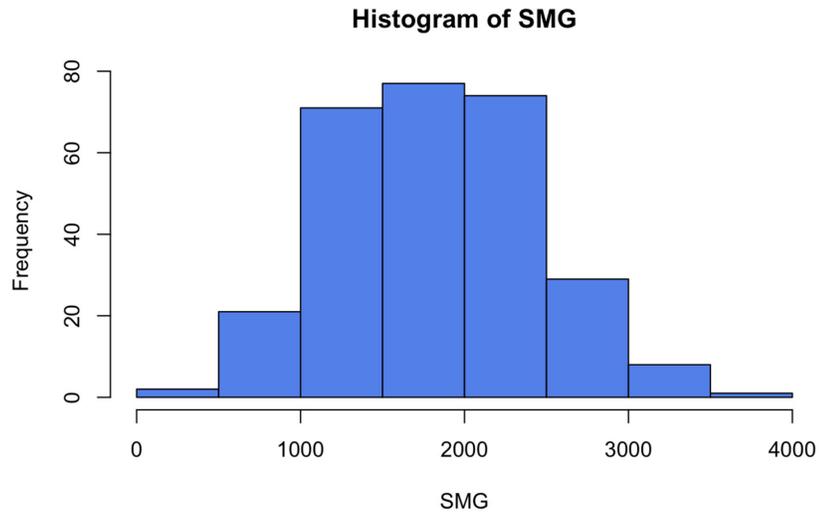
Shapiro-Wilk normality test:

data: inclusion_criteria_d\$SMD

W = 0.99133, p-value = 0.02626

Notes: Histogram appears to be slightly left skewed. Mean and median are close, a sign of normality. Additionally, skewness is low and kurtosis is close to 3, a sign of normally distributed data. However, the Shapiro-Wilk test p value is under 0.05, indicating a significant deviation from normality.

SMG distribution



Mean: 1801.91

Median: 1745.868

Kurtosis: 2.743534

Skewness: 0.2020788

Shapiro-Wilk normality test:

data: inclusion_criteria_c\$SMG

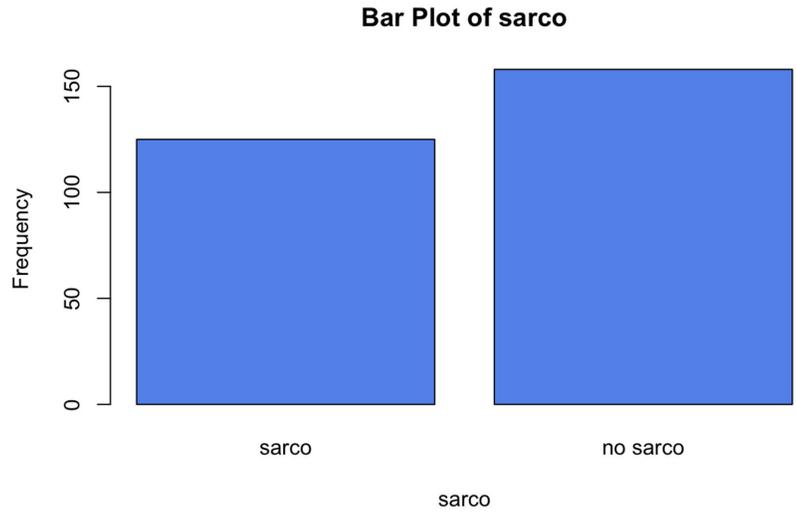
W = 0.99397, p-value = 0.3211

Notes: Histogram appears normal. Looking at mean and median, it is unclear how close they are. Skewness is low, with a slight right skew and Kurtosis is close to 3. However, the Shapiro-Wilk test p value is greater than 0.05, an indicator of normality.

sarco bar graph

sarco: 125

no sarco: 158

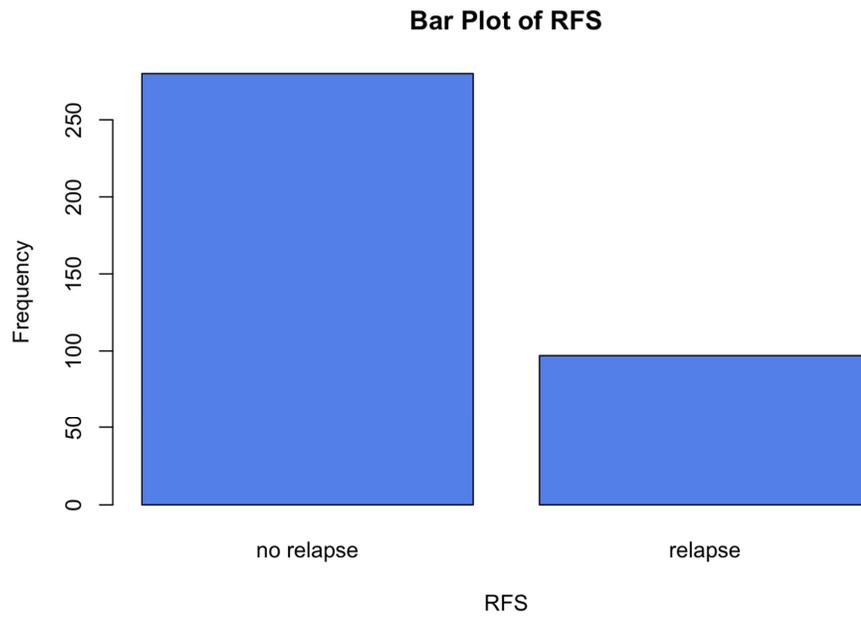


Notes: More patients without sarcopenia.

RFS bar graph

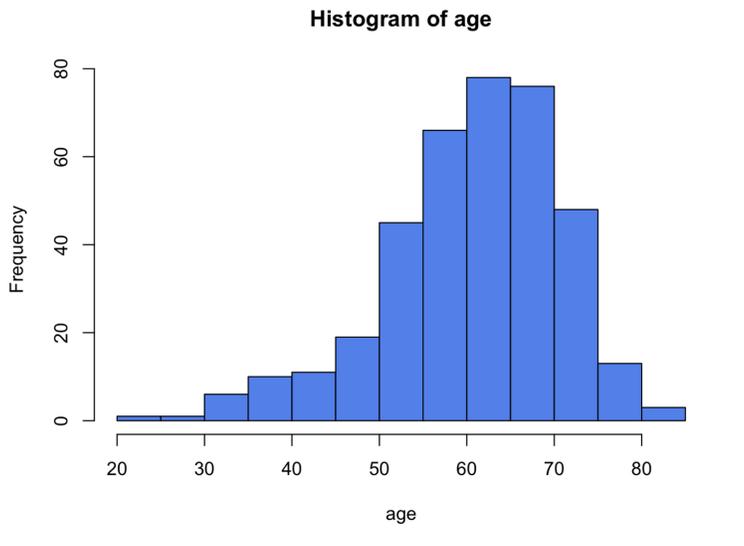
no relapse: 280

relapse: 97



Notes: More patients did not experience a relapse.

age histogram



Mean: 61.17772

Median: 62

Kurtosis: 3.72177

Skewness: -0.7434598

Shapiro-Wilk normality test:

data: inclusion_criteria_d\$age_at_diagnosis

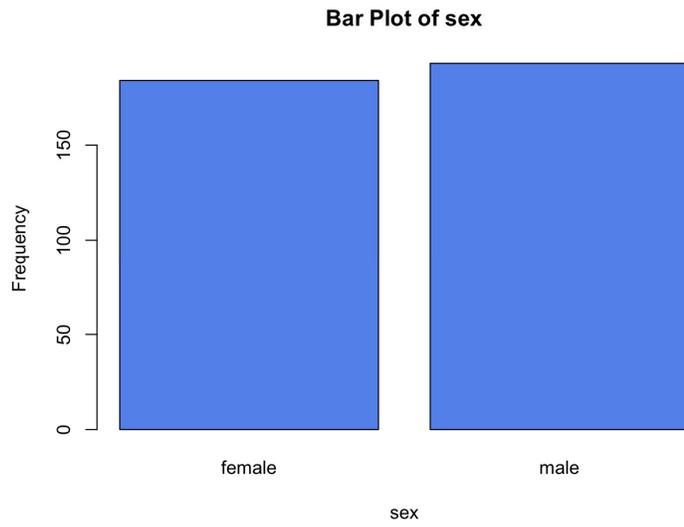
W = 0.96669, p-value = 1.431e-07

Notes: The histogram appears to be left skewed (more in younger category, which makes sense given our criteria of only including certain chemo regimens that are more toxic/commonly given to the younger CRC patients). The mean and median are close together. Kurtosis is close to 3 and skewness indicated the left skew further (it is slightly higher than normal). However, the Shapiro-Wilk normality test reveals a highly significant deviation from a normal distribution.

sex bar graph

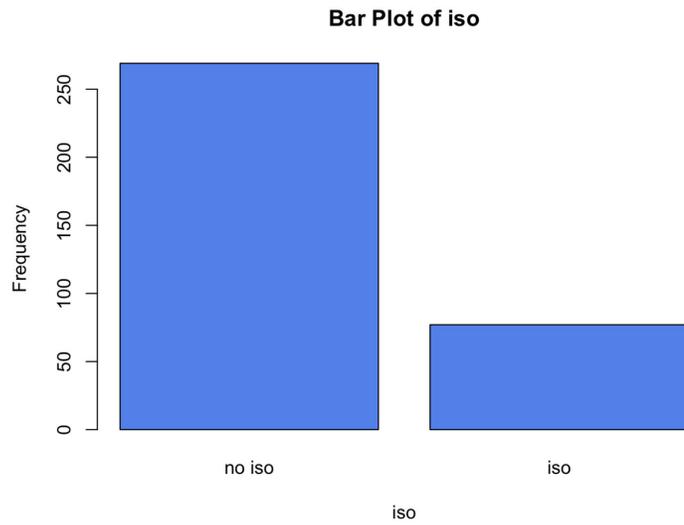
female: 184

male: 193



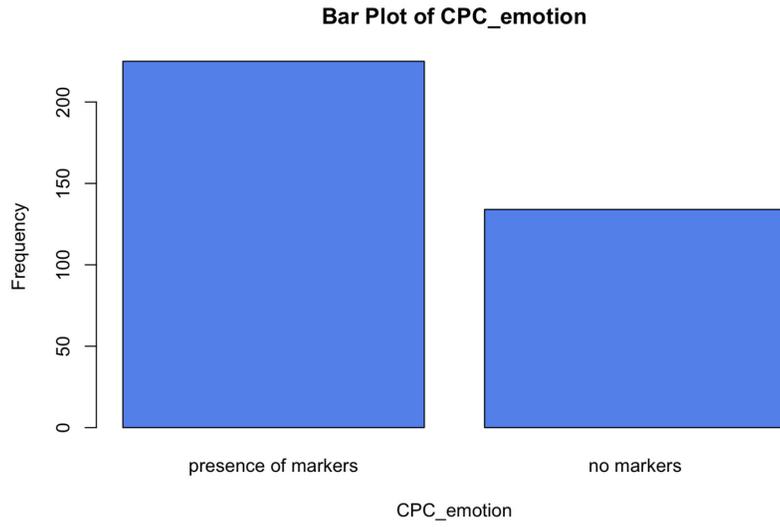
Notes: Slightly more males in this cohort.

iso bar graph
no iso: 269
marker of iso: 77



Notes: Majority had no markers of iso.

CPC_emotion bar graph
1 or more checkmarks: 225
no checkmarks: 134

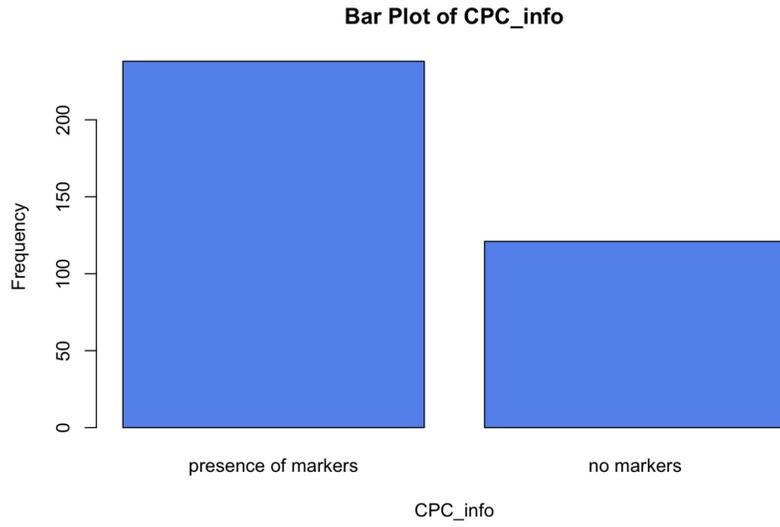


Notes: Majority had 1 or more markers of emotional concerns.

CPC_info bar graph

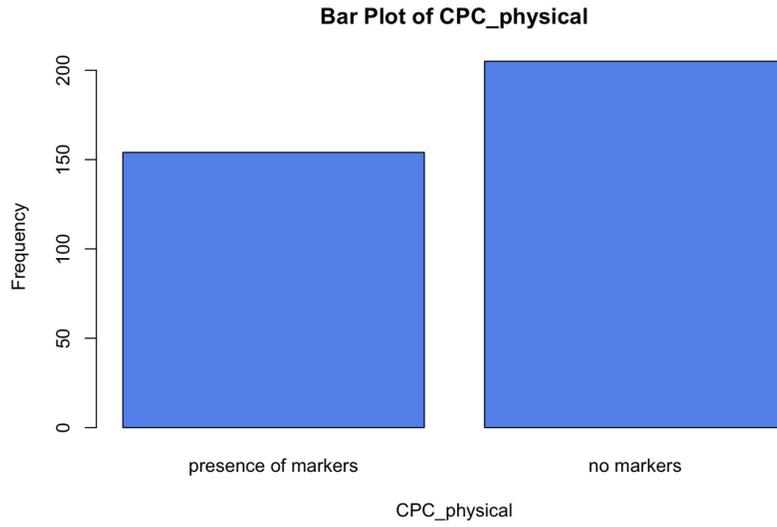
1 or more checkmarks: 238

no checkmarks: 121



Notes: Majority had 1 or more markers of informational concerns.

CPC_physical bar graph
1 or more checkmarks: 154
no checkmarks: 205

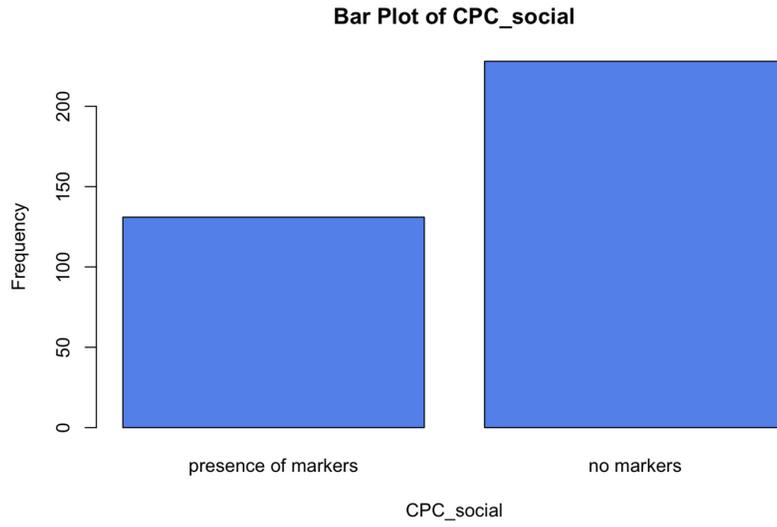


Notes: Majority reported no markers of physical concern (which is interesting, as concern about weight is accompanied in this/this may be related to body composition). However, there is not too uneven of spread, with high numbers in both groups.

CPC_social bar graph

1 or more checkmarks: 131

no checkmarks: 228

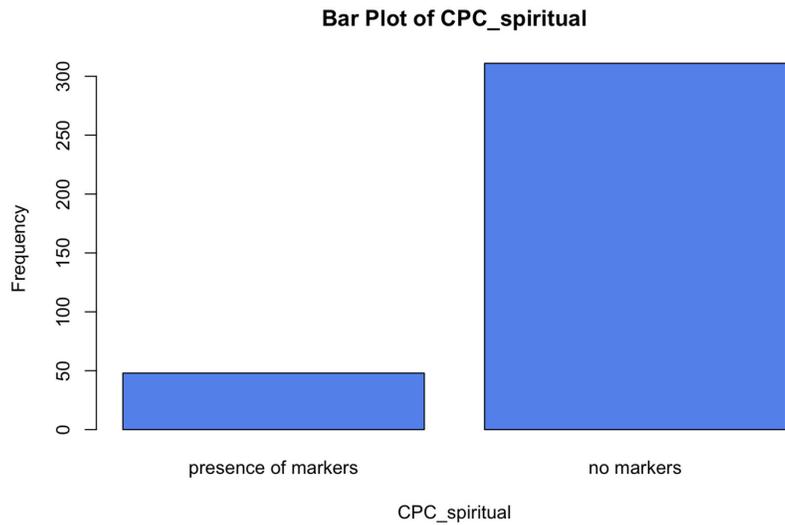


Notes: Majority had no markers of social concerns.

CPC_spiritual bar graph

1 or more checkmarks: 48

no checkmarks: 311

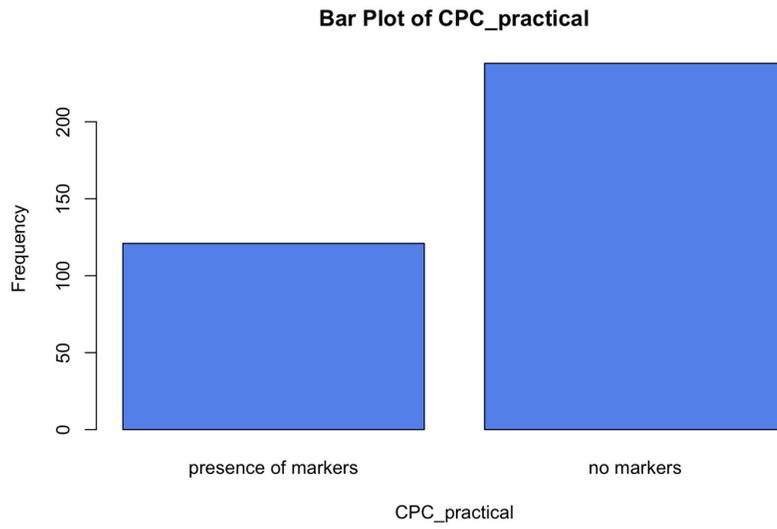


Notes: A large majority had no markers of spiritual concern. This more uneven distribution of patients (compared to other plots) is what I would expect.

CPC_practical bar graph

no checkmarks: 121

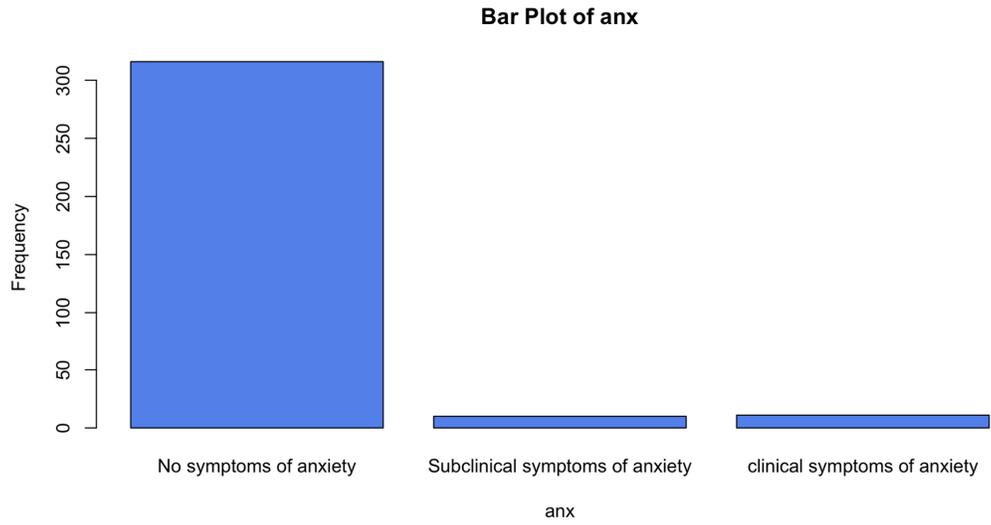
1 or more checkmarks: 238



Notes: Almost double the number reported no markers of practical concern.

anx bar graph

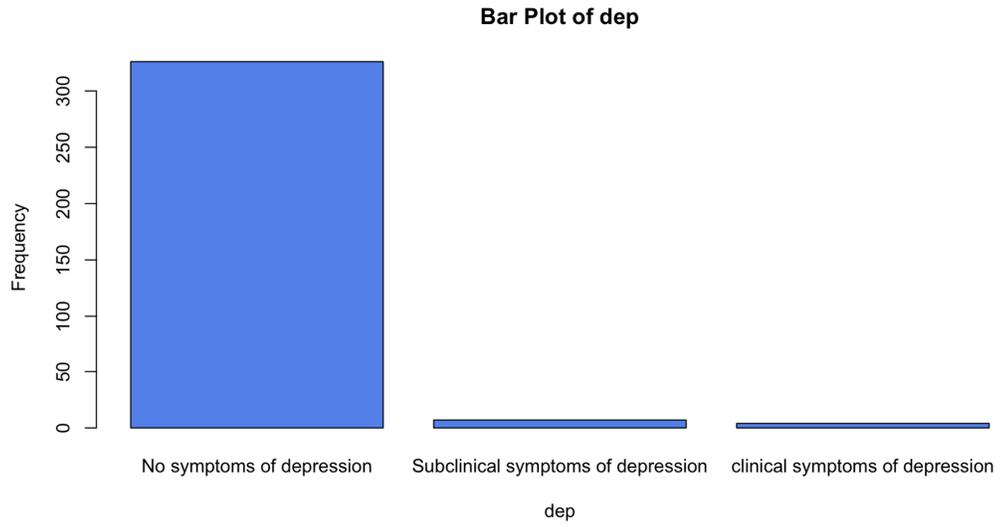
no symptoms of anxiety: 316
subclinical symptoms of anxiety: 10
clinical symptoms of anxiety: 11



Notes: Almost all reported no symptoms of anx. Likely not enough diversity to study in further analyses.

dep bar graph

no symptoms of depression: 326
subclinical symptoms of depression: 7
clinical symptoms of depression: 4



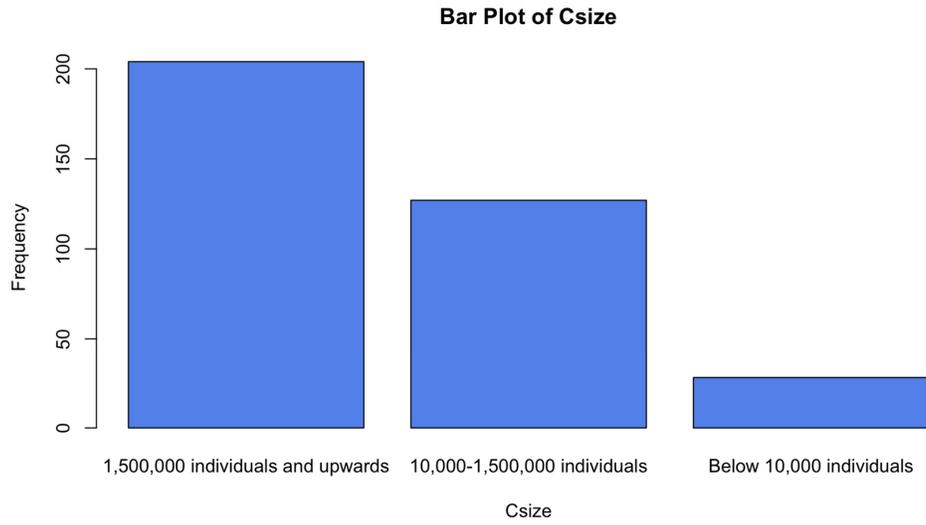
Notes: Same as anx above.

Csize bar graph

1,500,000 individuals and upwards: 204

10,000-1,500,000 individuals: 127

Below 10,000 individuals: 28



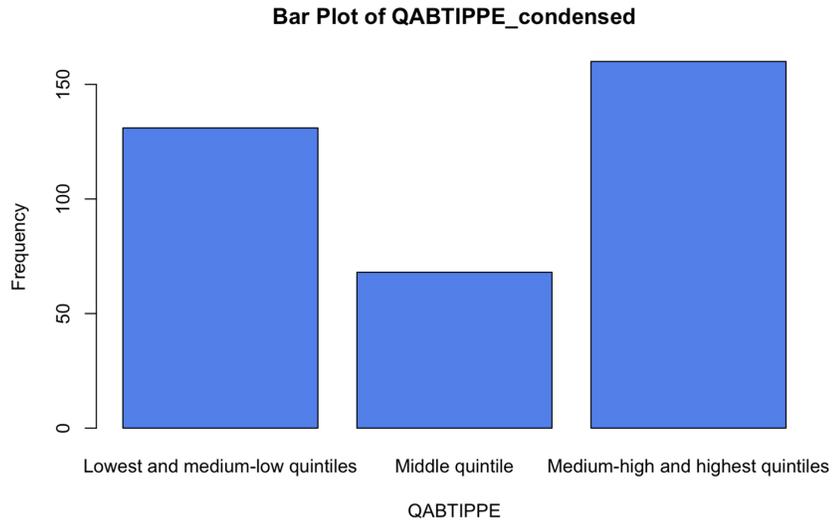
Notes: As expected, more in larger cities (Vancouver) than smaller towns.

QABTIPPE bar graph

Lowest and medium-low quintiles: 131

Middle quintile: 68

Medium-high and highest quintiles: 160



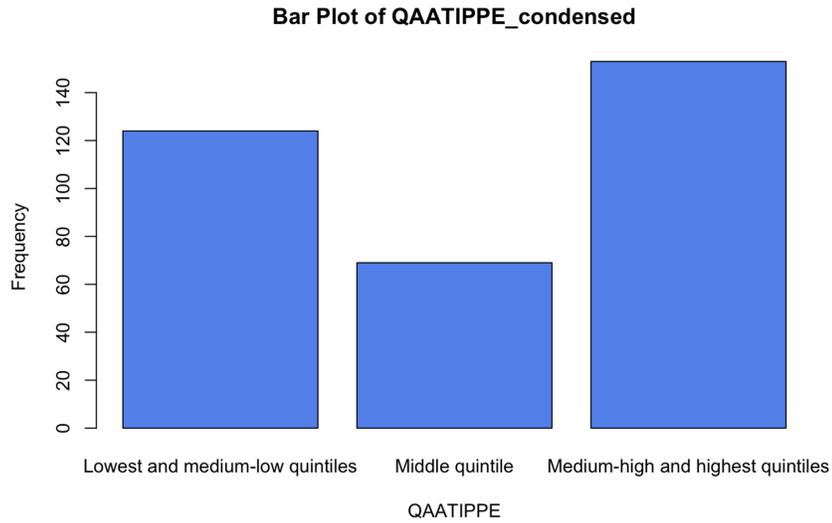
Notes: Interestingly, more individuals are on either end vs. the middle quintile, with the majority on the higher end.

QAATIPPE bar graph

Lowest and medium-low quintiles: 130

Middle quintile: 69

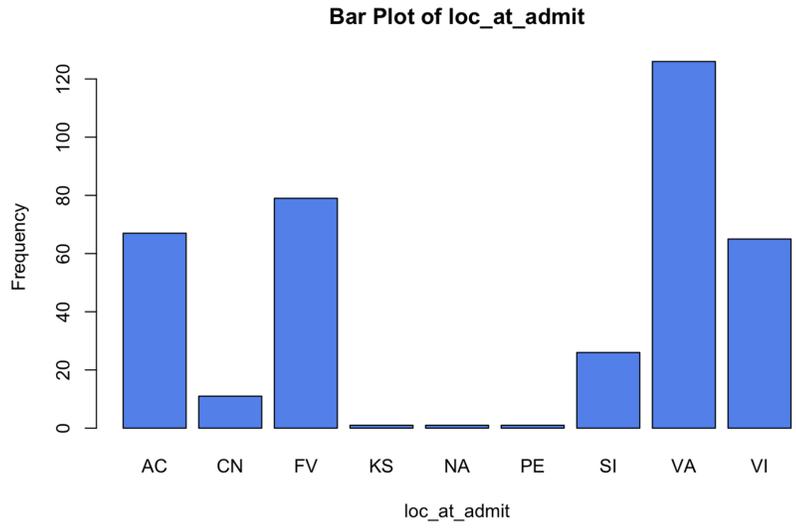
Medium-high and highest quintiles: 160



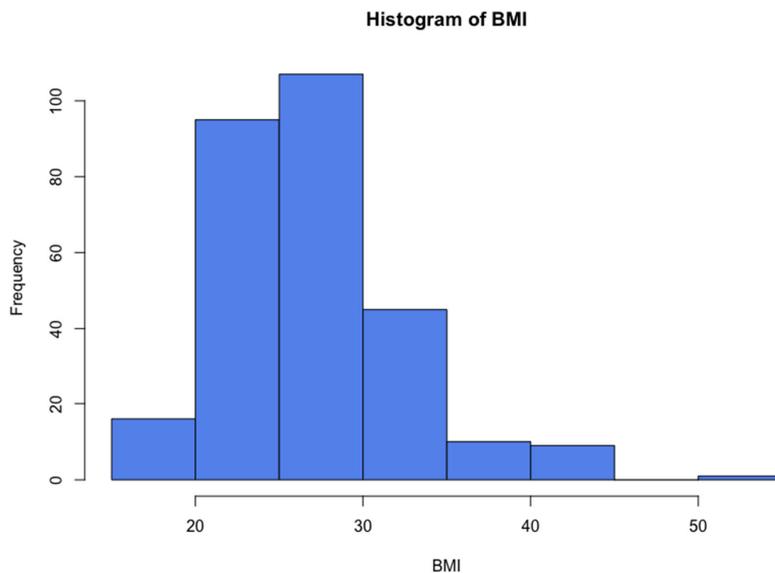
Note: The same pattern as before tax, with slight movement from the lower to middle quintiles. The after tax (disposable) income is more reported in the literature and with this being almost identical in distribution, will use this moving forward. With the large spread of people, this could be very interesting to study moving forward.

loc_at_admit bar graph

Abbotsford: 67
North: 11
Fraser Valley: 79
Kamloops: 1
Nanaimo: 1
Penticton: 1
Southern Interior: 26
Vancouver: 126
Vancouver Island (i.e., Victoria): 65



BMI distribution



Mean: 26.96323

Median: 26.11253

Kurtosis: 5.603979

Skewness: 1.213236

Shapiro-Wilk normality test:

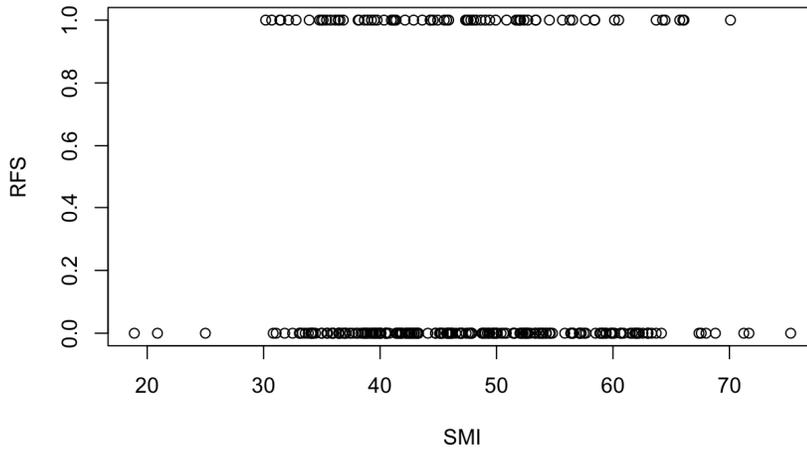
data: inclusion_criteria_c\$SMI

W = 0.99119, p-value = 3.538e-10

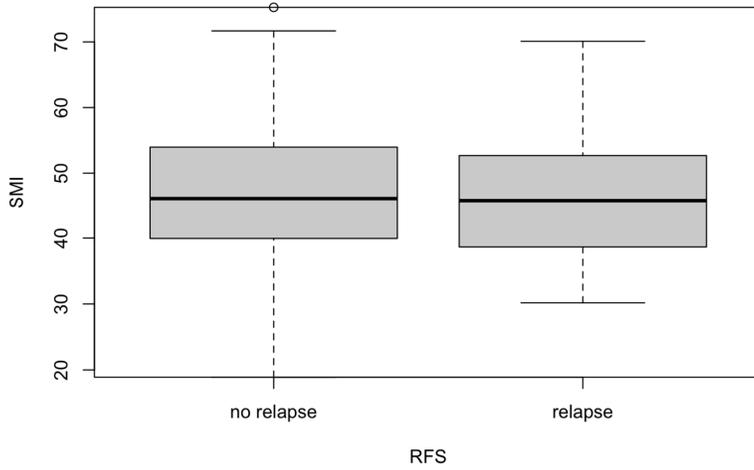
Notes: Histogram appears to be left skewed. Mean and median are close, a sign of normality. However, the Shapiro-Wilk test p value is under 0.05, indicating a significant deviation from normality.

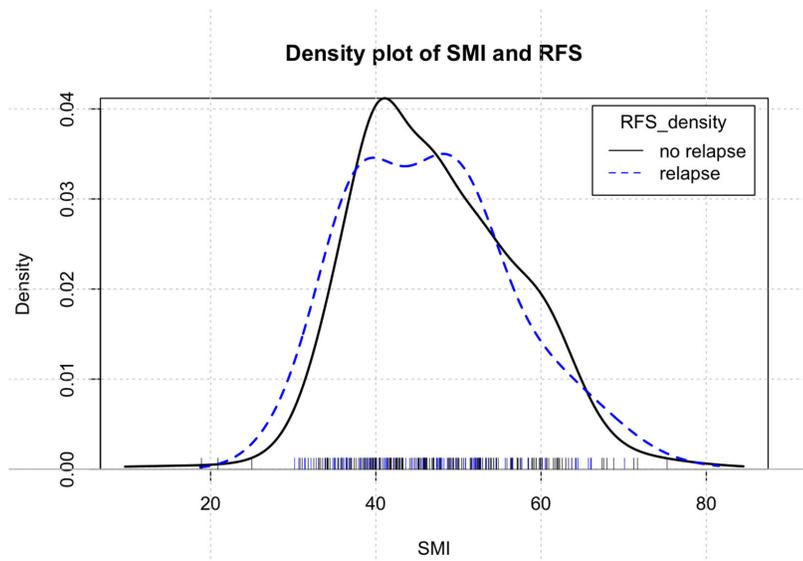
Body comp. and RFS
SMI and RFS

Relationship between SMI and RFS



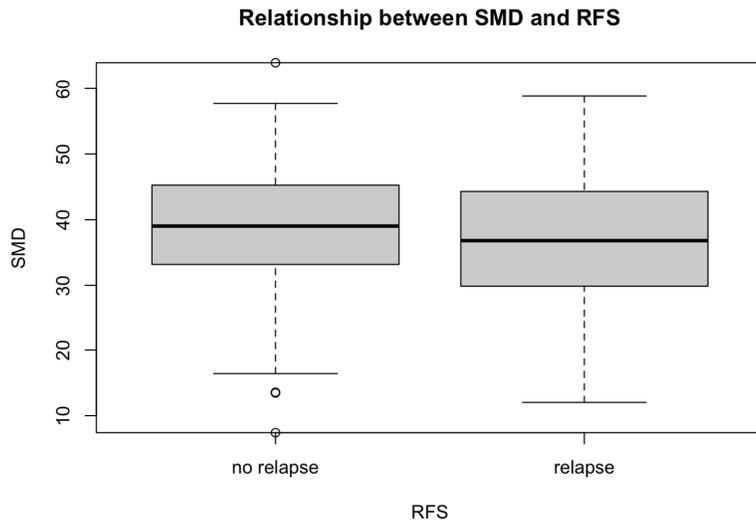
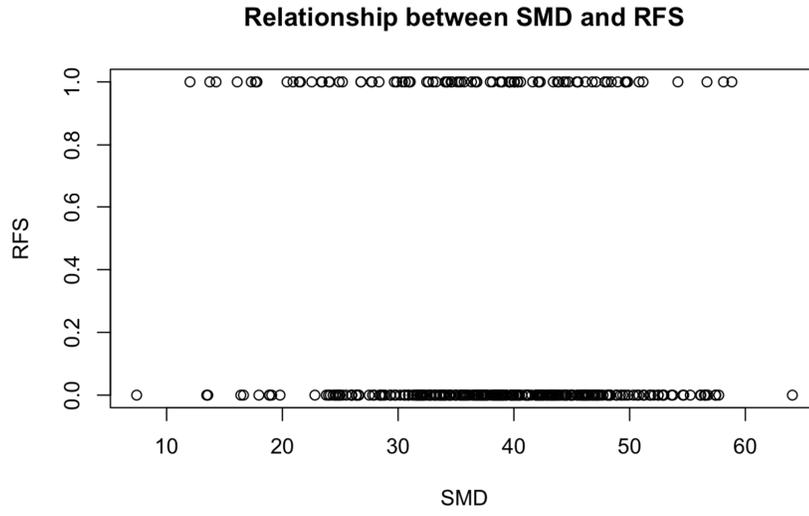
Relationship between SMI and RFS

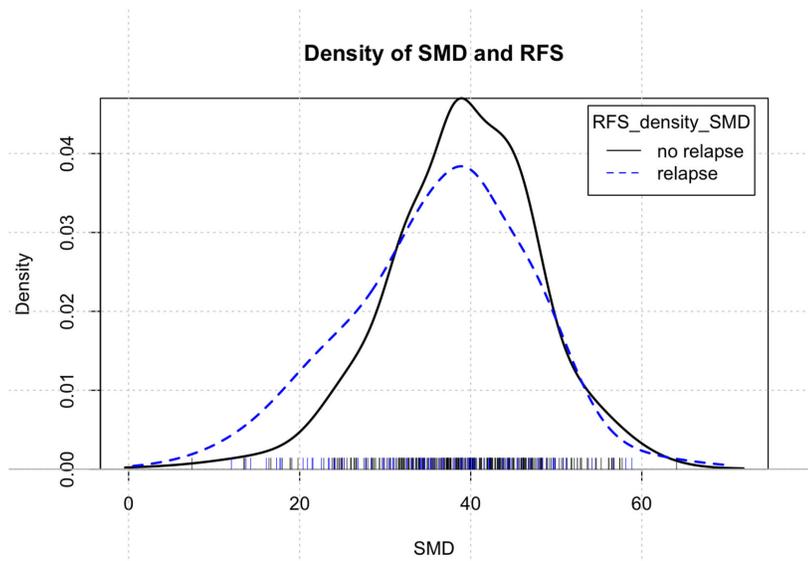




Notes: No strong evidence of a relationship between SMI and RFS. There are more individuals that do not have a relapse but can't see evidence of a relationship between SMI and RFS from the scatter plot. Additionally, the medians appear to be about the same for both those who do and do not experience a relapse. The density plot reveals similar results, with perhaps slightly higher density of individuals with recurrence having lower SMI's but this is not super apparent.

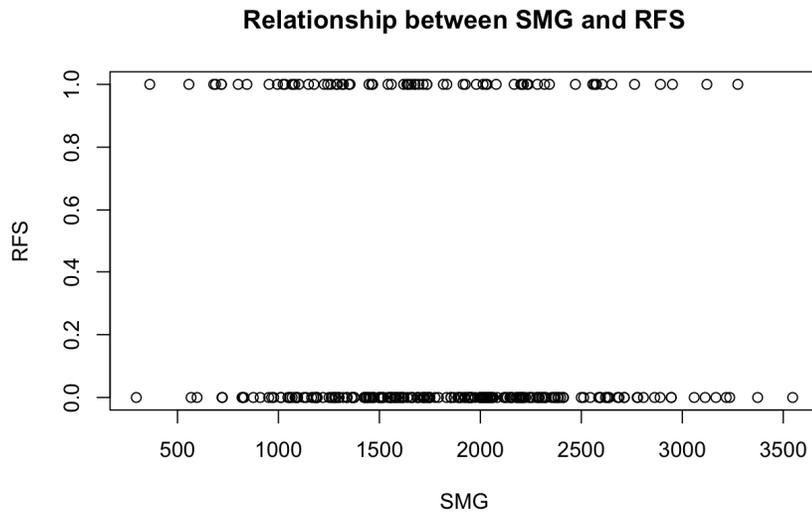
SMD and RFS scatter plot

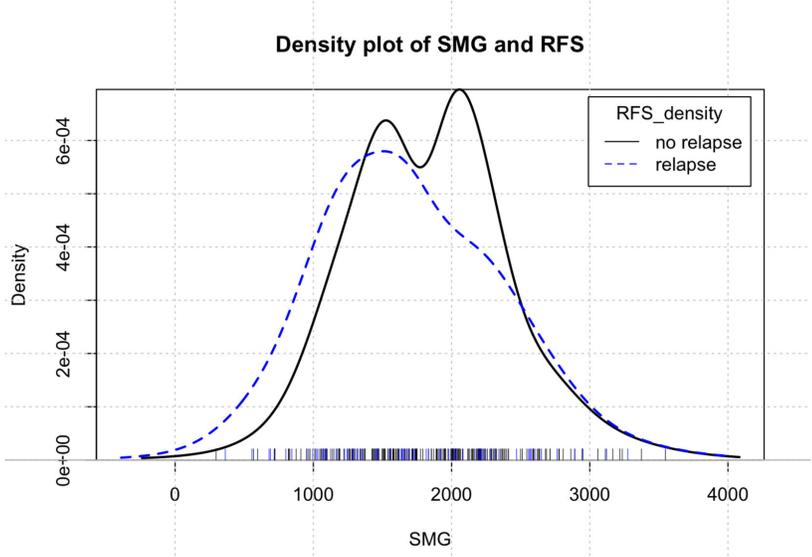
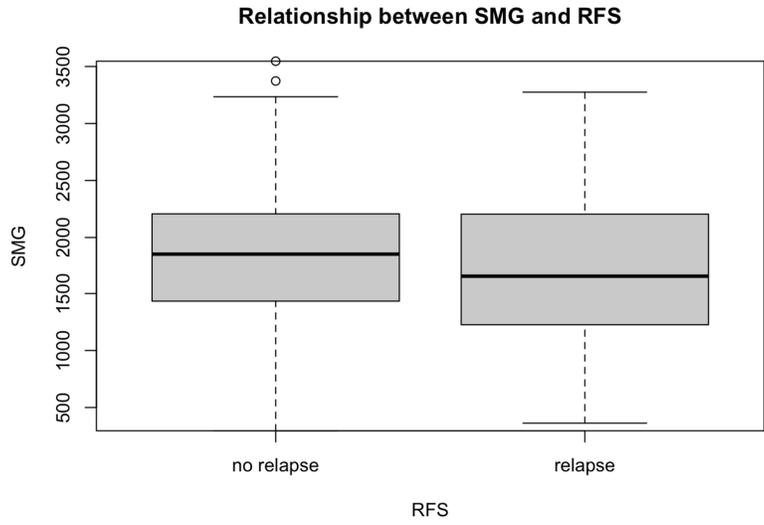




Notes: Perhaps higher density of individuals with lower SMD's (i.e., increased adipose tissue infiltration in skeletal muscle) experience a relapse. This is shown in all 3 plots above but is very slight (likely not a high correlation).

SMG and RFS scatter plot



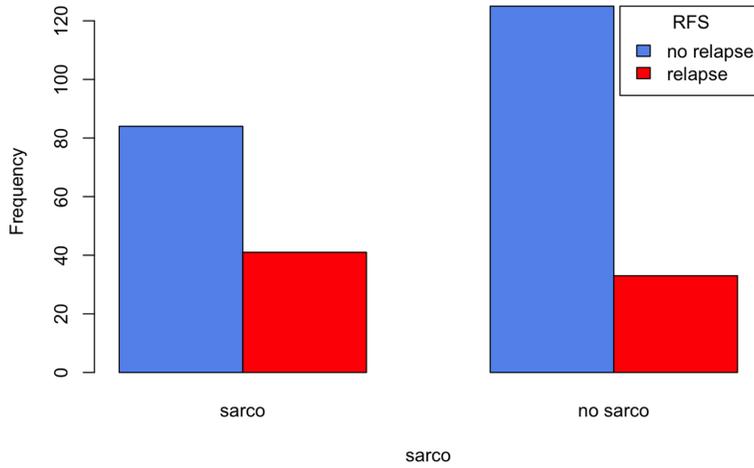


Notes: The mean and medians are slightly different in box plot. Scatter and box plot reveals that perhaps those with lower SMGs experience more relapse (i.e., RFS=1). Additionally, the density of those who experience a relapse starts at a lower SMG.

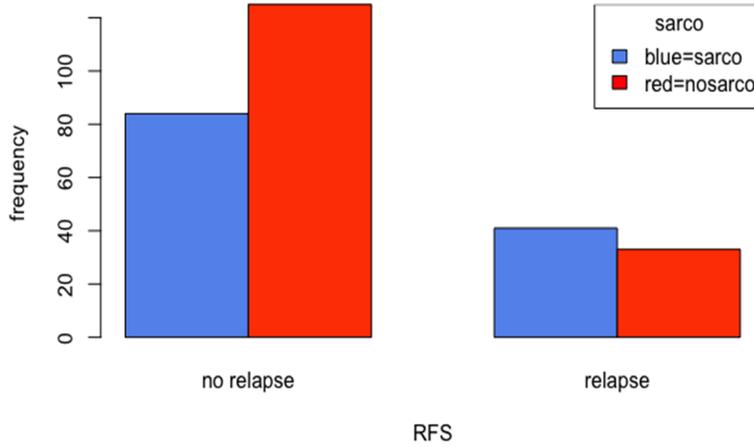
sarco and RFS bar graph

	sarco	No sarco	
No relapse	84	125	209
Had a relapse	41	33	74
	125	158	283

Relationship between sarco and RFS



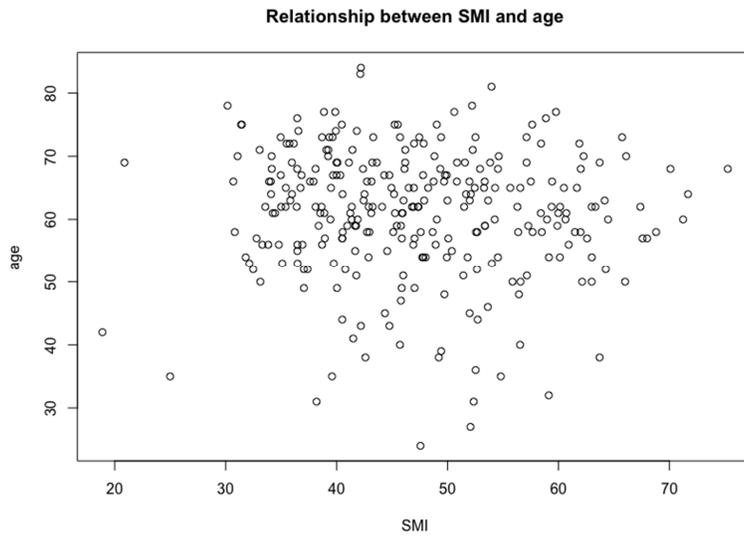
Relationship between sarco and RFS



Notes: Of those who have sarco, more do not experience a relapse. This is the same as those without sarco. However, if looking at those that experienced a relapse, 55% of the group is made up of those who are sarcopenic (even though majority of people are not sarcopenic in the total population). If looking at those who did not experience a relapse, 60% of the group is made up of those who are not sarcopenic. Note, there are more individuals without sarcopenia than with overall.

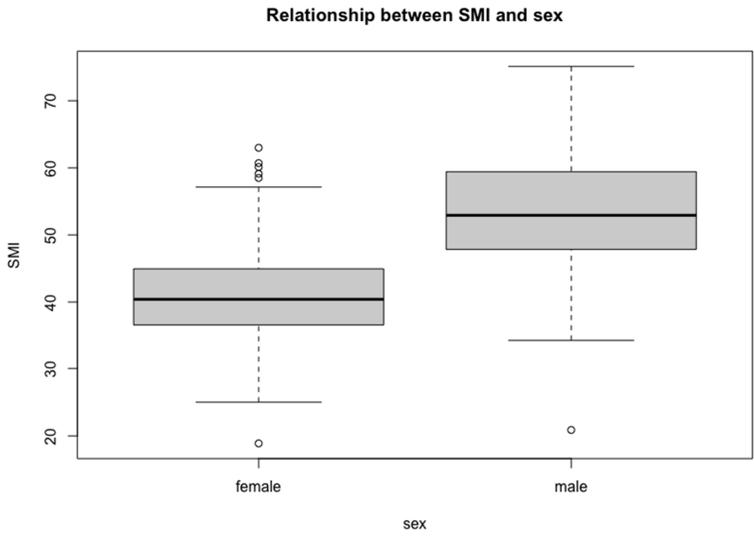
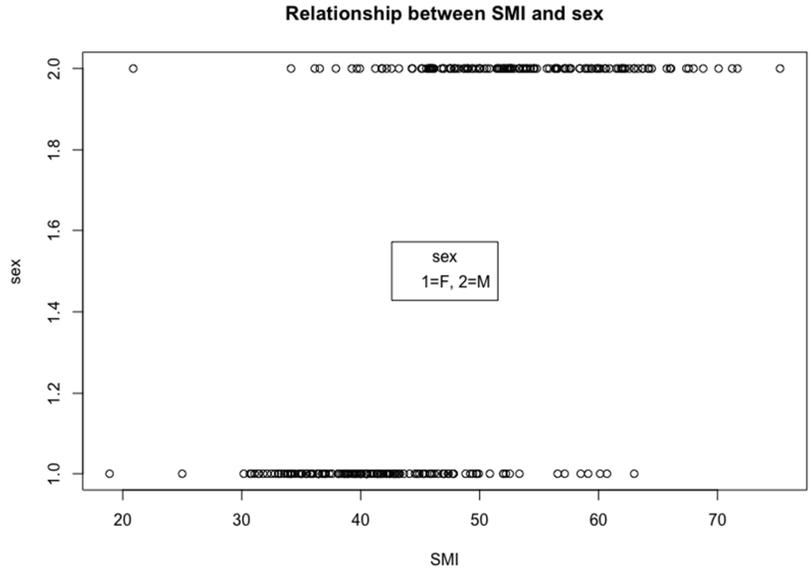
Body comp. and covariables

SMI and age



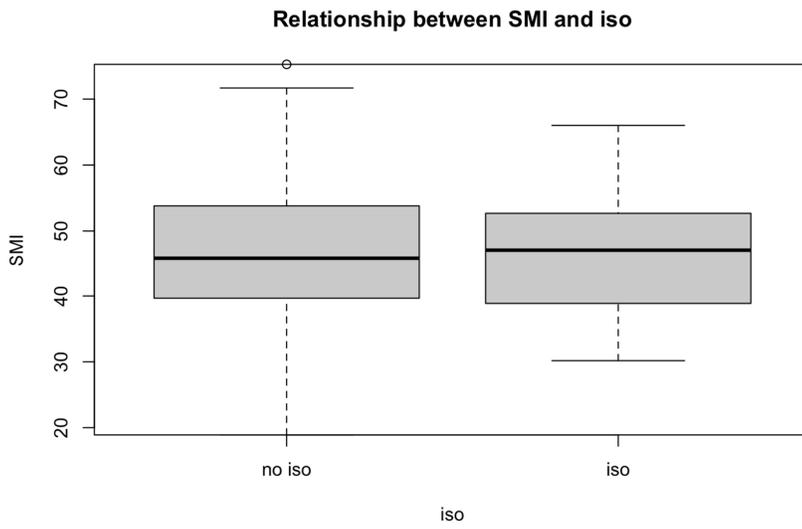
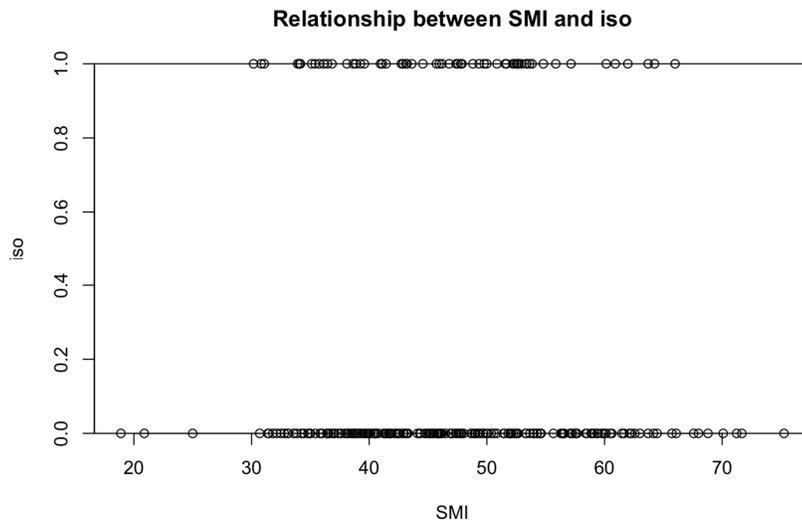
Notes: No visual evidence of relationship.

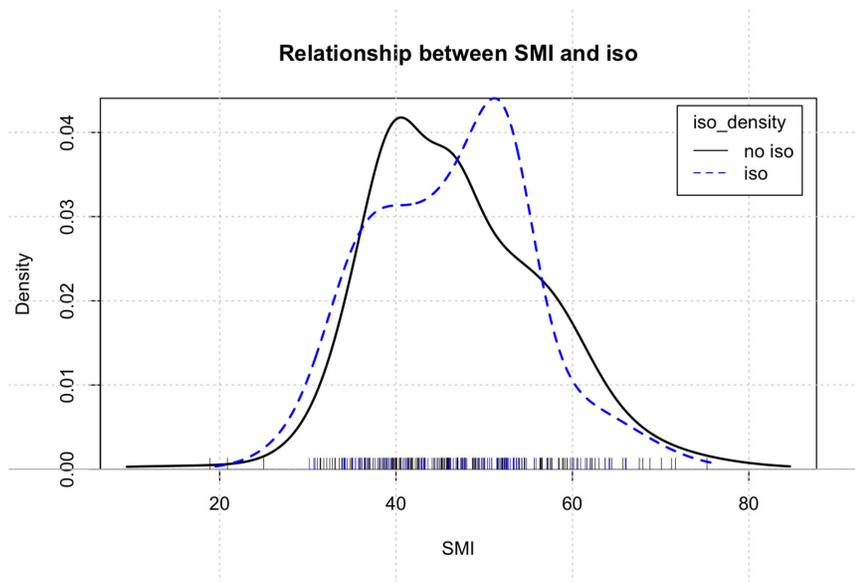
SMI and sex



Notes: Males appear to have a significantly higher SMI.

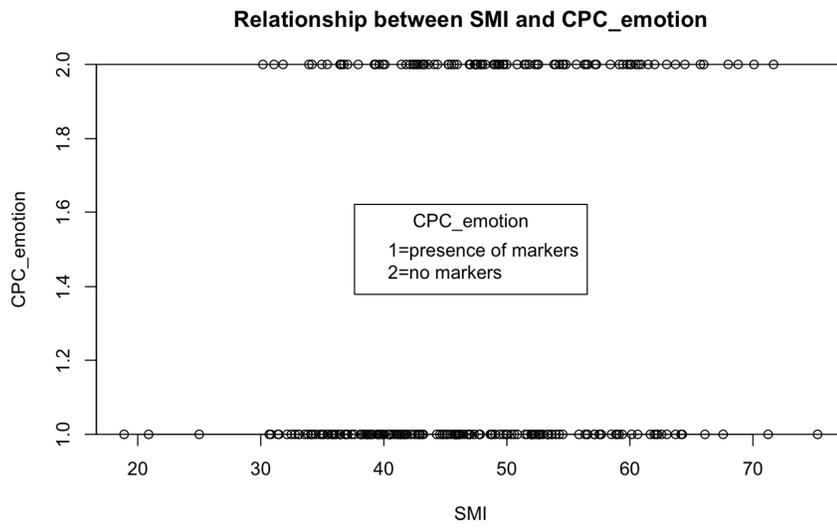
SMI and iso

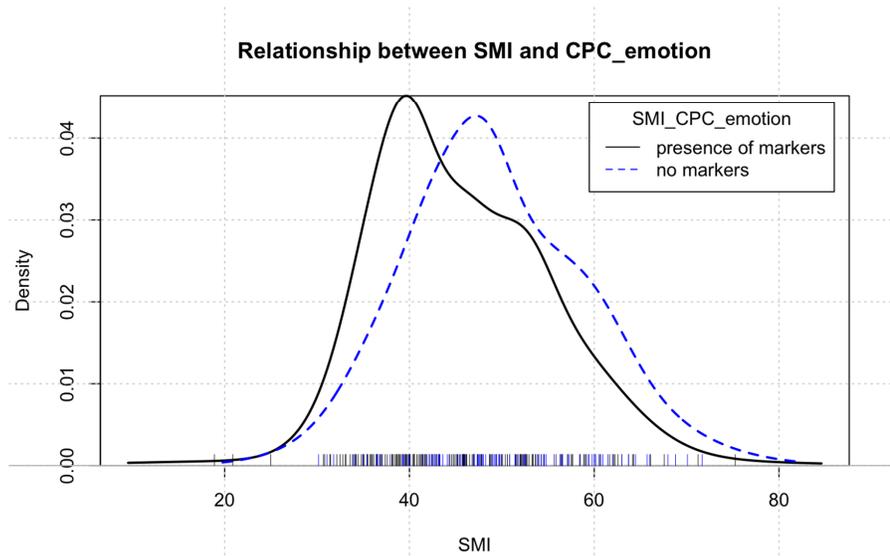
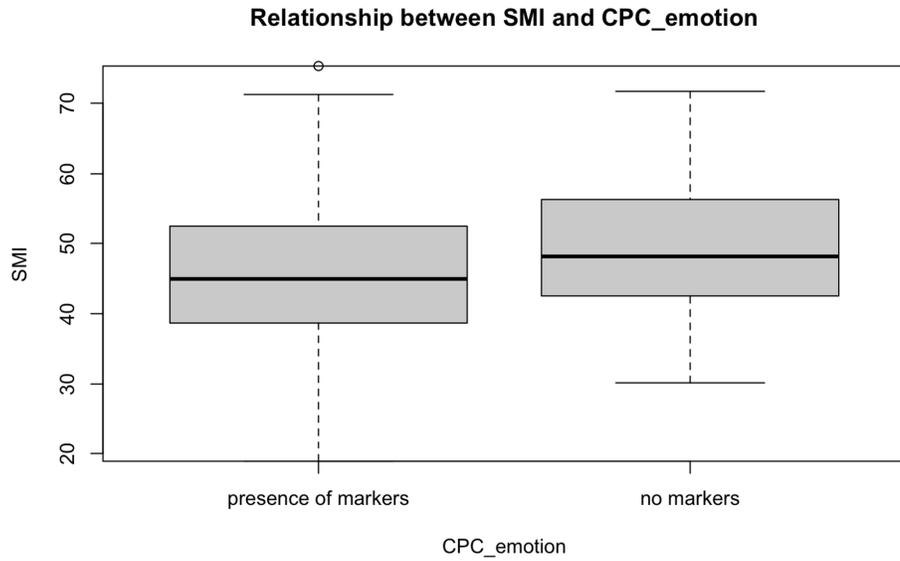




Notes: No strong evidence of a relationship.

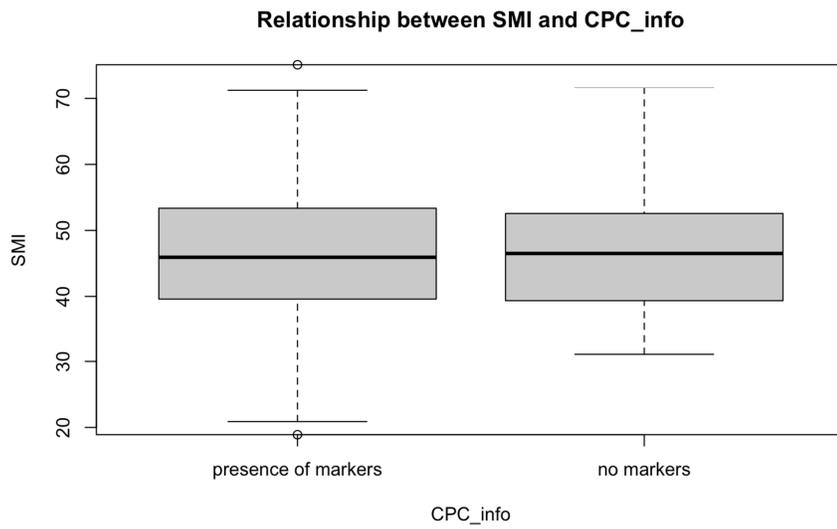
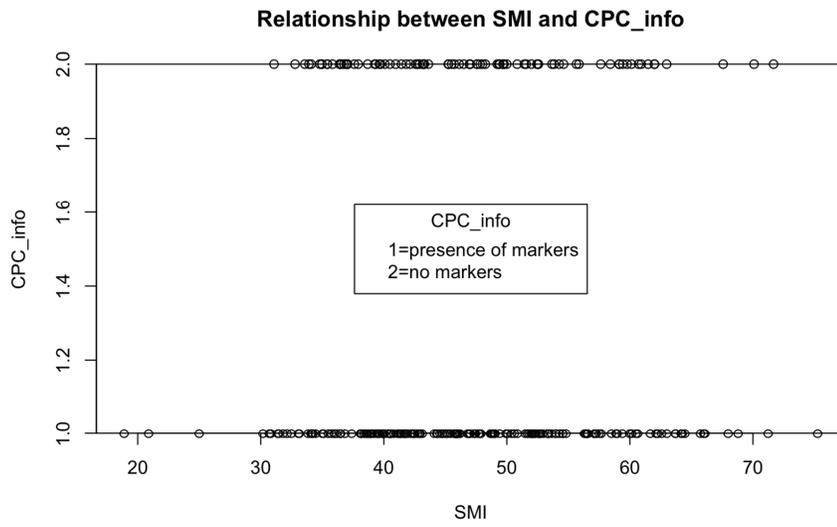
SMI and CPC_emotion

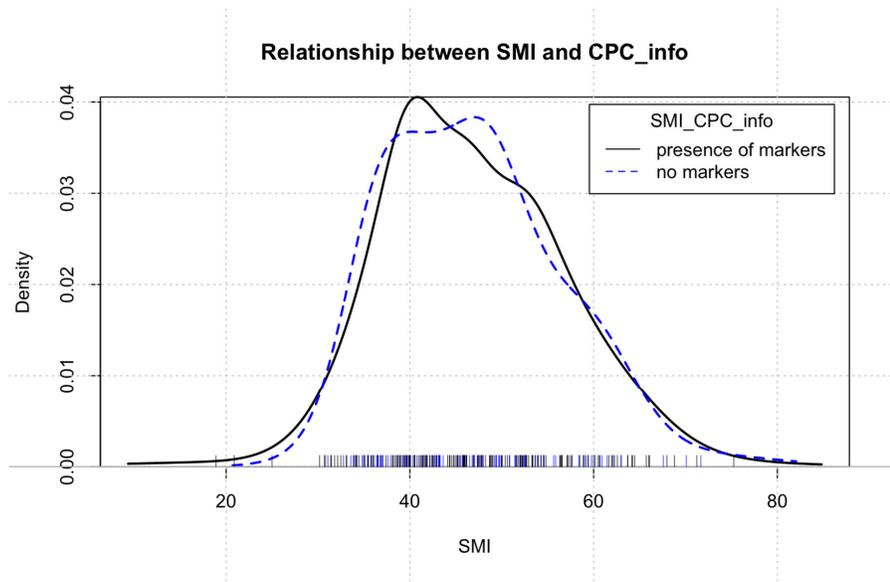




Notes: There is still much overlap in boxplots etc. but it does appear that the SMI of those with emotional concerns is lower. It might be worth studying correlation for these variables.

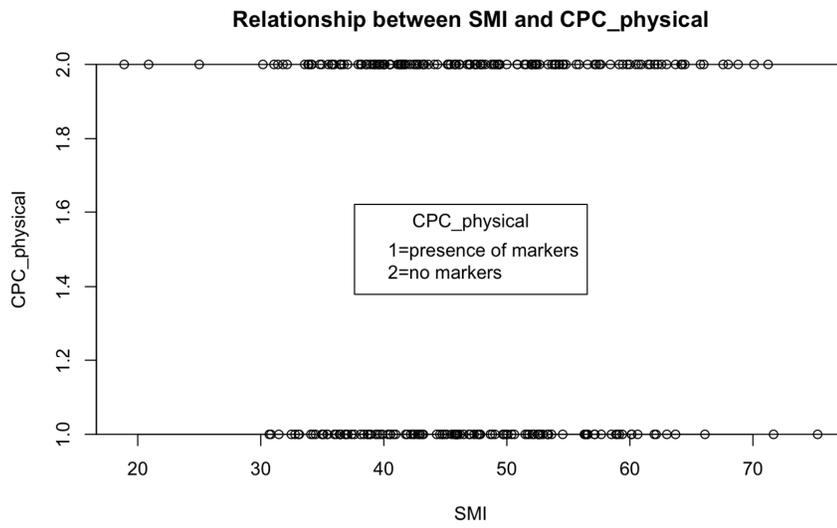
SMI and CPC_info

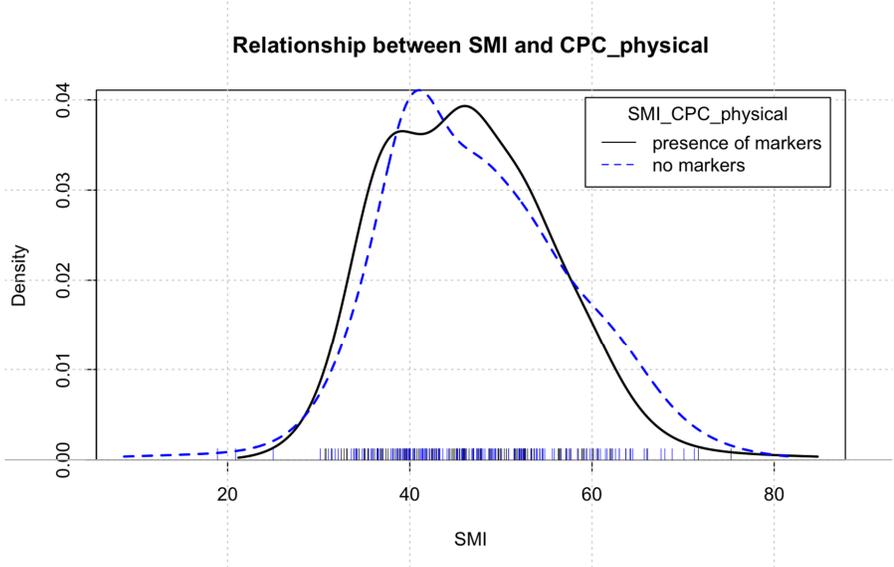
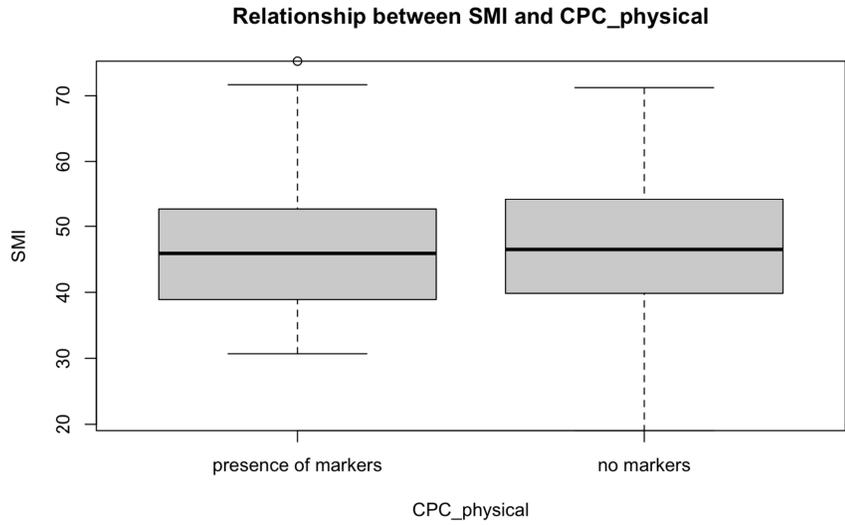




Notes: No strong evidence of relationship here.

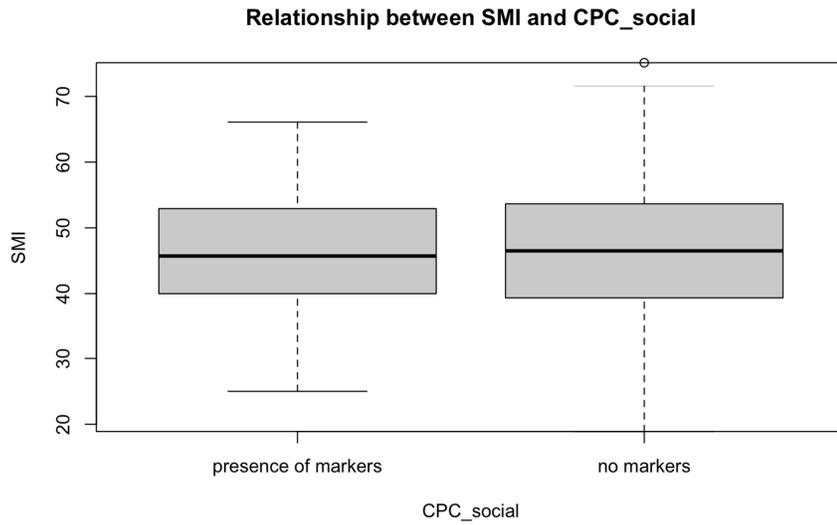
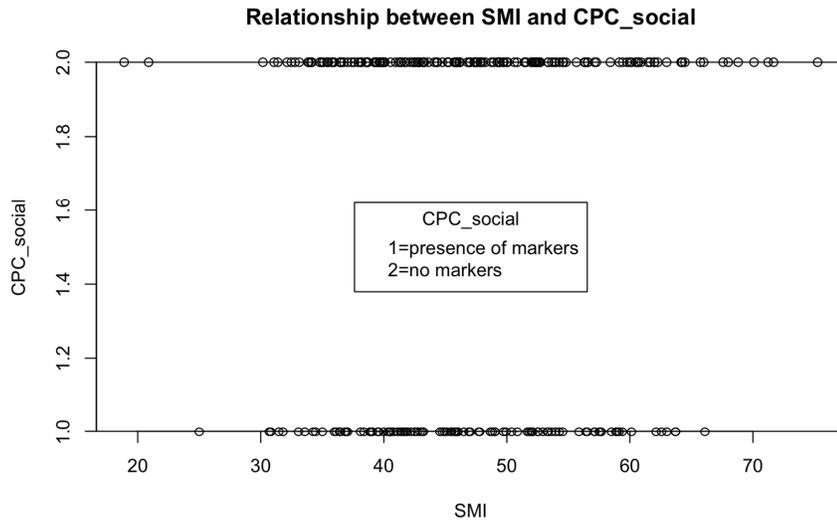
SMI and CPC_physical

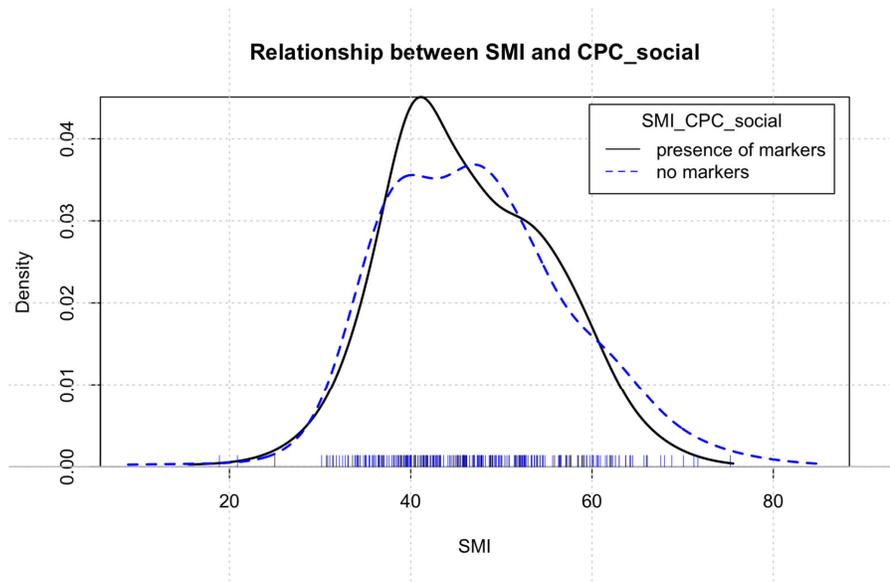




Notes: No strong evidence of relationship here.

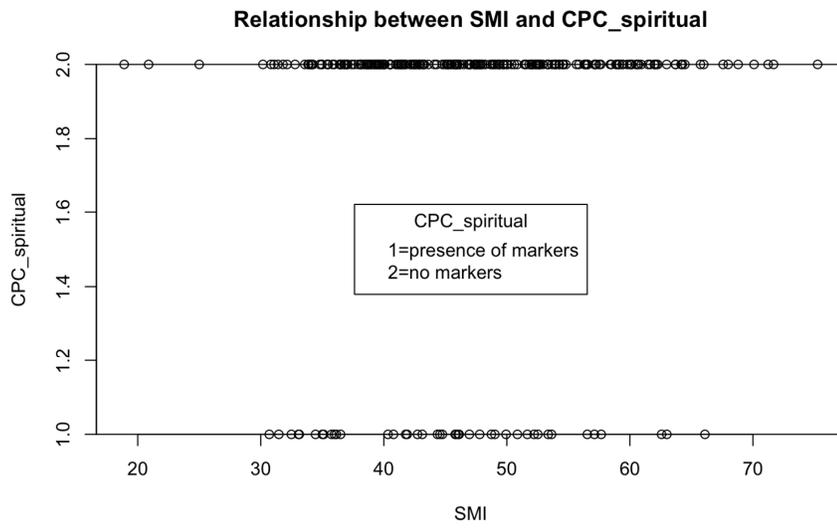
SMI and CPC_social

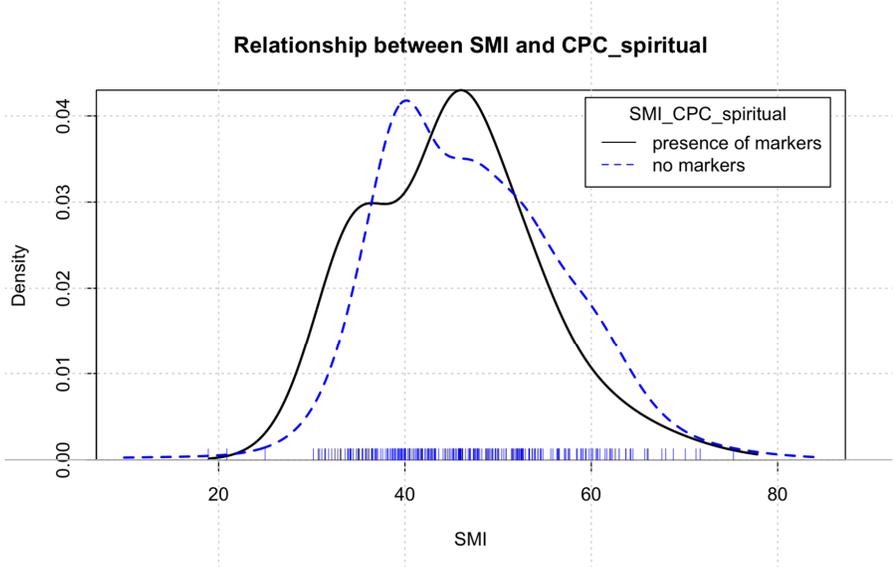
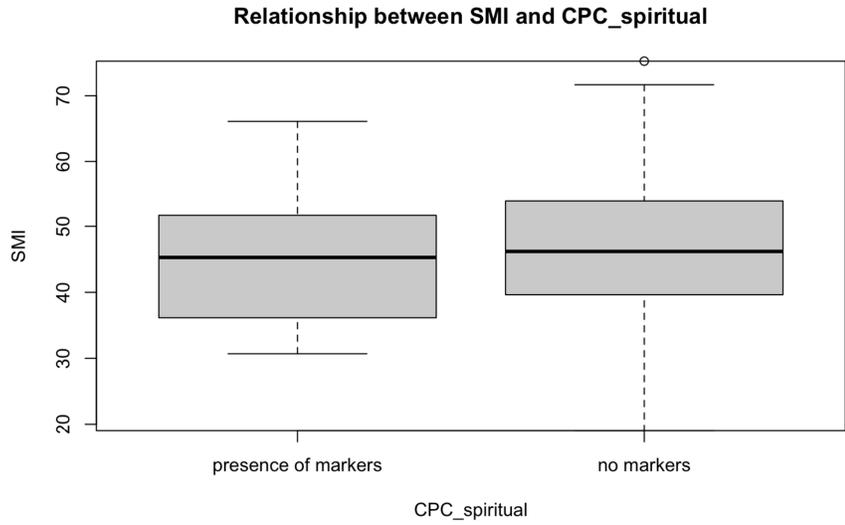




Notes: No strong evidence of a relationship.

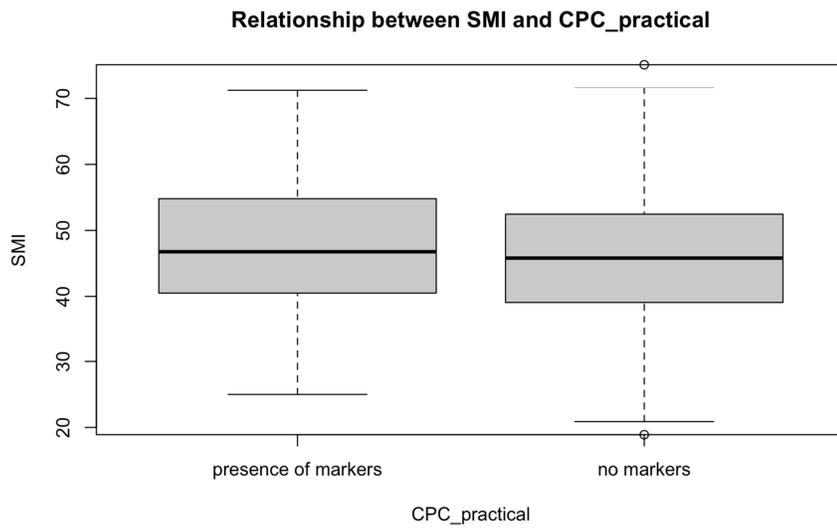
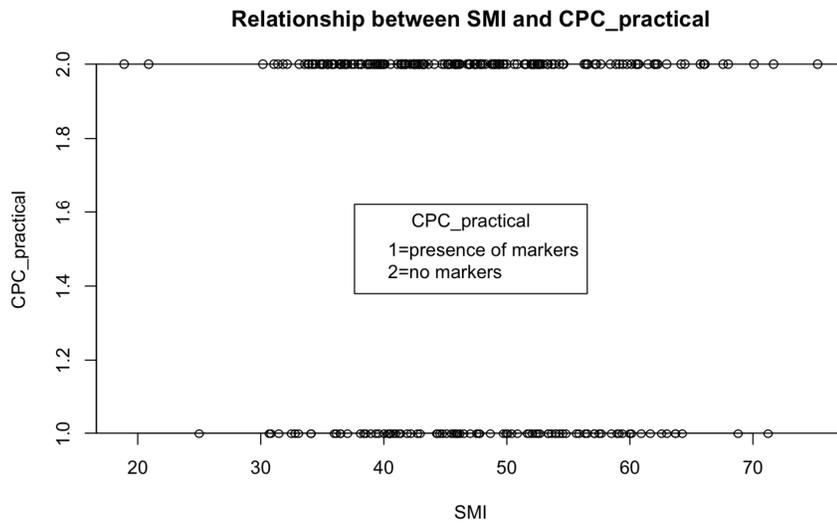
SMI and CPC_spiritual

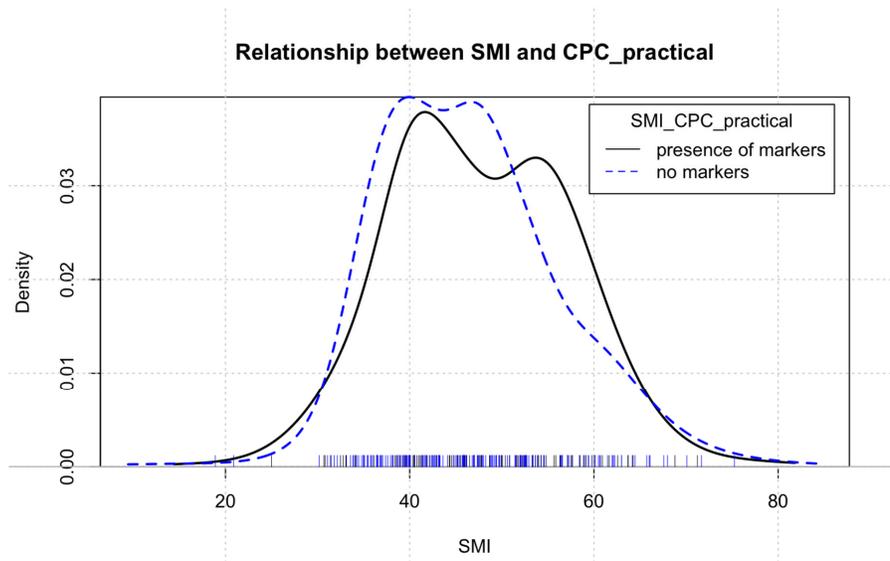




Notes: Potential that those with no markers of spiritual concerns have a slightly higher SMI (when looking at density plot, that curve is shifted to the right), than those with the presence of spiritual concerns.

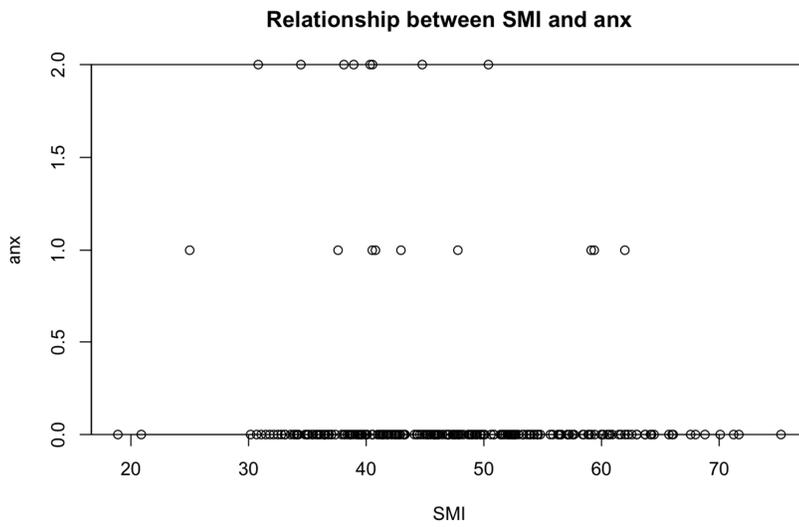
SMI and CPC_practical

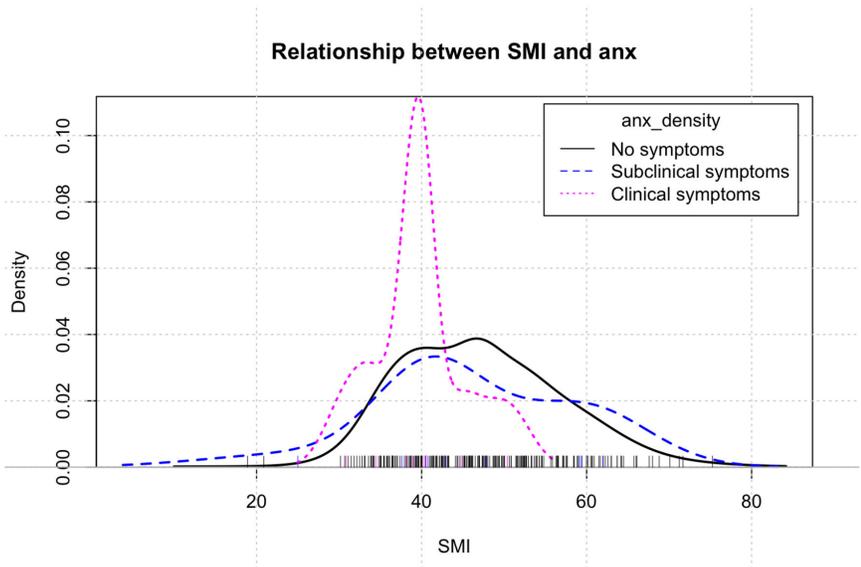
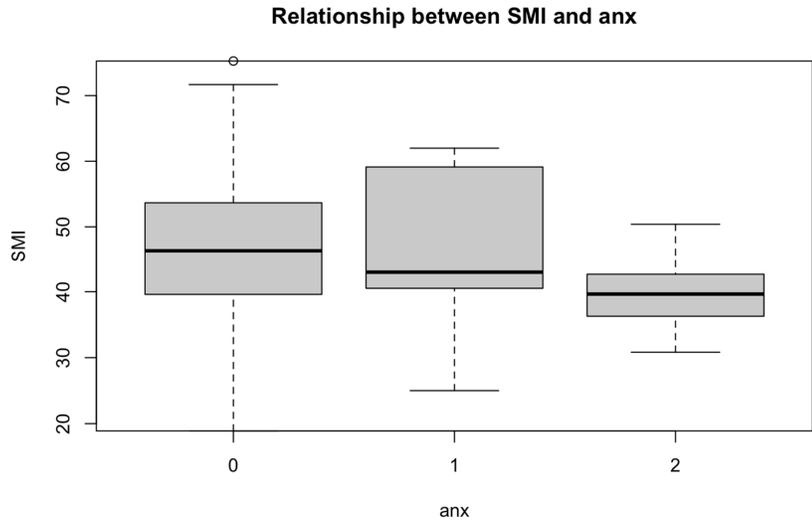




Notes: No strong evidence of relationship. However, potential that the SMI of those with markers of physical concerns (e.g., weight, fatigue) is slightly higher.

SMI and anx



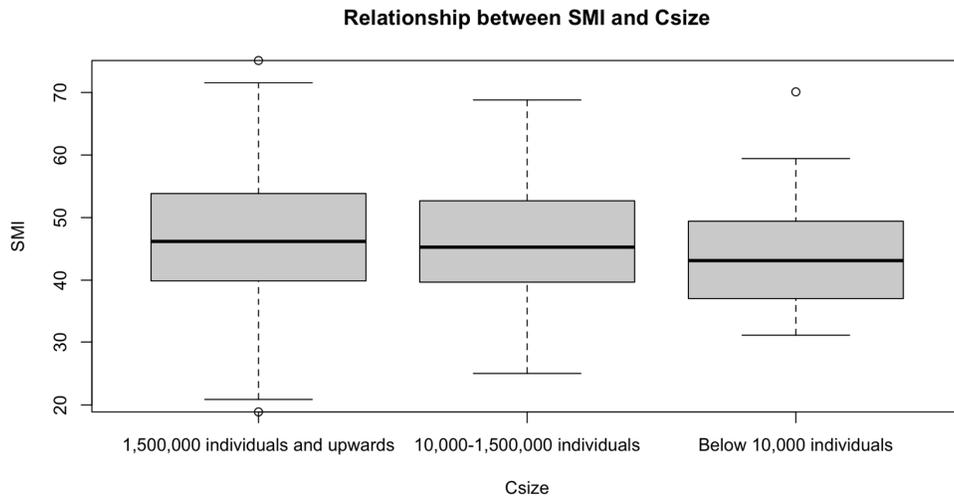
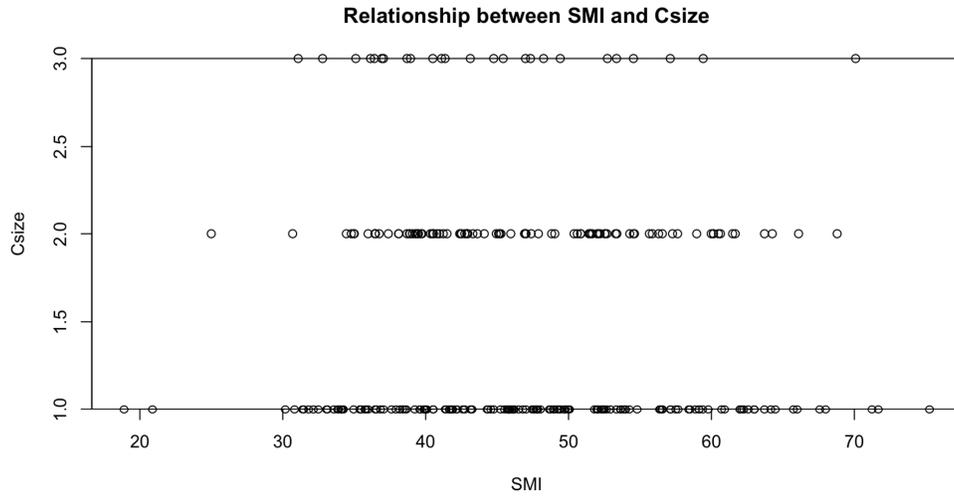


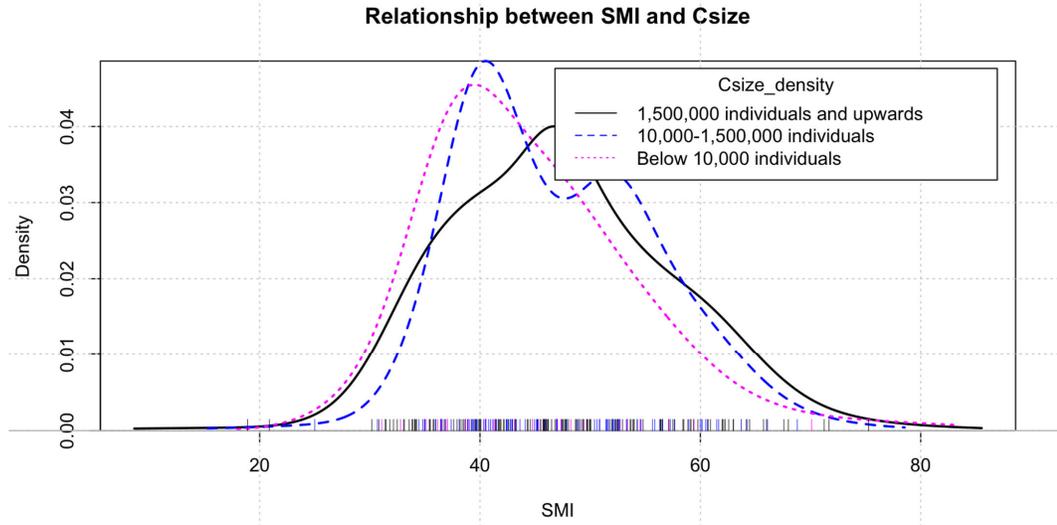
Notes: Plotted still, but not enough people in these categories to study I do not believe.

SMI and dep

Notes: There is not enough spread within dep to study anything meaningful (only 7 people with subclinical symptoms and 4 with clinical, the rest reported no symptoms)

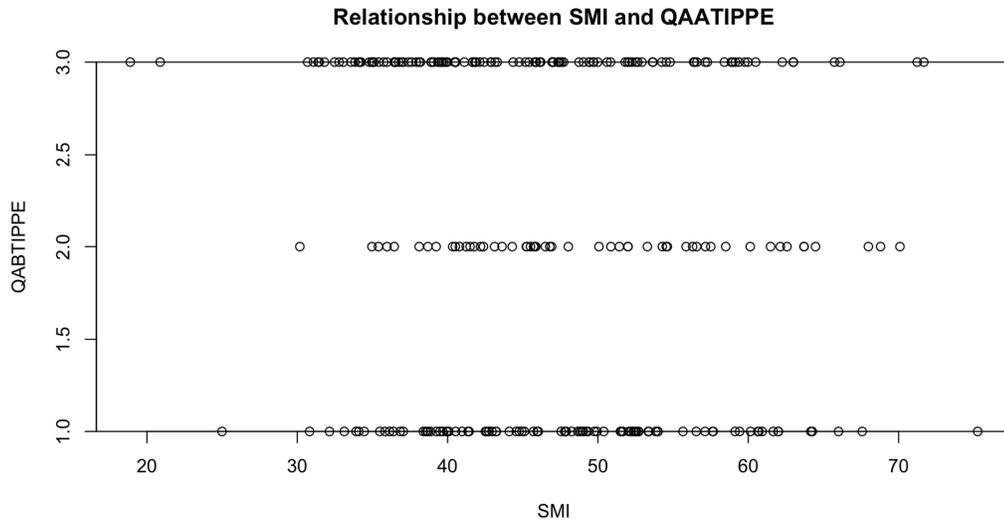
SMI and Csize

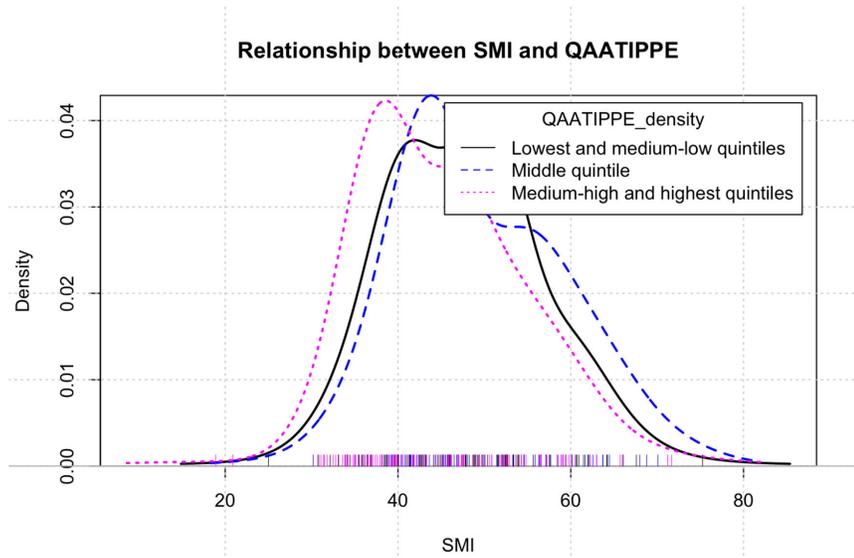
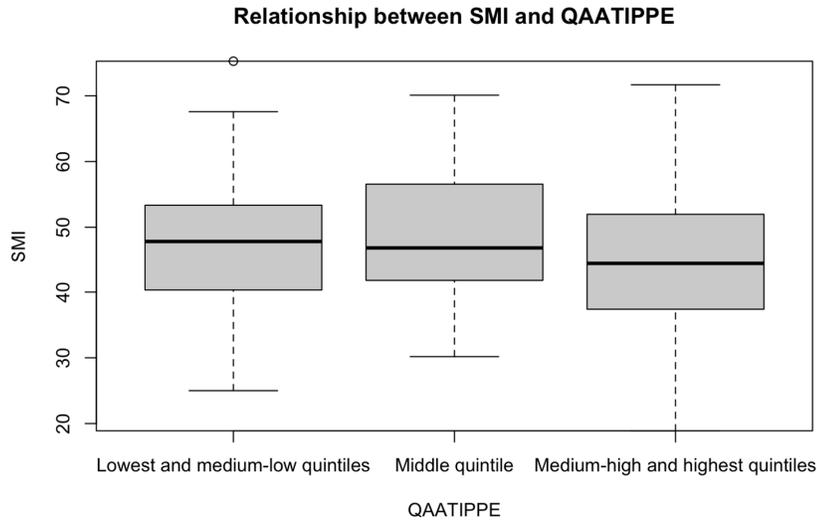




Notes: Potential that those from smaller places have a slightly lower SMI. Although do not predict this correlation to be very strong (there is a lot of overlap in plots). There is also less people and less of a range in the group from smaller places.

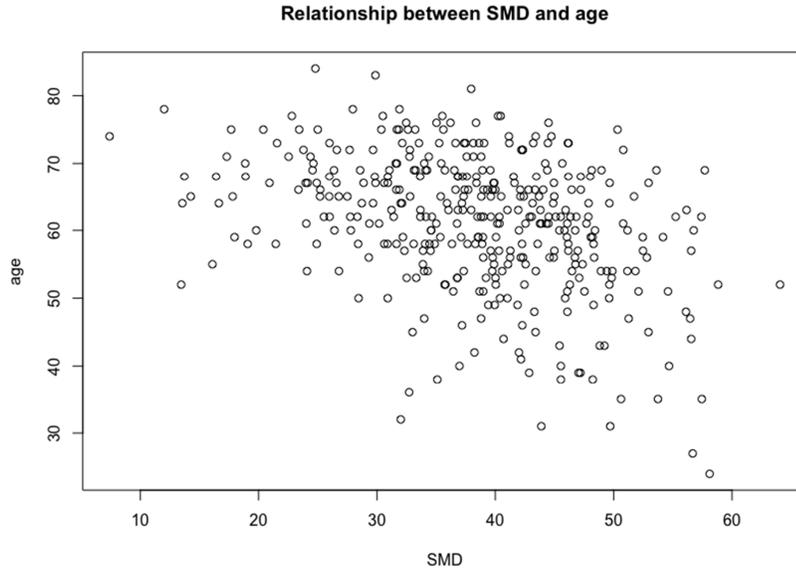
SMI and QAATIPPE





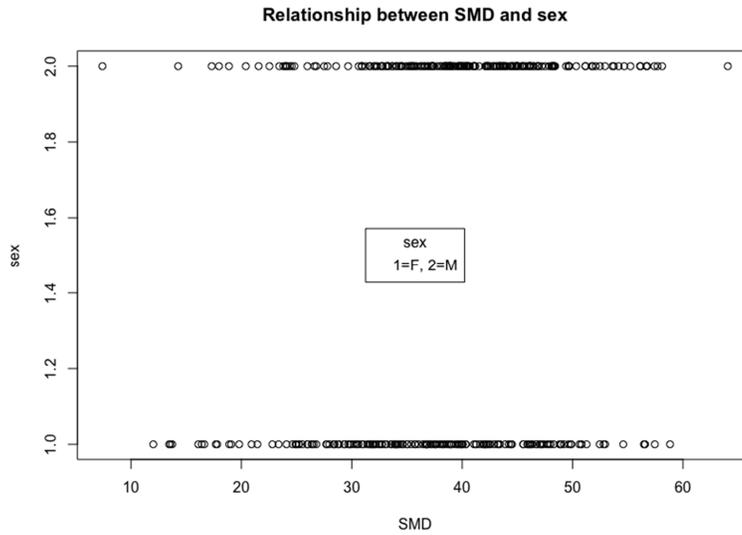
Notes: Potential that those in the middle quintile have a higher SMI than those in the lowest and highest categories, interestingly. However, this is very slight (if any association at all exists).

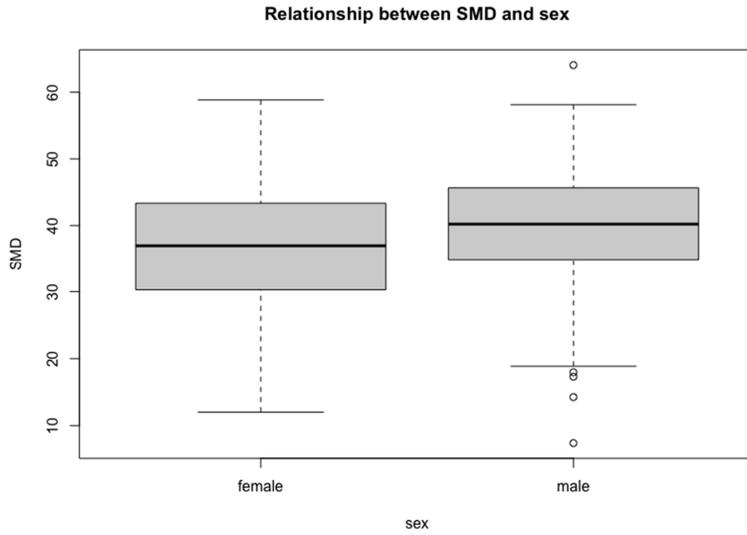
SMD and age



Notes: Weak evidence of a potential relationship.

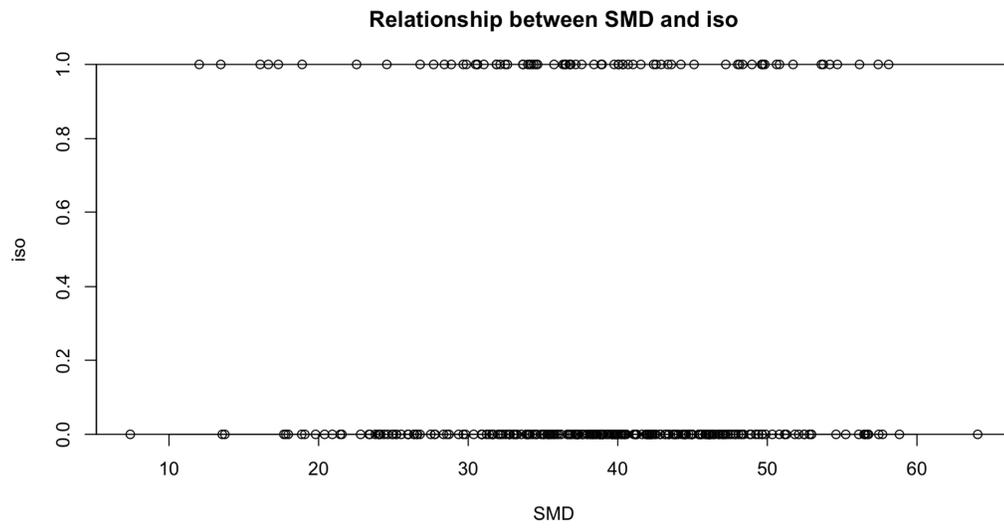
SMD and sex

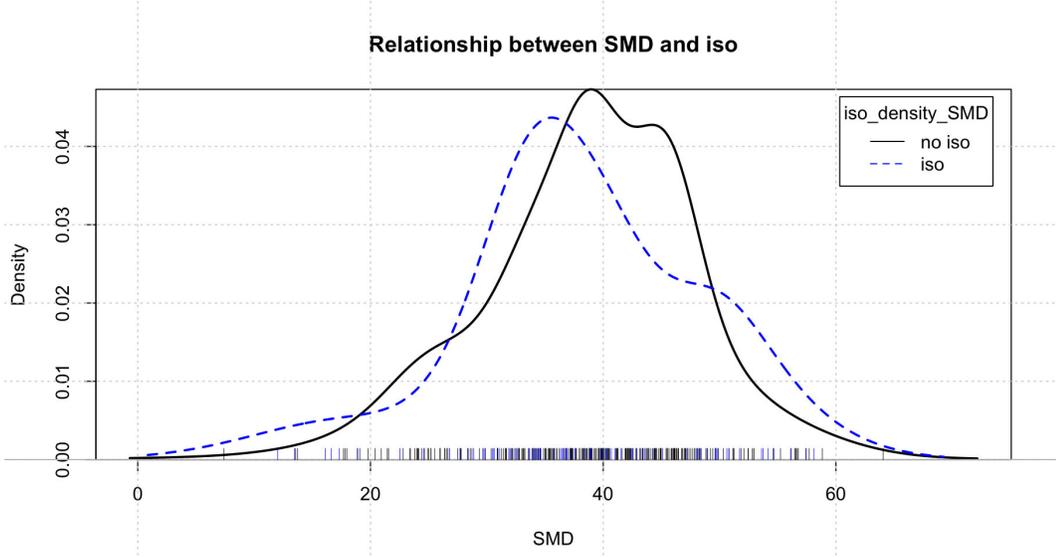
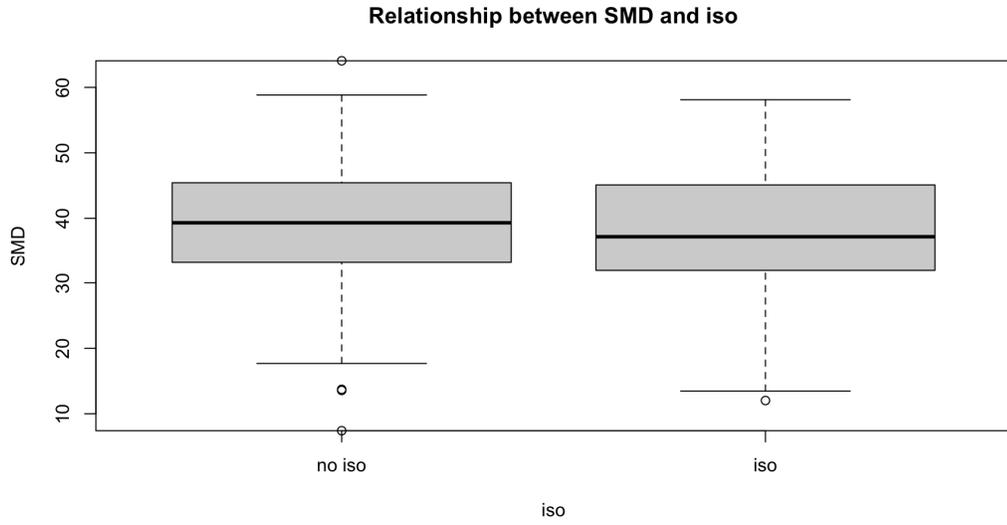




Notes: No strong evidence of a relationship.

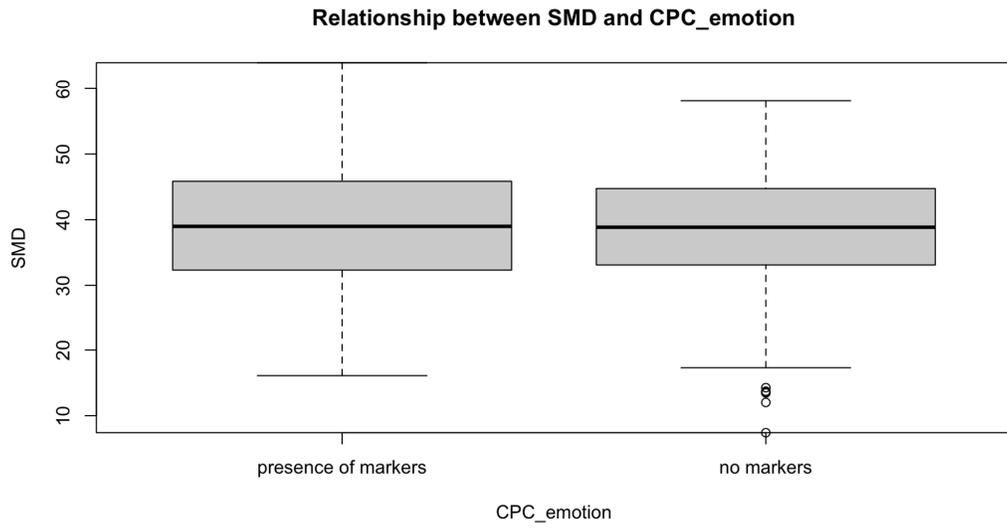
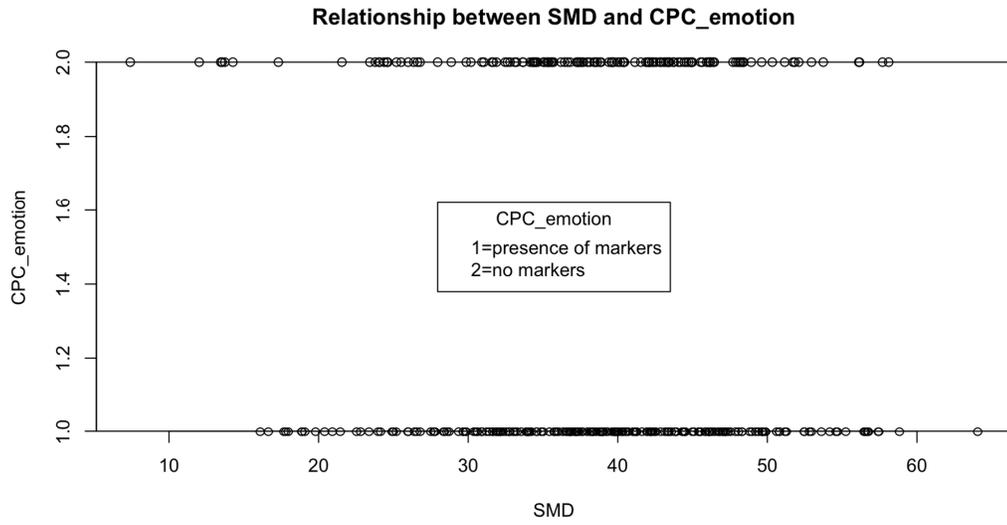
SMD and iso

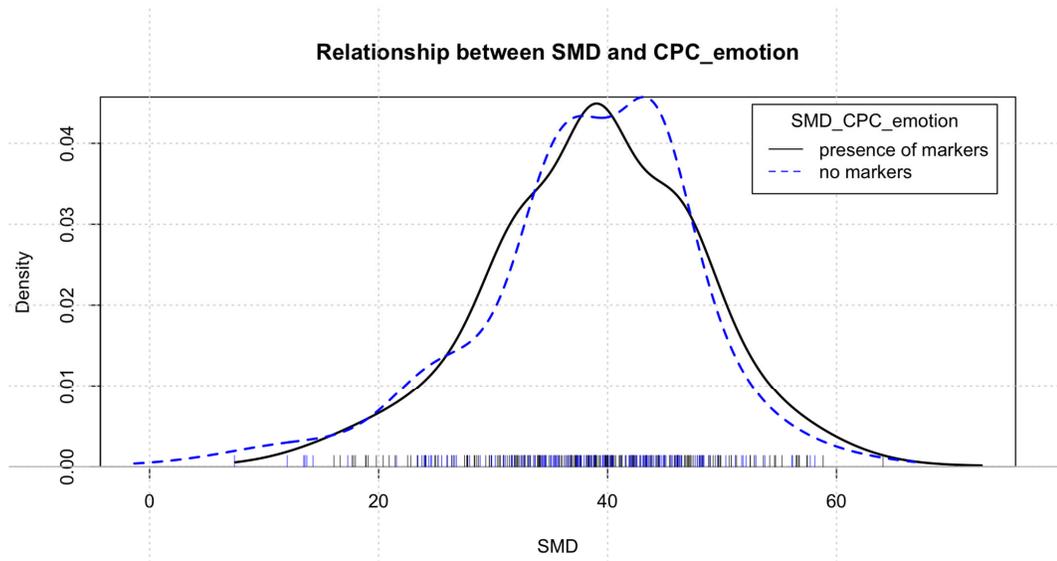




Notes: Potentially that those without iso have higher SMD. However, there is some higher SMD's in the group with iso/overlap at the higher range, so the association would not be high.

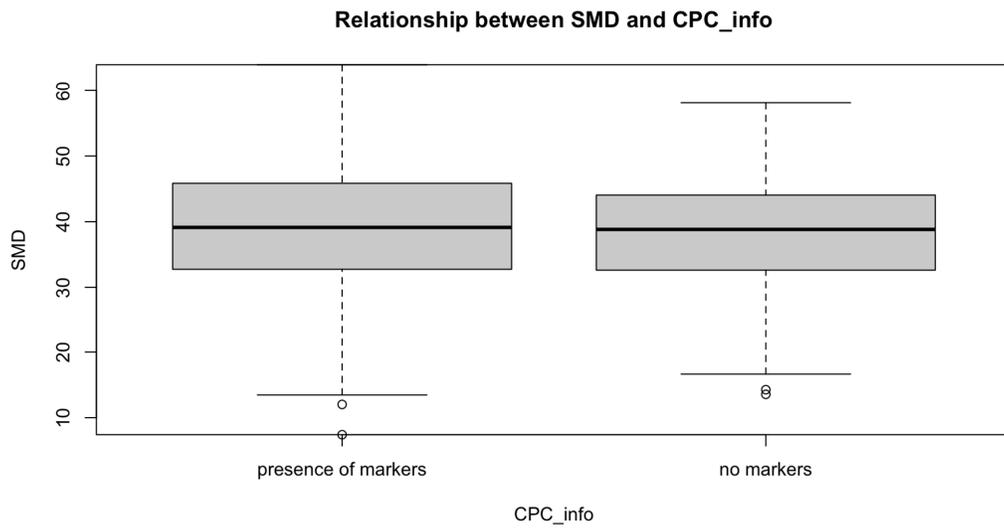
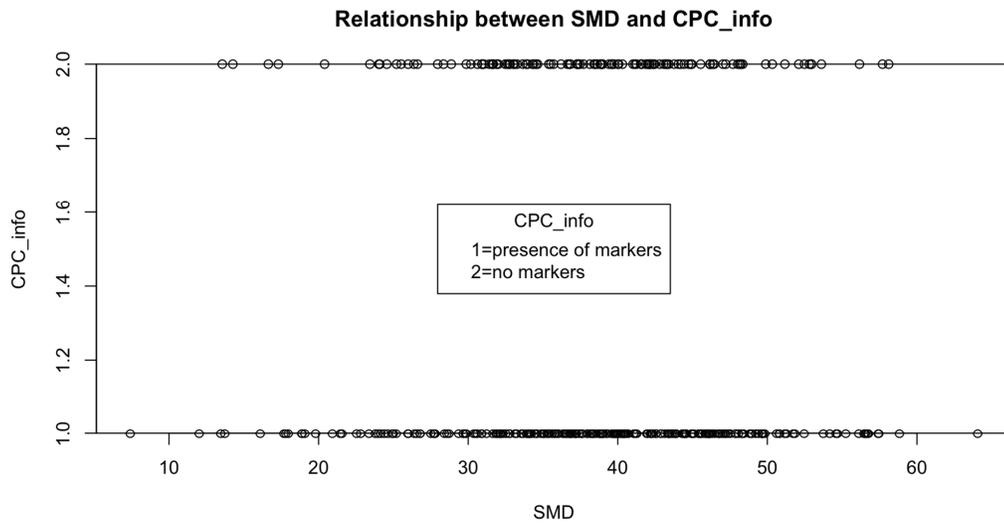
SMD and CPC_emotion

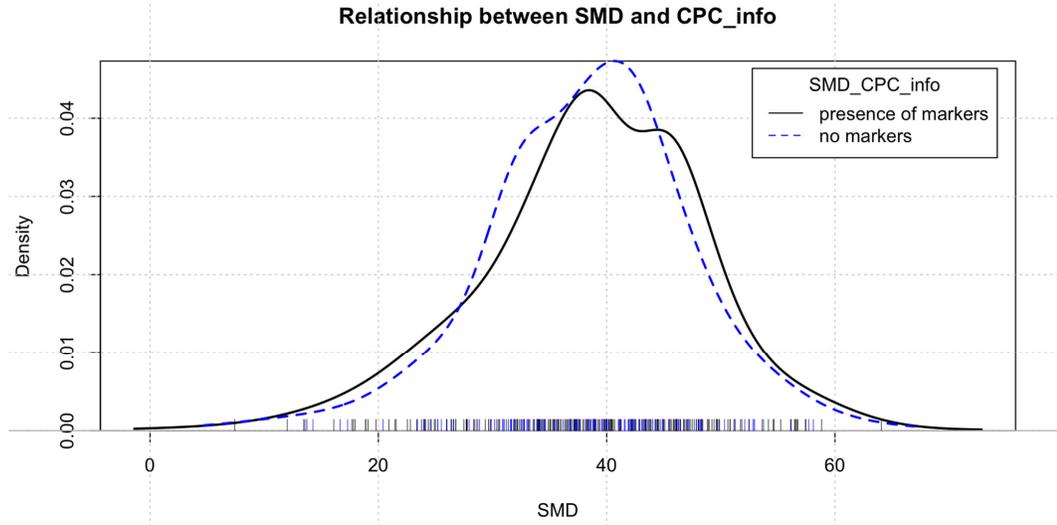




Notes: No evidence of relationship, similar in spread and mean/median values.

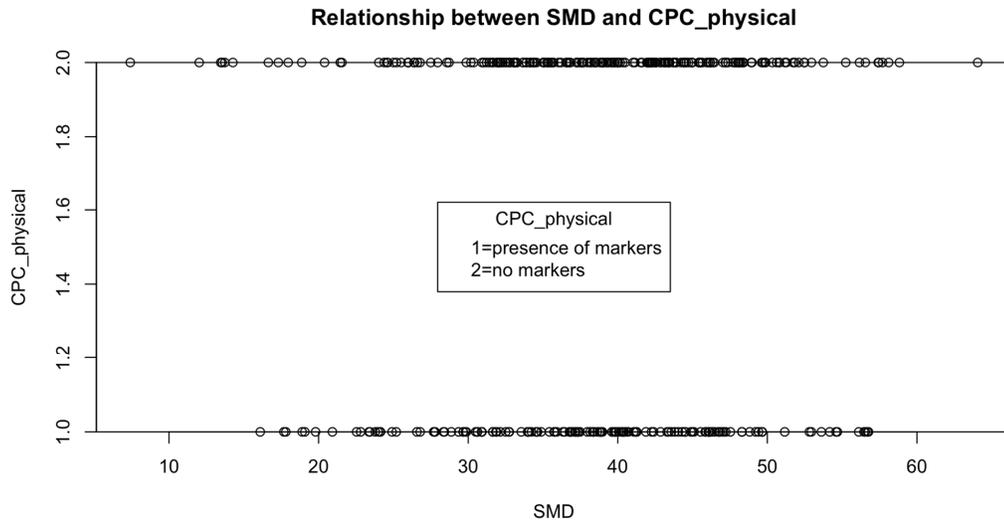
SMD and CPC_info

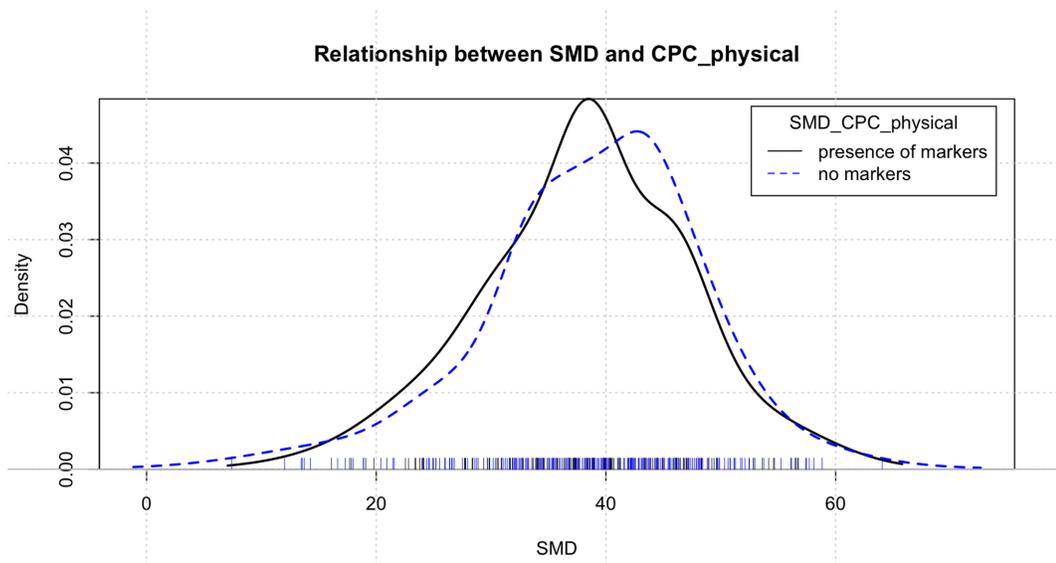
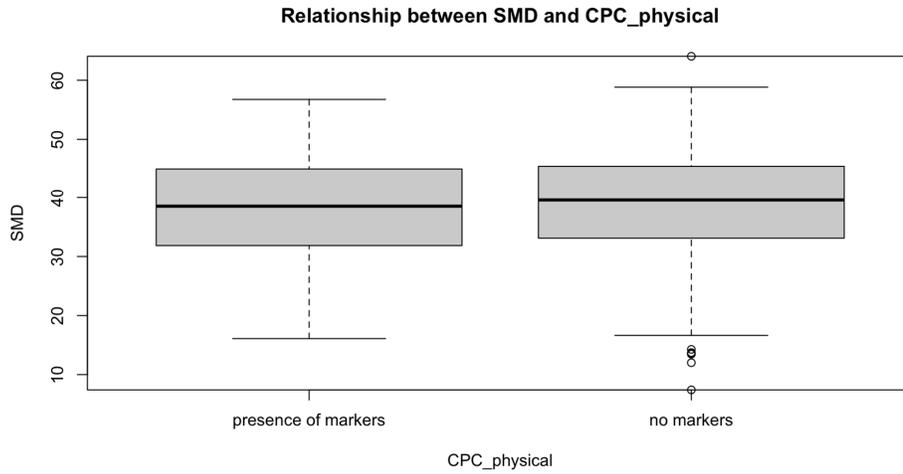




Notes: No strong evidence of relationship (much overlap between groups). But, if anything, potentially those with informational concerns have a slightly higher SMD.

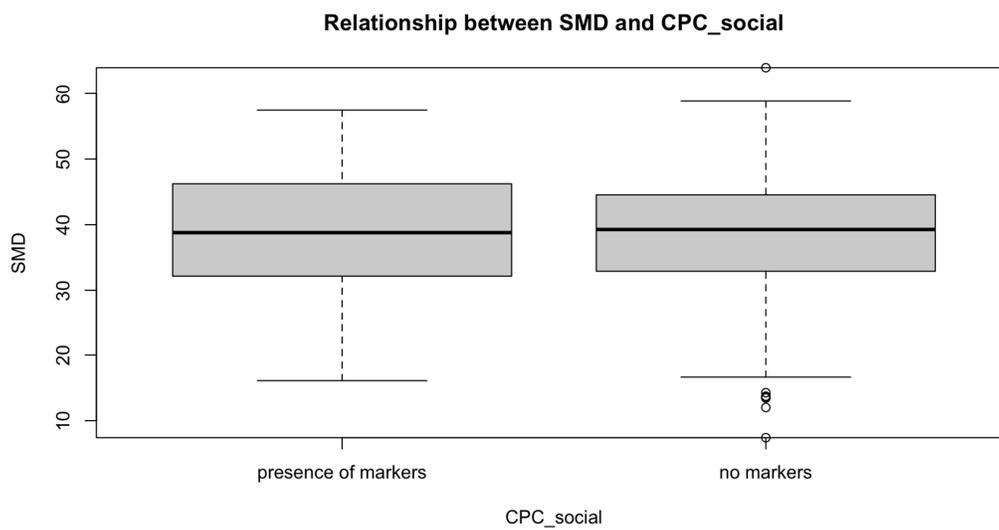
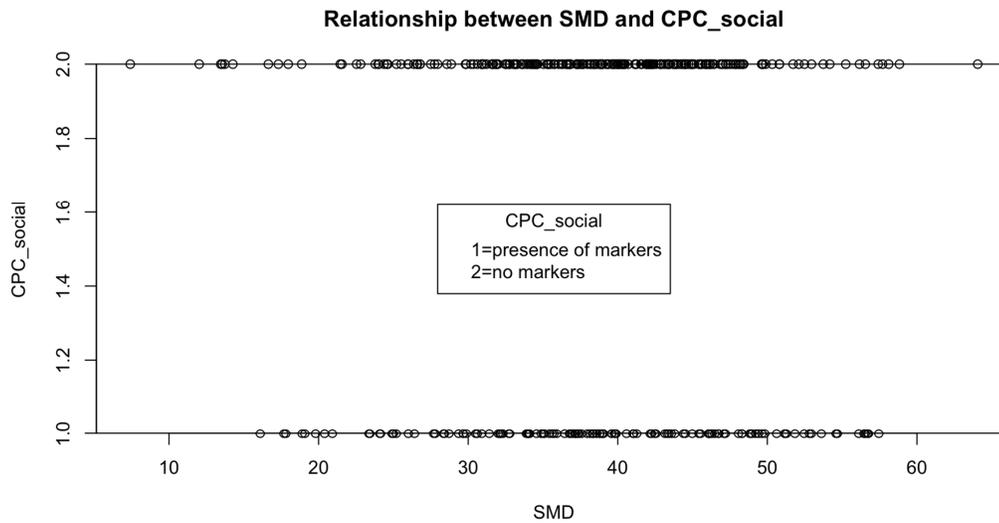
SMD and CPC_physical

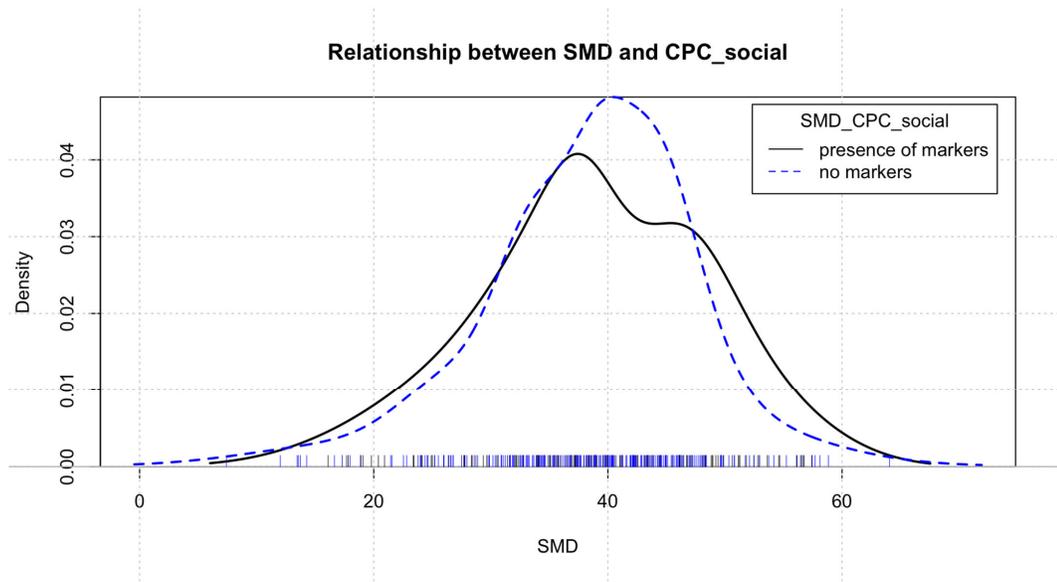




Notes: No strong evidence of relationship. Potentially slightly higher SMD in those without physical concerns.

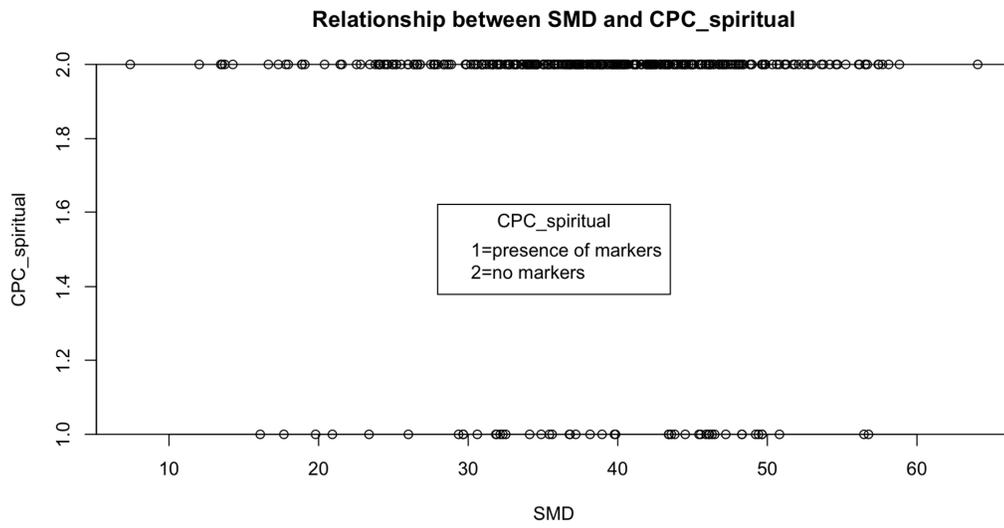
SMD and CPC_social

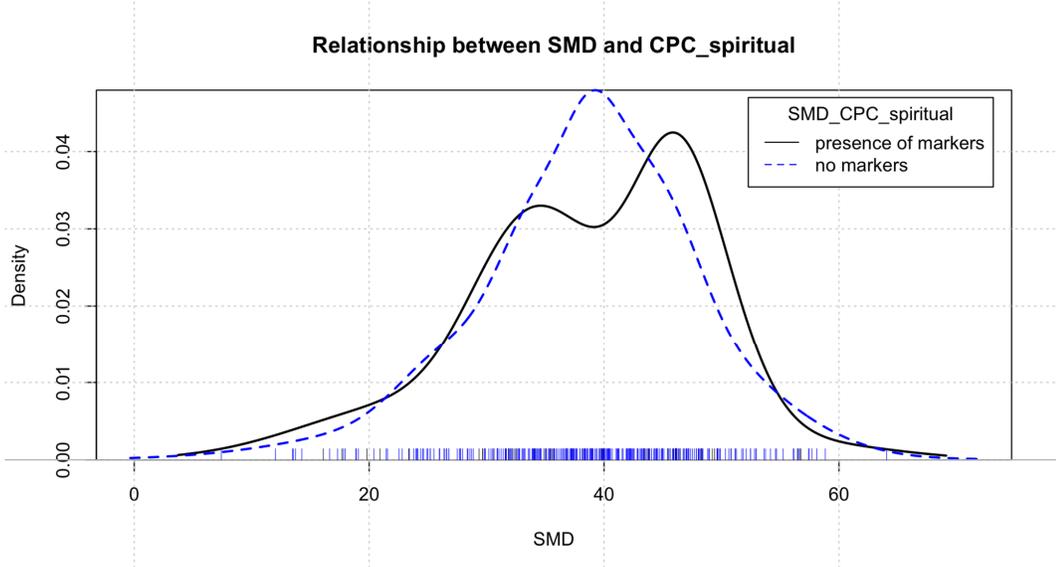
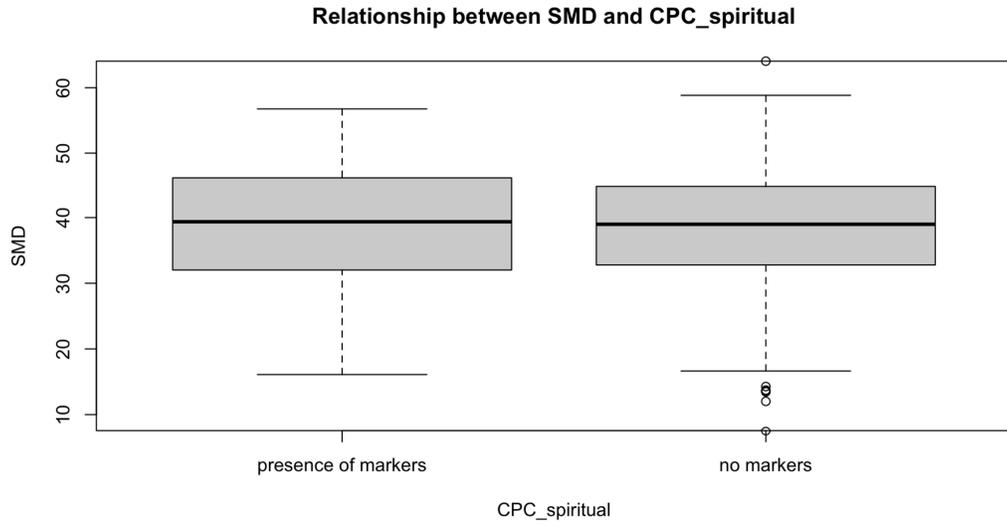




Notes: No strong evidence of any relationship.

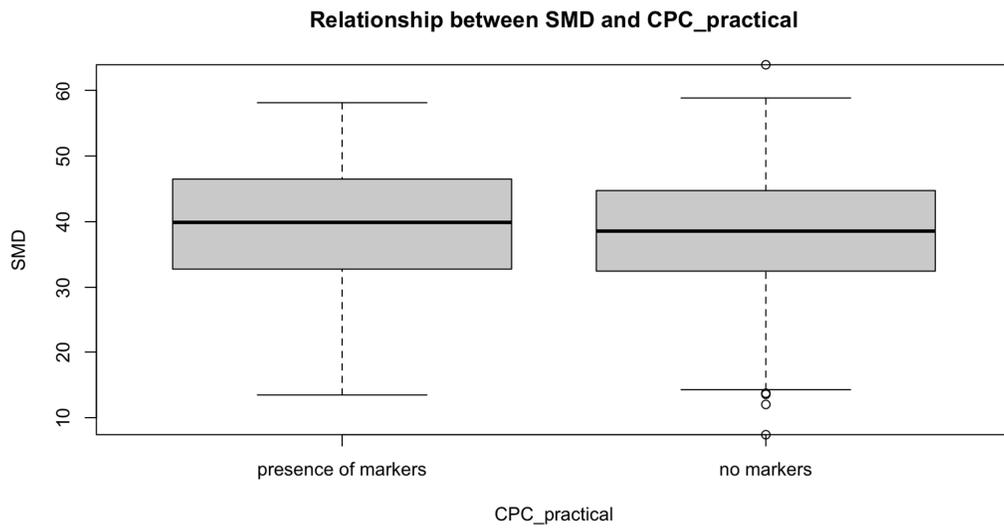
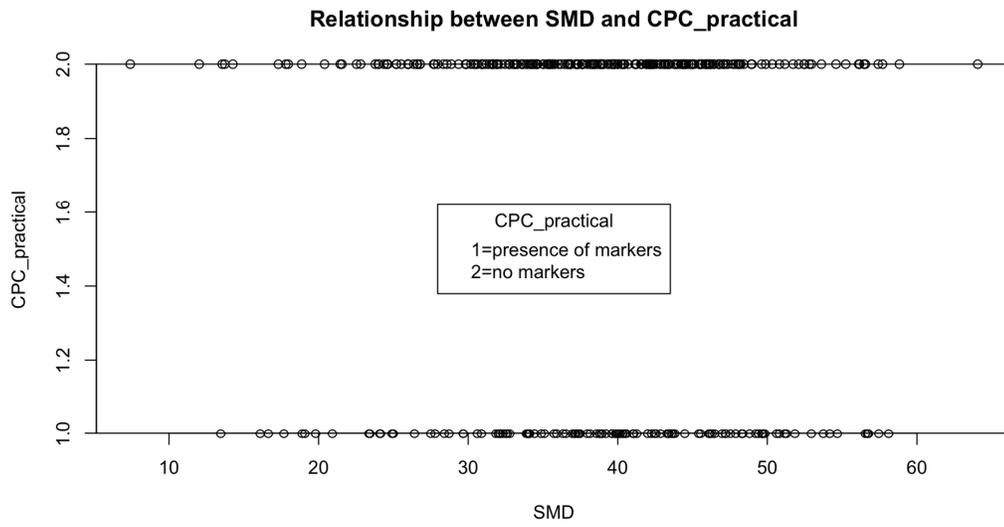
SMD and CPC_spiritual

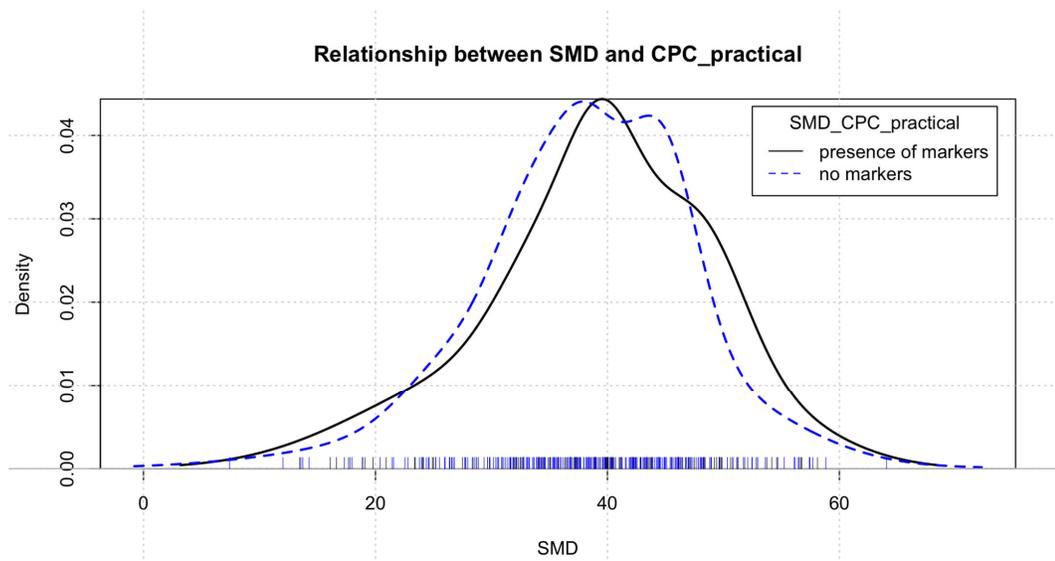




Notes: No clear evidence of a relationship.

SMD and CPC_practical





Notes: No strong evidence of relationship. However, potentially those with practical concerns have higher SMD (interestingly).

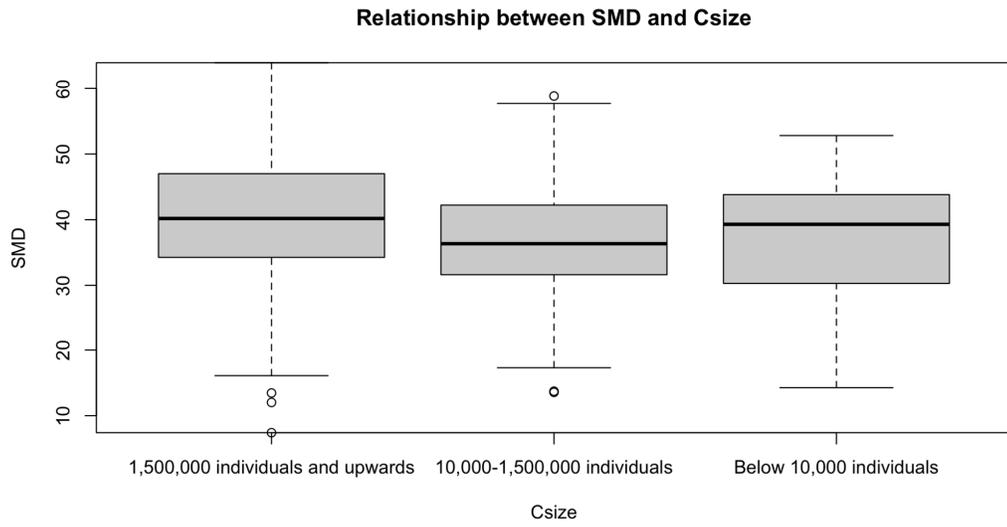
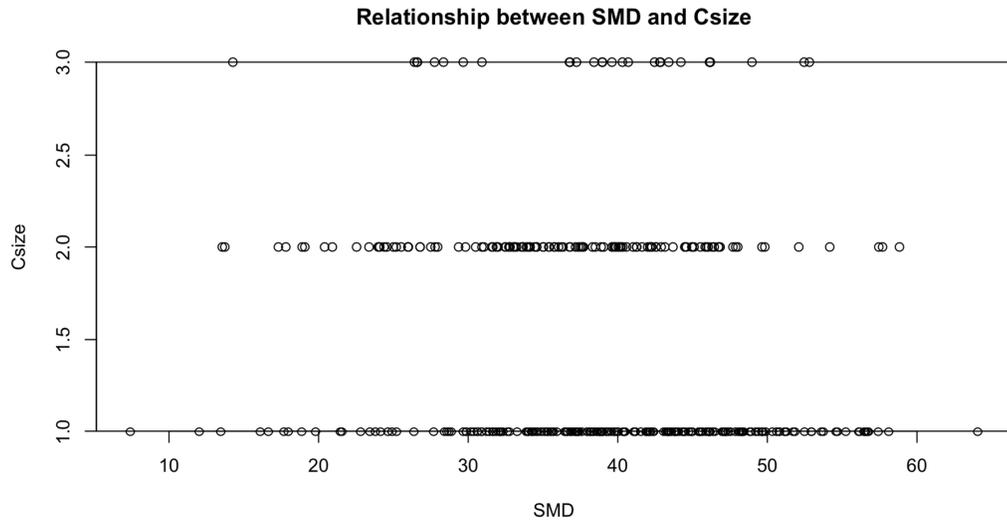
SMD and anx

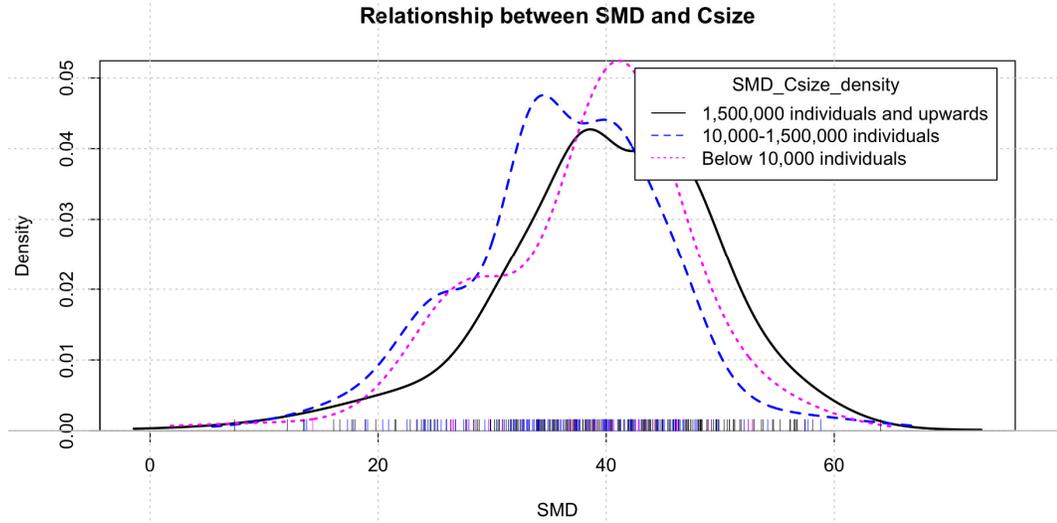
Notes: There is not enough spread within anx to study anything meaningful.

SMD and dep

Notes: There is not enough spread within dep to study anything meaningful.

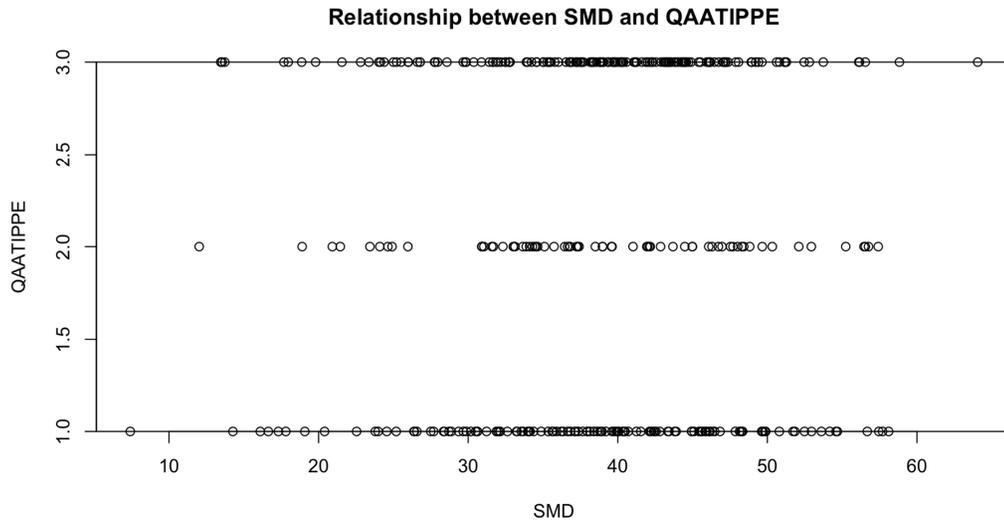
SMD and Csize

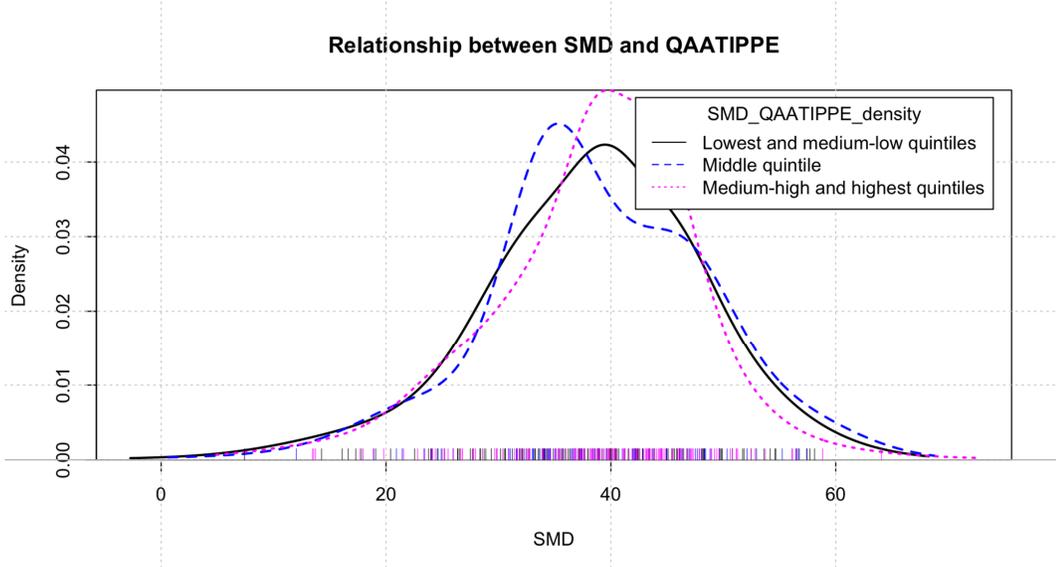
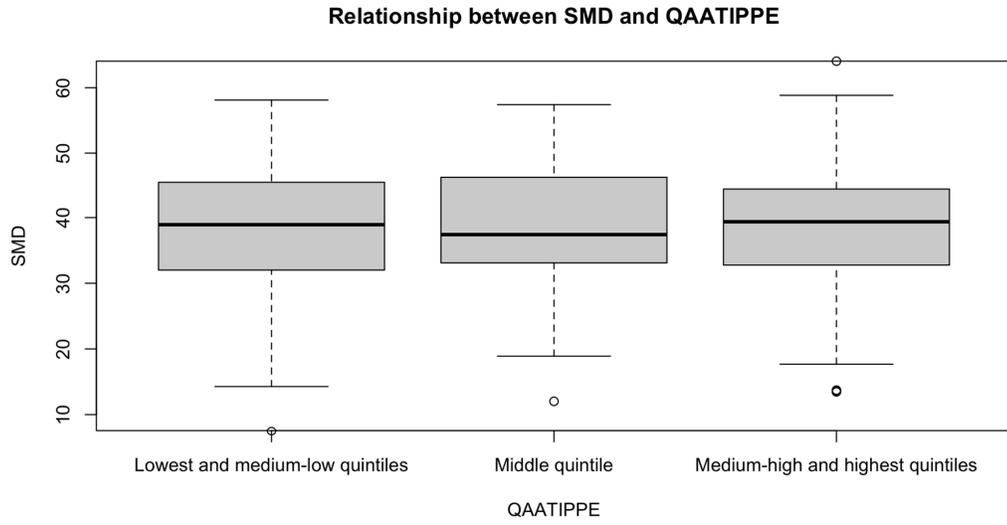




Notes: Those from larger locations appear to have higher SMDs. However, interestingly, those from the lowest locations appear to be in the middle for SMD, with those from the middle Csize being the lowest in SMD.

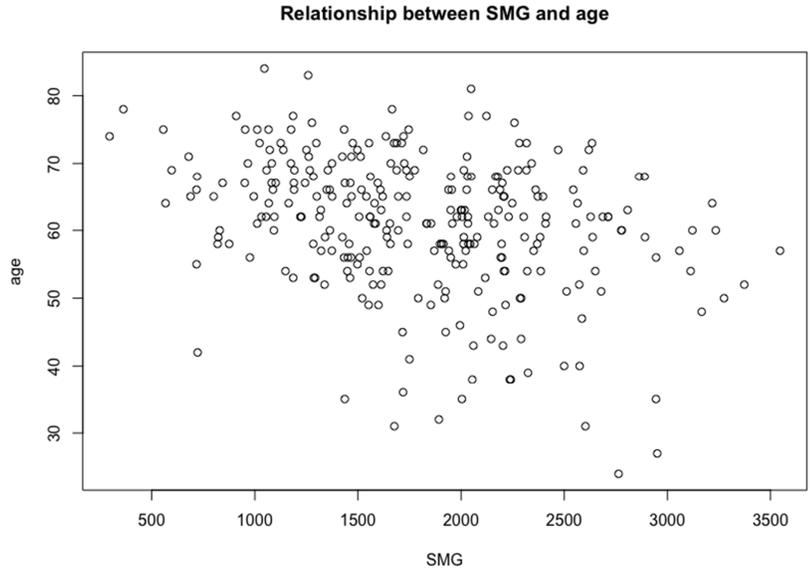
SMD and QAATIPPE





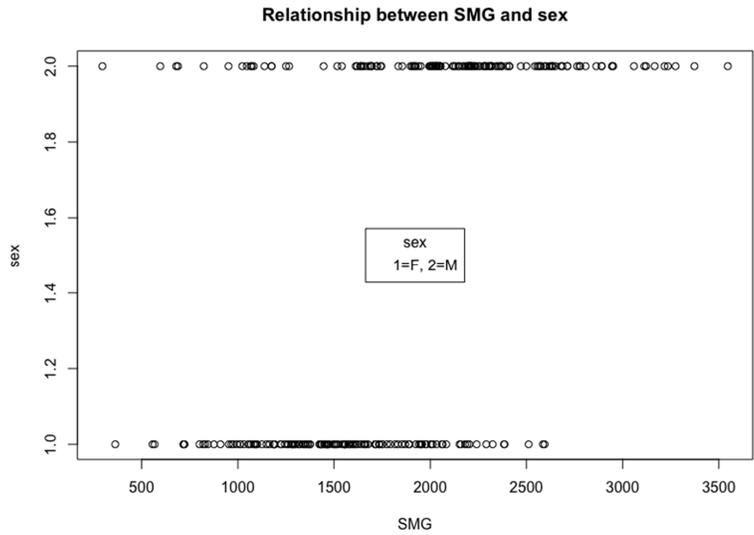
Notes: No strong evidence of any relationship.

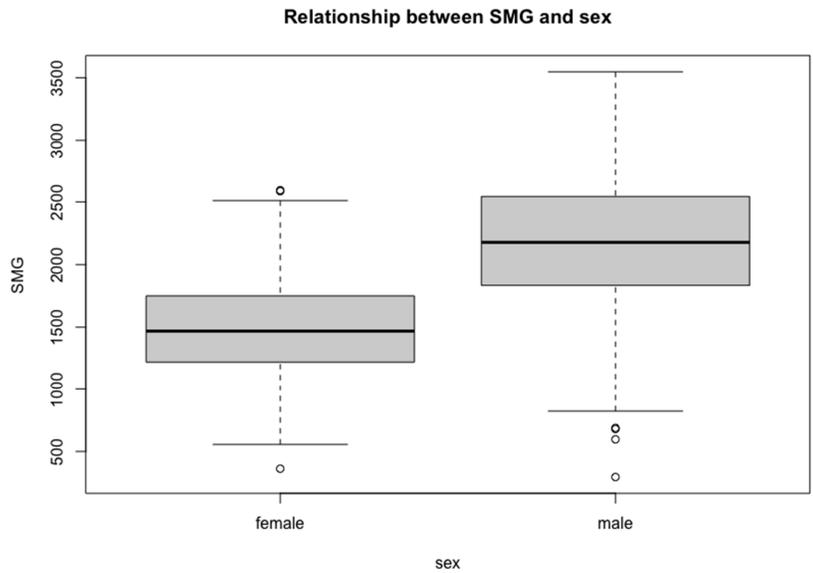
SMG and age



Notes: Weak evidence of relationship (i.e., those with higher SMG are younger).

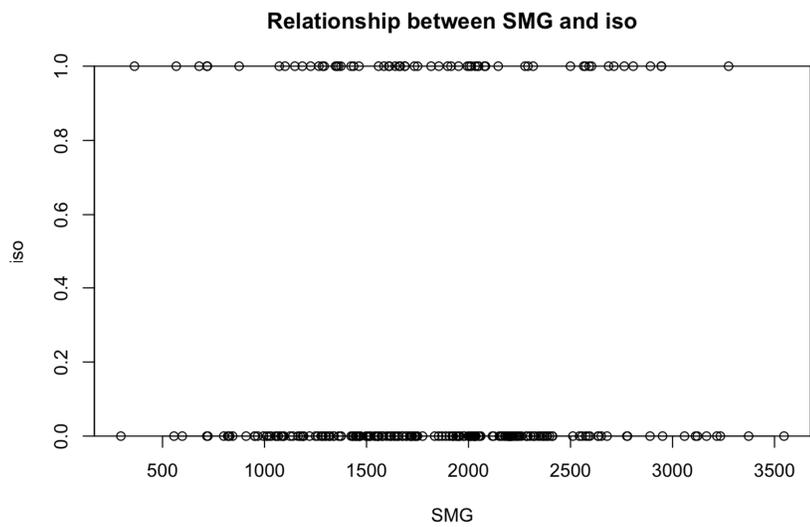
SMG and sex

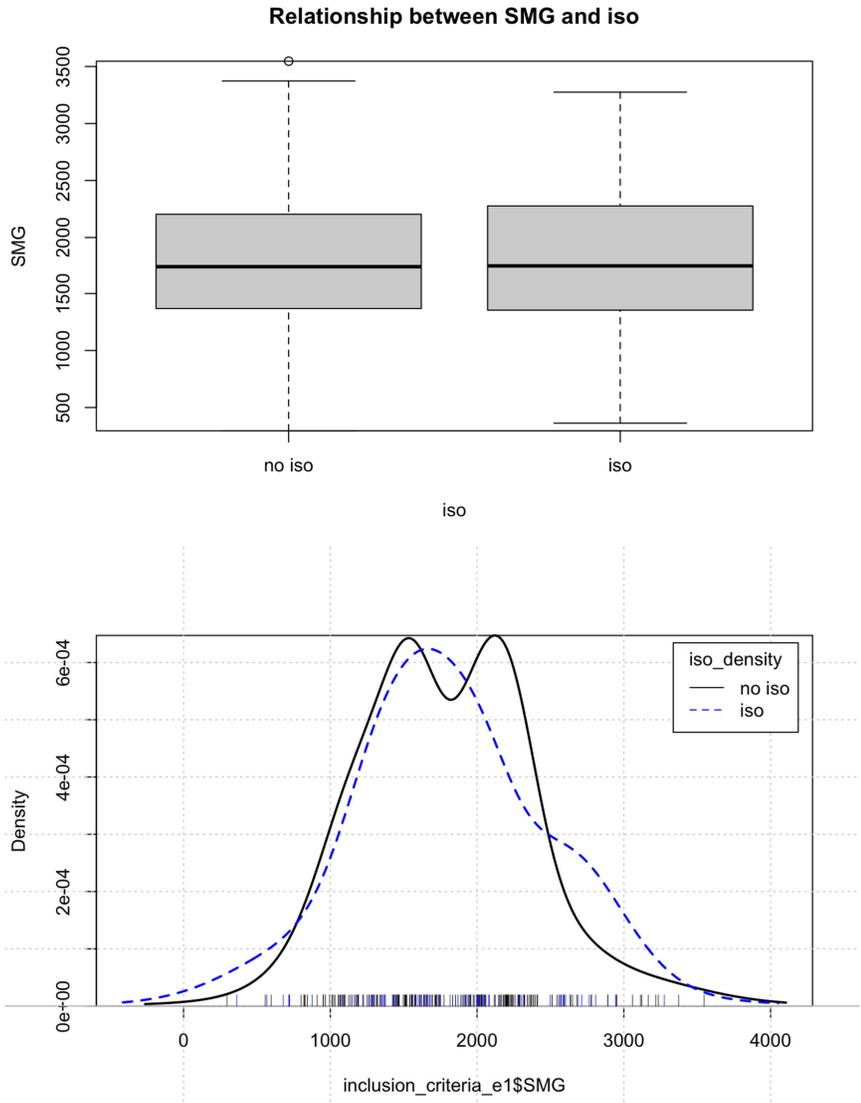




Notes: Strong evidence of potential relationship in which males have a higher SMG than females.

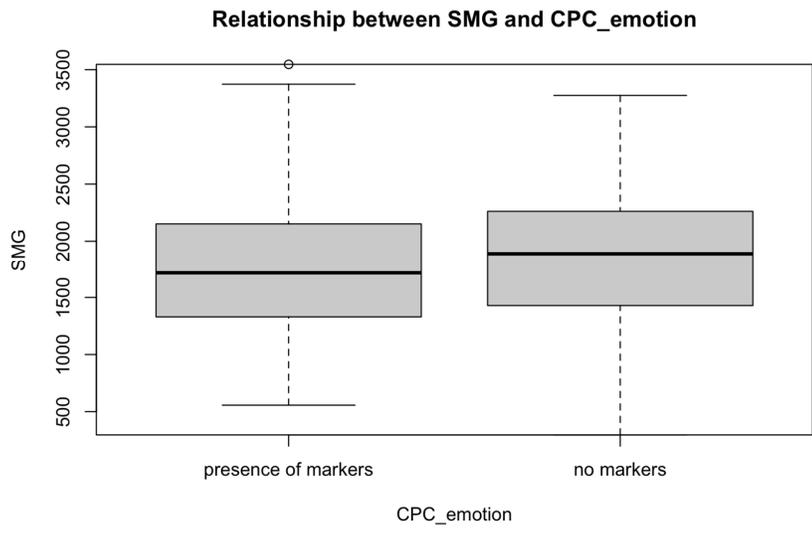
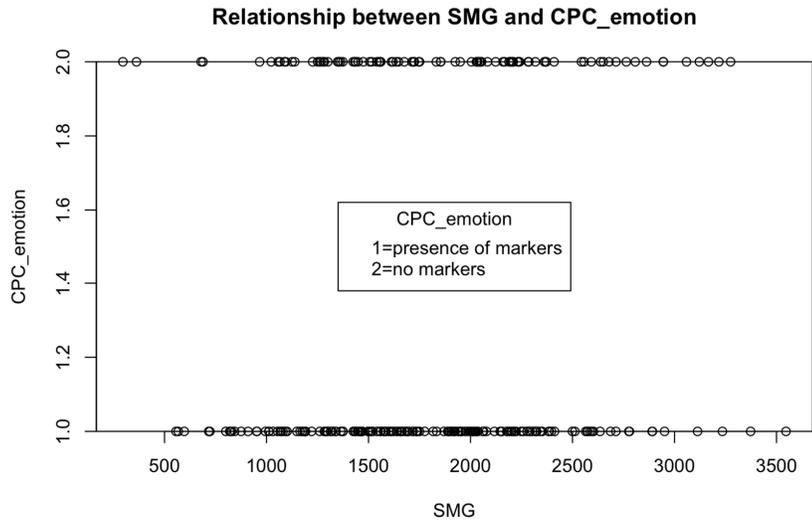
SMG and iso

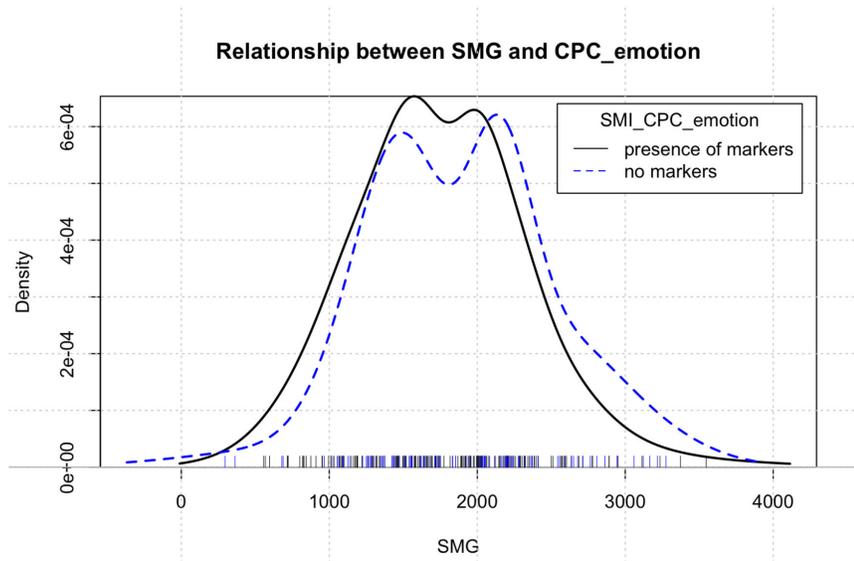




Notes: No evidence of relationship. Medians appear almost exactly equal in boxplot.

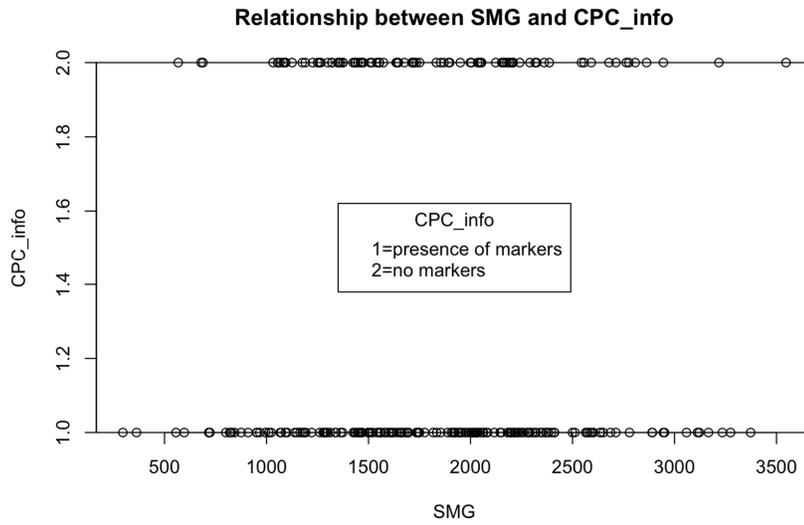
SMG and CPC_emotion

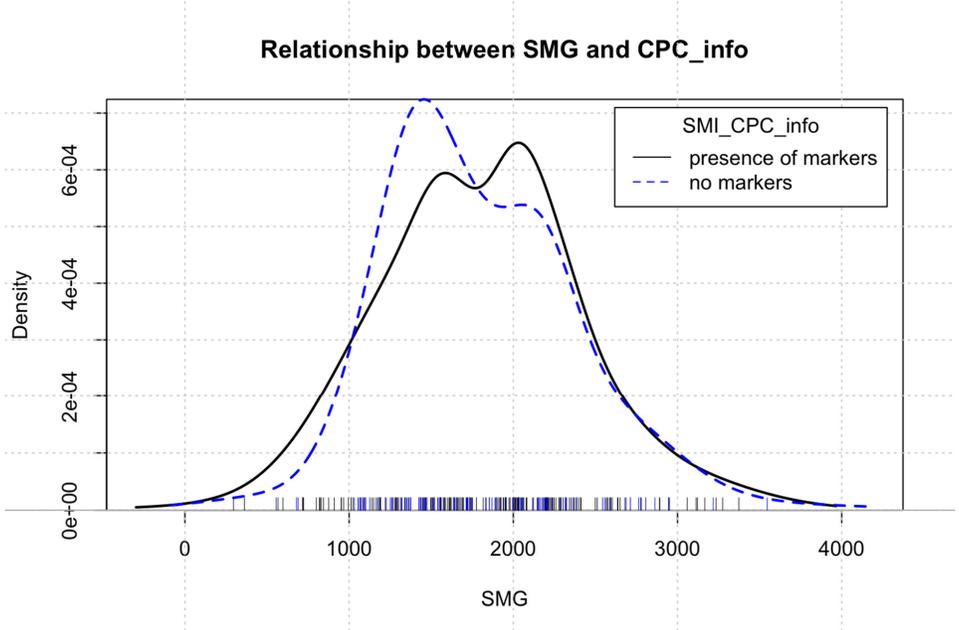
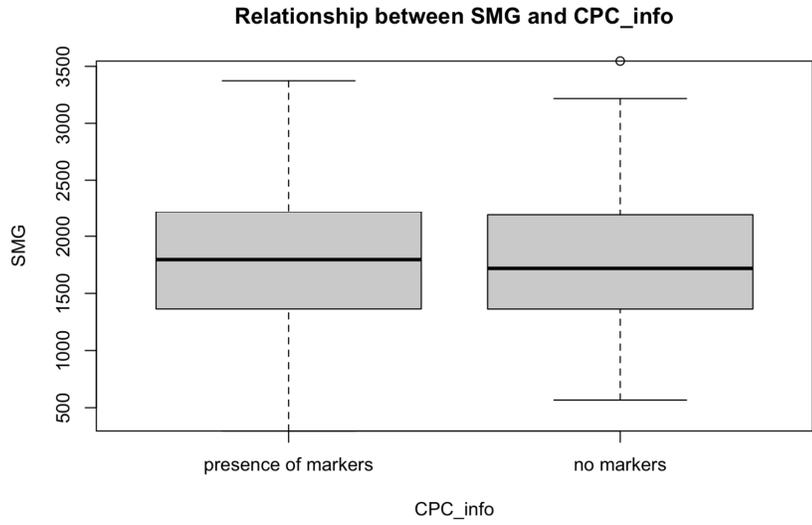




Notes: Potential that those without any emotional concerns have a slightly higher (i.e., better) SMG. However, correlation will likely not be high.

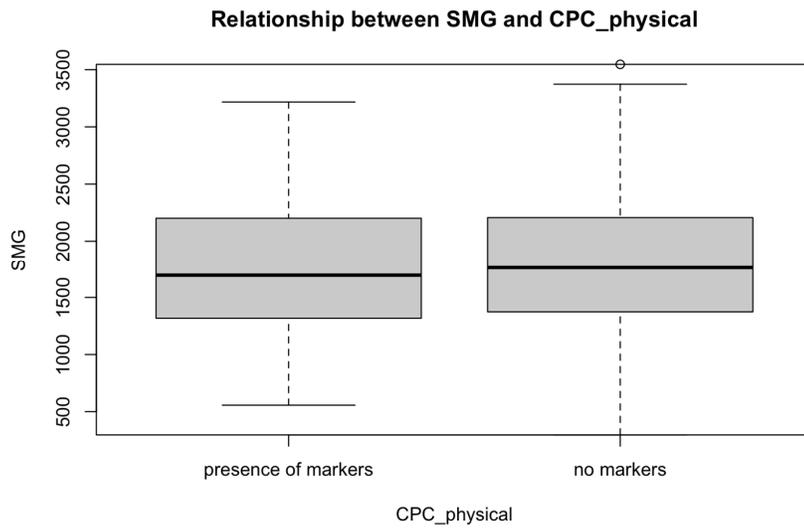
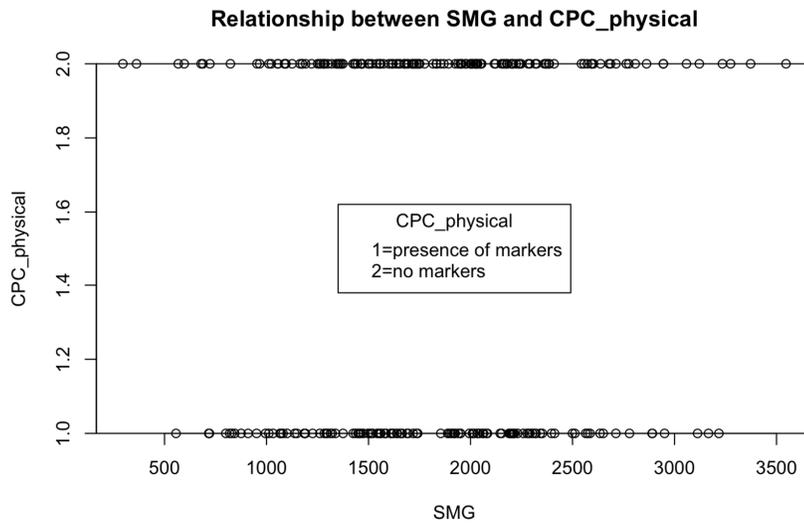
SMG and CPC_info

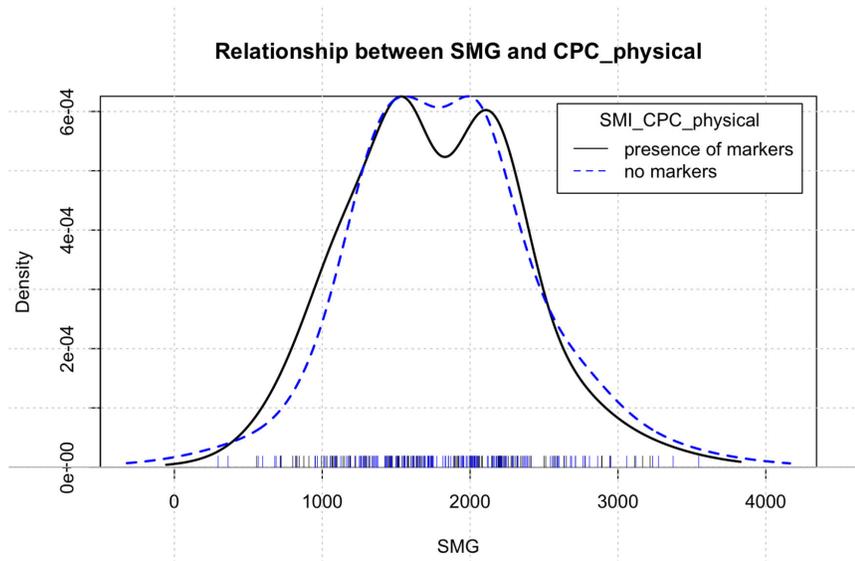




Notes: No strong evidence of a relationship.

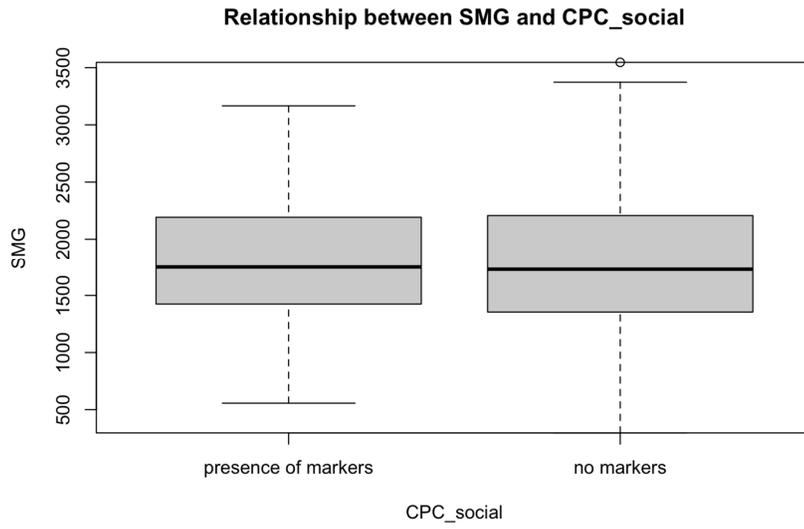
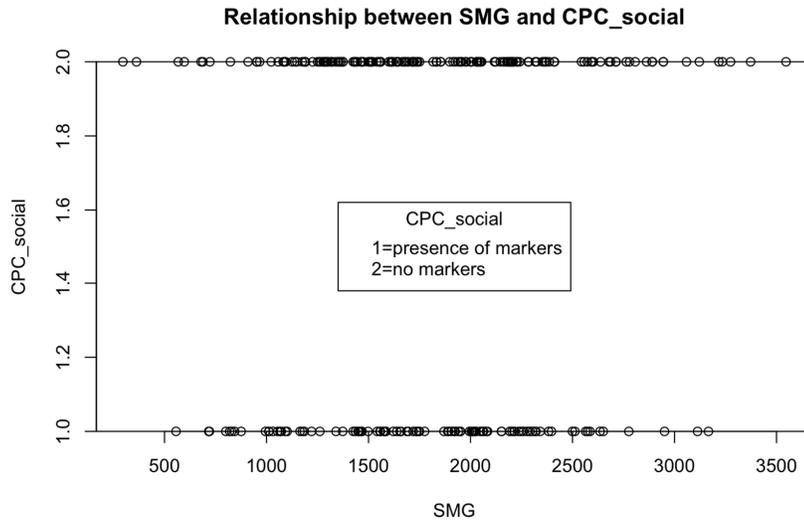
SMG and CPC_physical

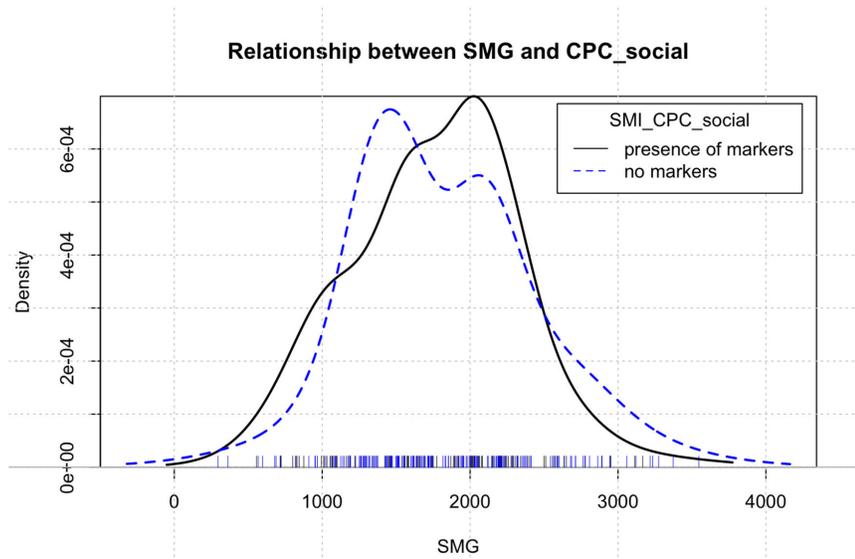




Notes: No strong evidence of a relationship.

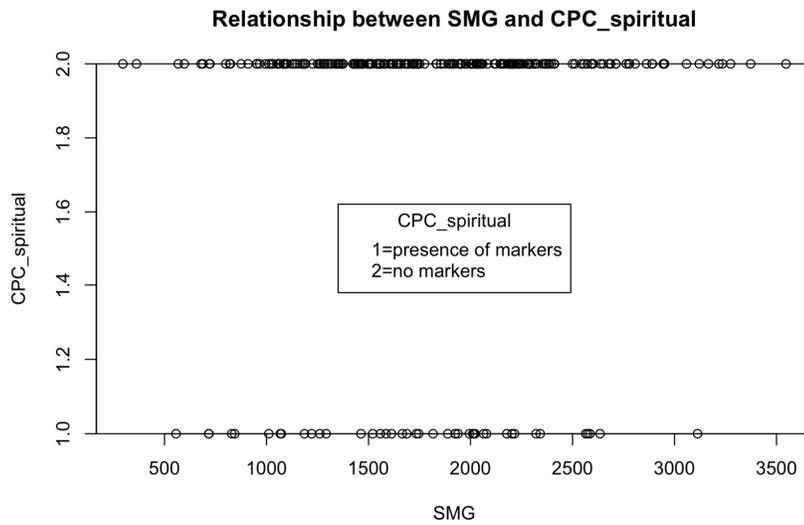
SMG and CPC_social

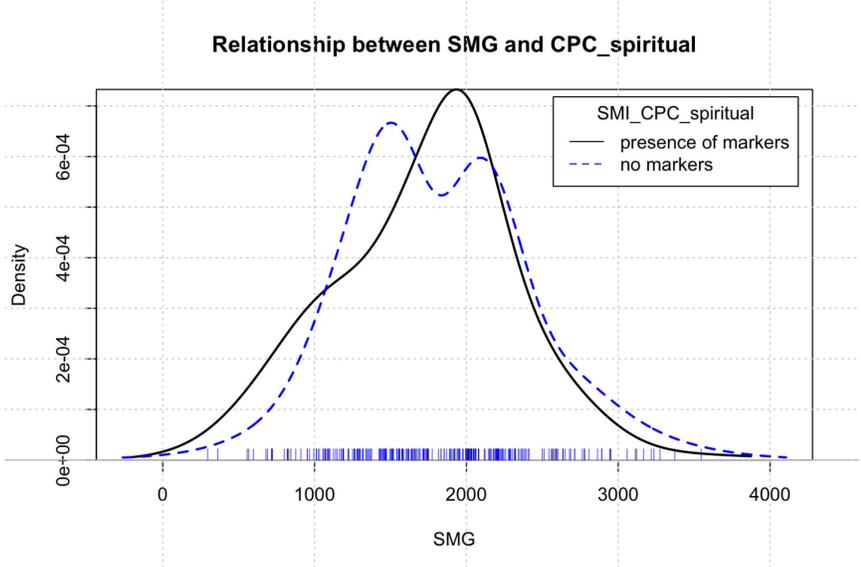
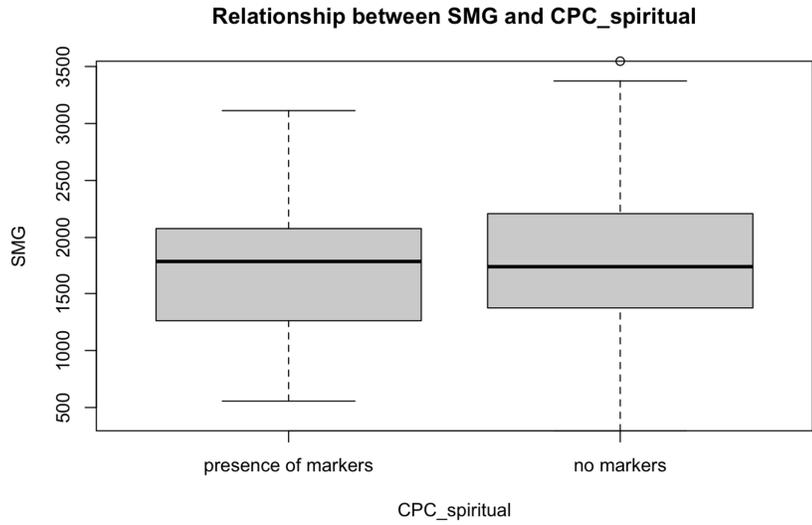




Notes: No strong evidence of a relationship. Potential that those with no social concerns have a slightly higher SMG overall. However, this group is larger and just has more data points in general.

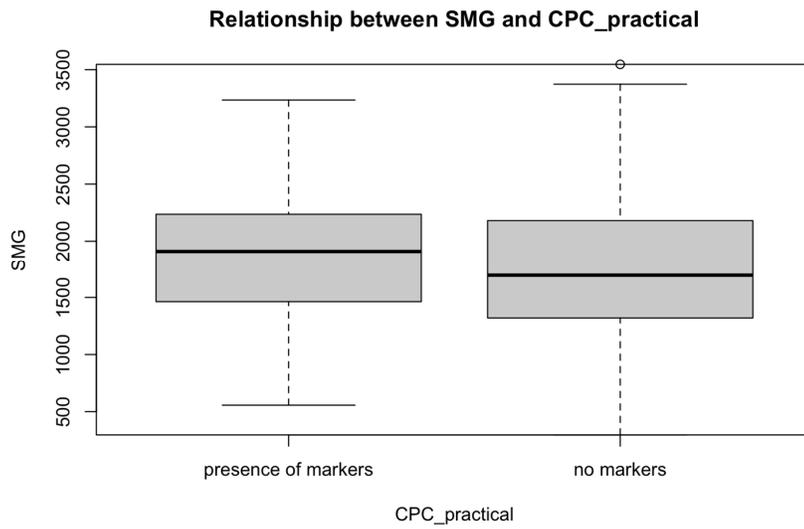
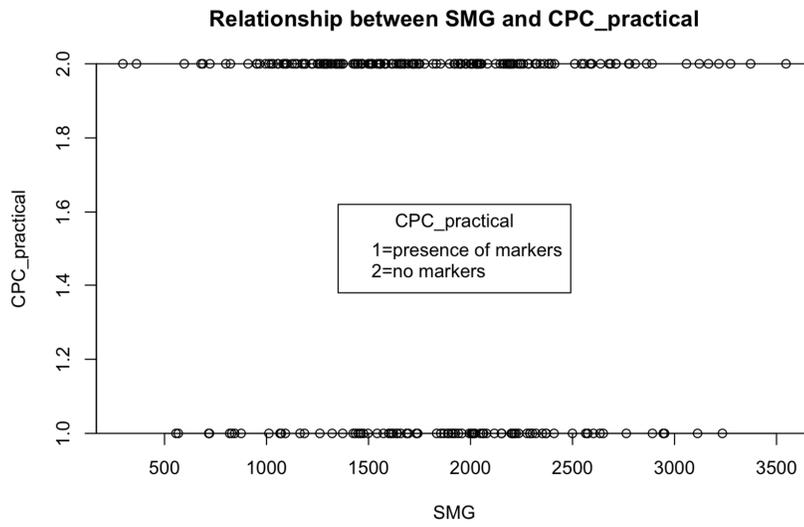
SMG and CPC_spiritual

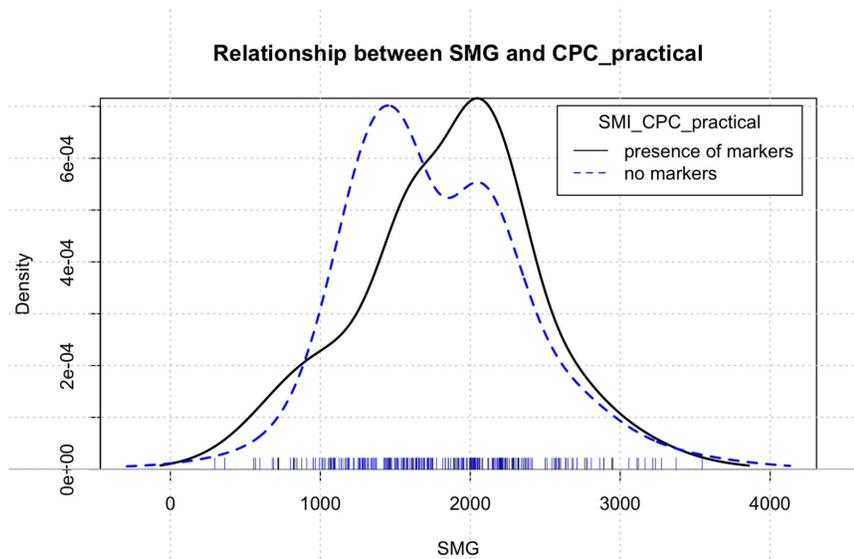




Notes: No strong evidence of a relationship. Potential that those with no spiritual concerns have a slightly higher SMG overall. However, this group is larger in size and range of values overall.

SMG and CPC practical





Notes: Potential that those with practical concerns have a slightly higher SMG as a group (likely not strong (if any) correlation).

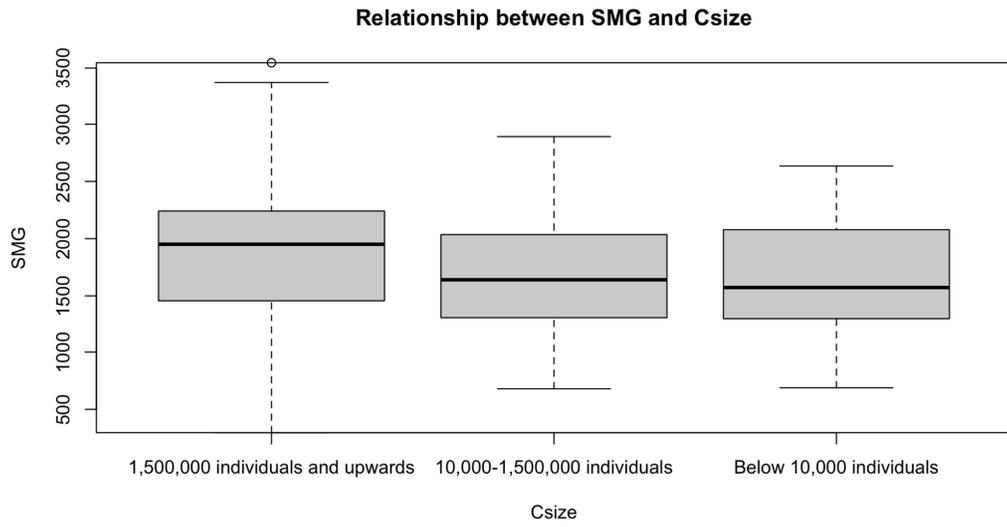
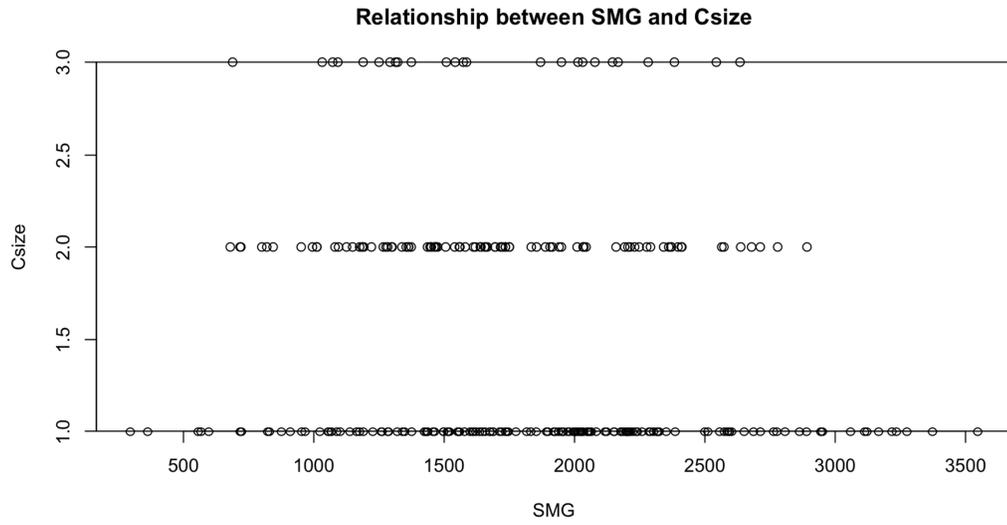
SMG and anx

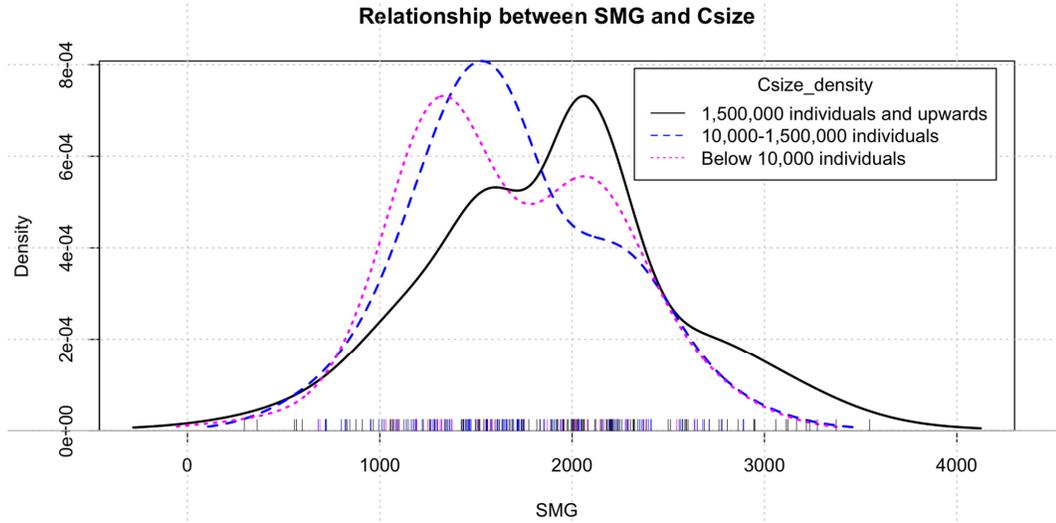
Notes: There is not enough spread within anx to study anything meaningful (only 10 people with subclinical symptoms and 11 with clinical, the rest reported no symptoms)

SMG and dep

Notes: There is not enough spread within dep to study anything meaningful (only 7 people with subclinical symptoms and 4 with clinical, the rest reported no symptoms)

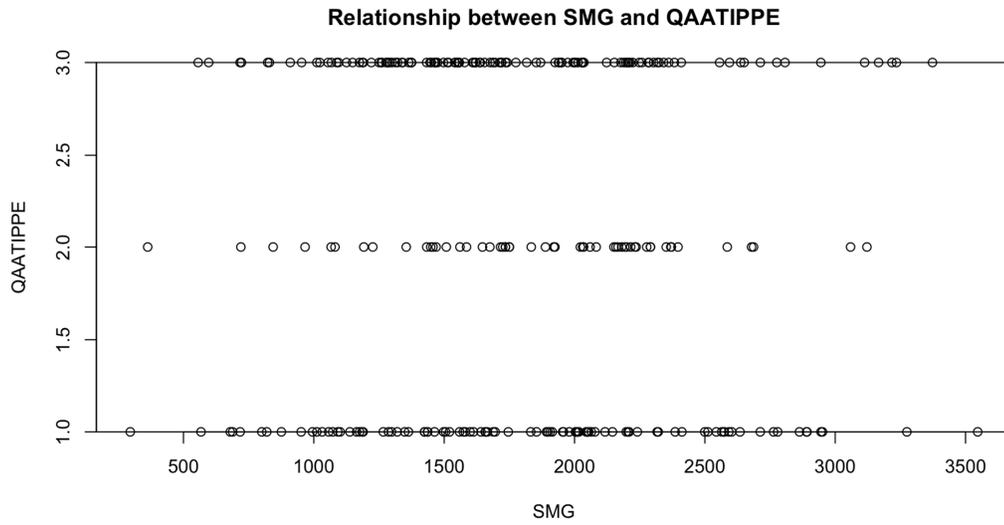
SMG and Csize

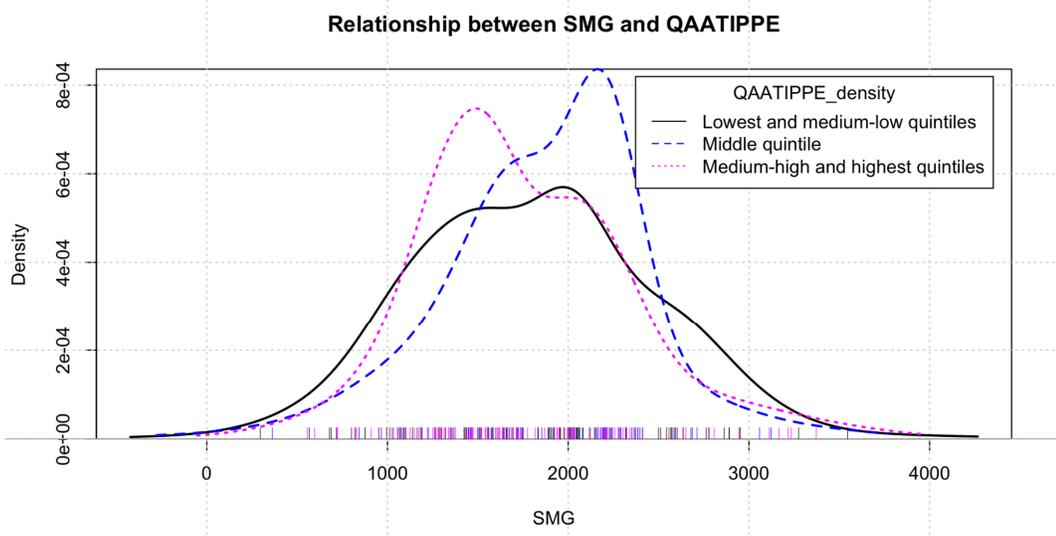
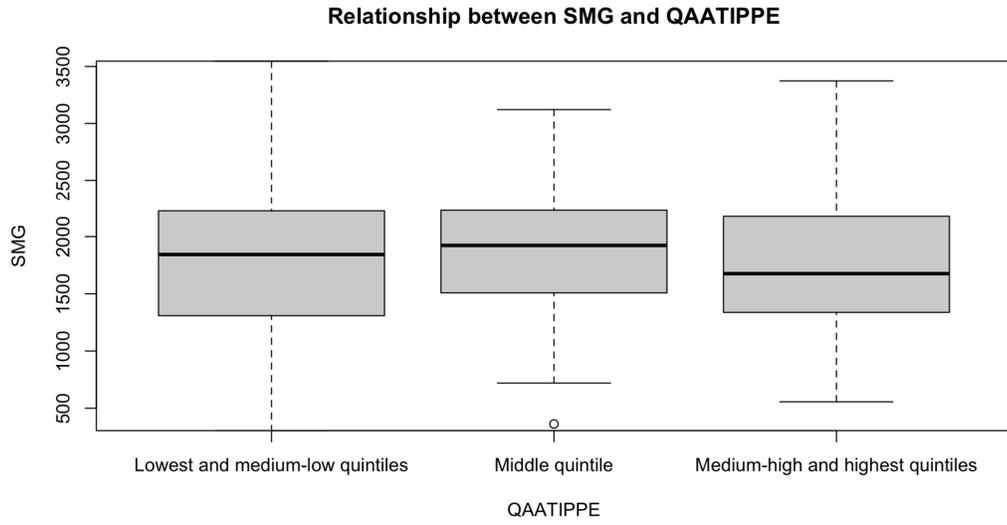




Notes: Potential that those from larger communities have slightly higher SMG overall. However, there is much overlap.

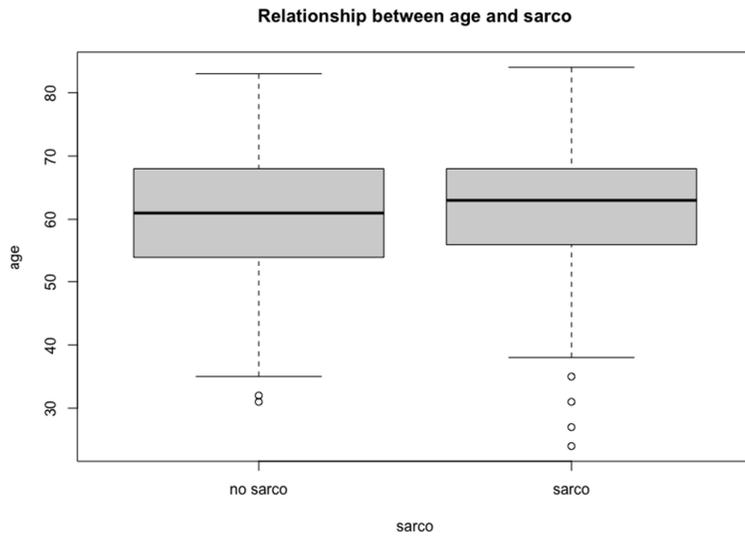
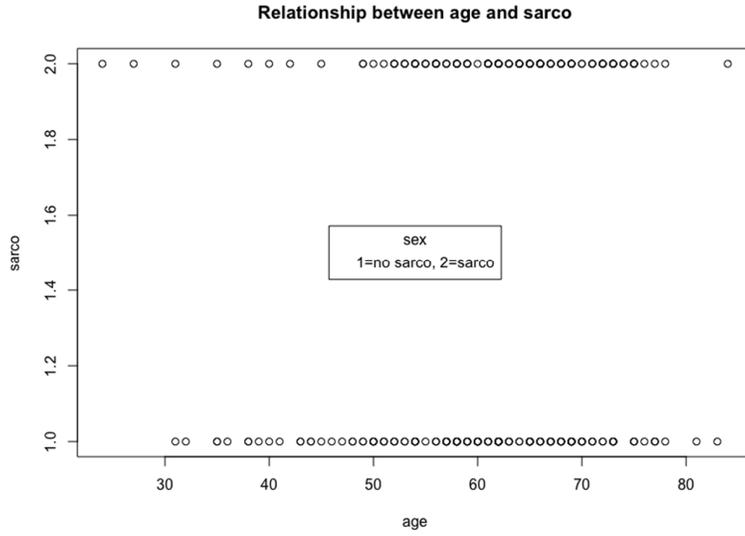
SMG and QAATIPPE





Notes: Potential that those in the middle quintile have higher SMG than those in higher group. However, not large association.

sarco and age

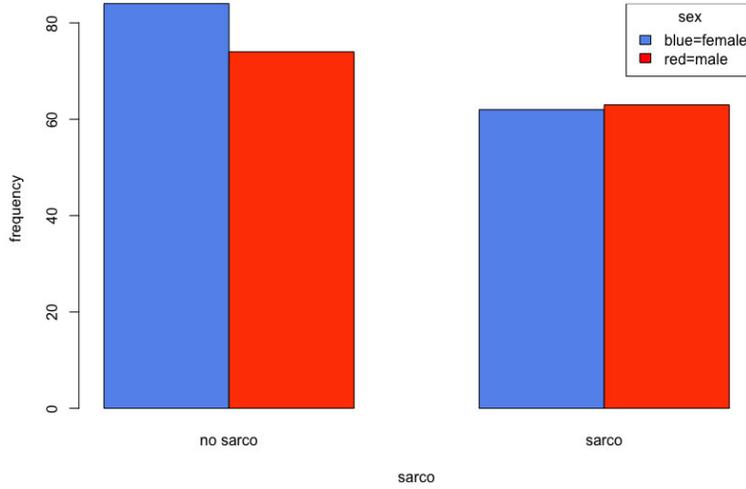


Notes: No evidence of relationship.

sarco and sex

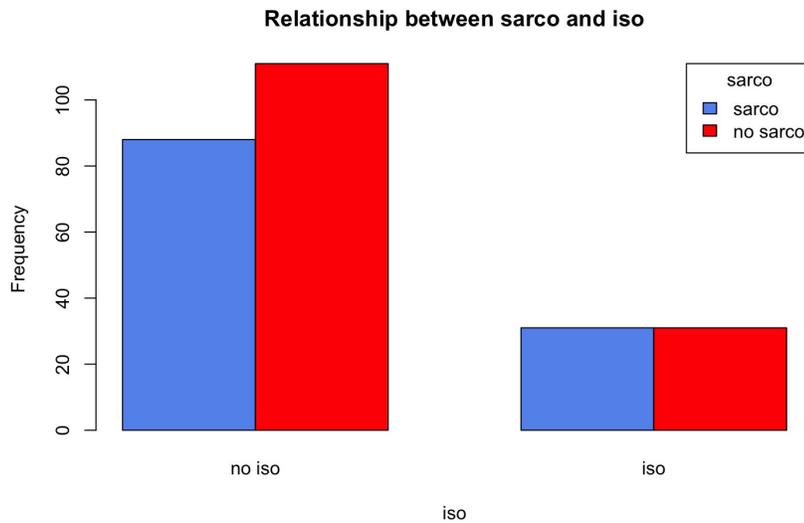
	No sarco	sarco	
Female	84	62	146
Male	74	63	137
	158	125	283

Relationship between sex and sarco



sarco and iso bar graph

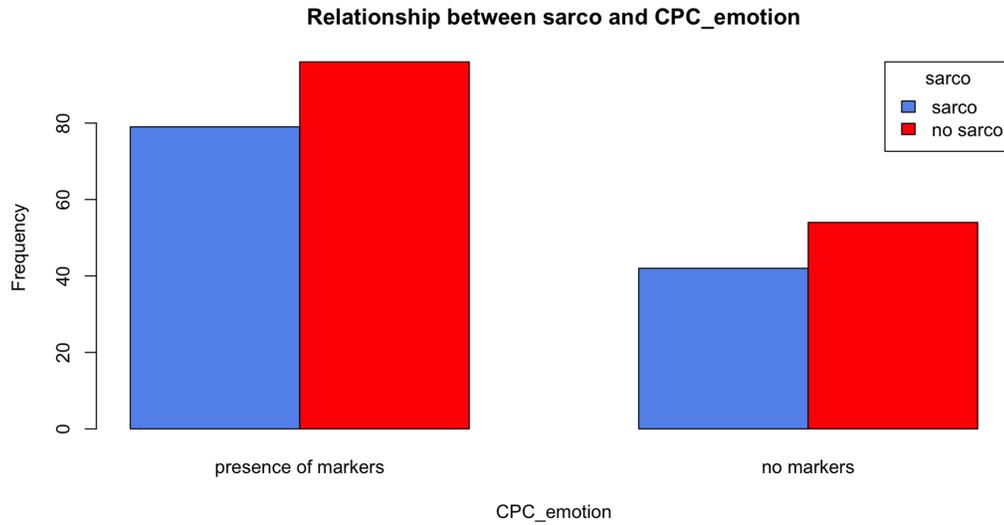
	No iso	iso	
sarco	88	31	119
No sarco	111	31	142
	199	62	261



Notes: Want to look at if iso influences body comp. so plotted this way. Of those without markers of iso, more individuals also did not have sarco. When looking at those with iso, there are an even number of individuals with sarco as without. Likely not a strong relationship here.

sarco and CPC_emotion bar graph

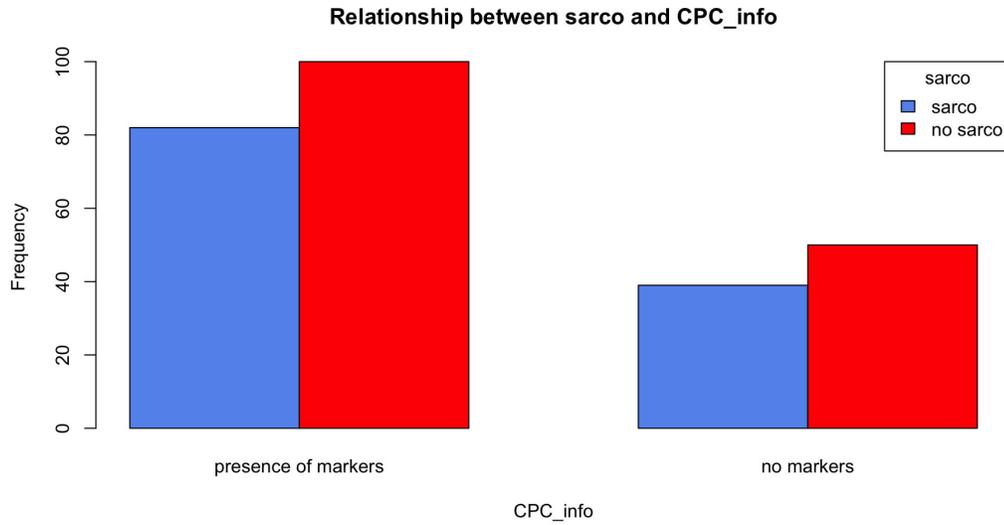
	1 or more checkmarks	No checkmarks	
sarco	79	42	121
No sarco	96	54	150
	175	96	271



Notes: Of those with emotional concerns, there are more without sarcopenia. The same trend exists in those without markers. No evidence of a relationship.

sarco and CPC_info bar graph

	1 or more checkmarks	No checkmarks	
sarco	82	39	121
No sarco	100	50	150
	182	89	271

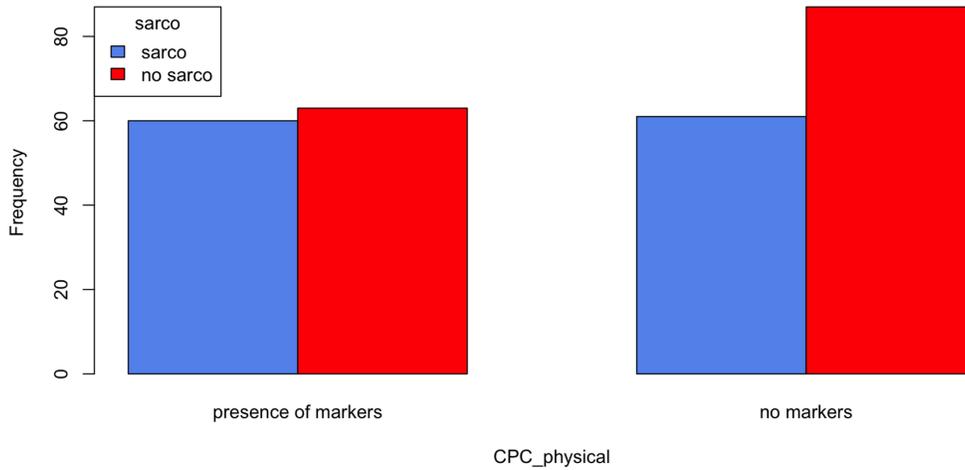


Notes: Same as CPC_emotion. No evidence of relationship.

sarco and CPC_physical bar graph

	1 or more checkmarks	No checkmarks	
sarco	60	61	121
No sarco	63	87	150
	123	148	271

Relationship between sarco and CPC_physical

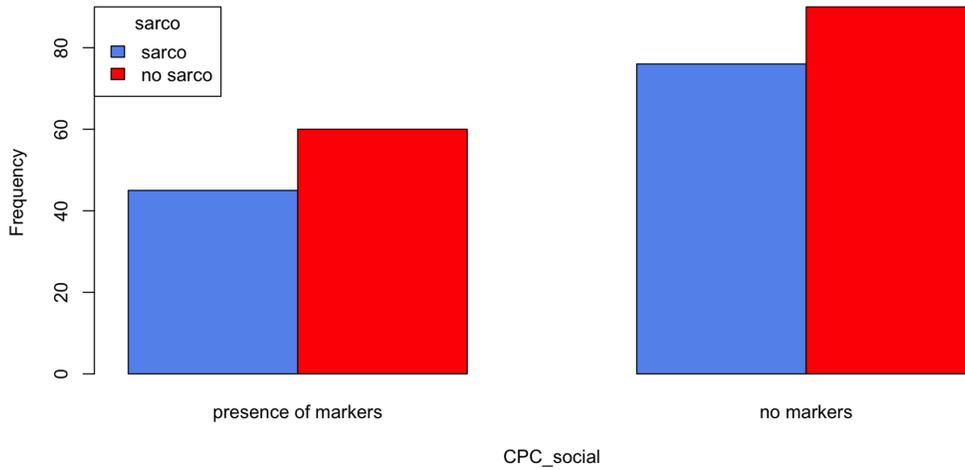


Notes: Of those without physical concerns, more individuals also did not have sarco. When looking at those with concerns, there are an even number of individuals with sarco as without. Likely not a strong relationship here.

sarco and CPC social bar graph

	1 or more checkmarks	No checkmarks	
sarco	45	76	121
No sarco	60	90	150
	105	166	271

Relationship between sarco and CPC_social

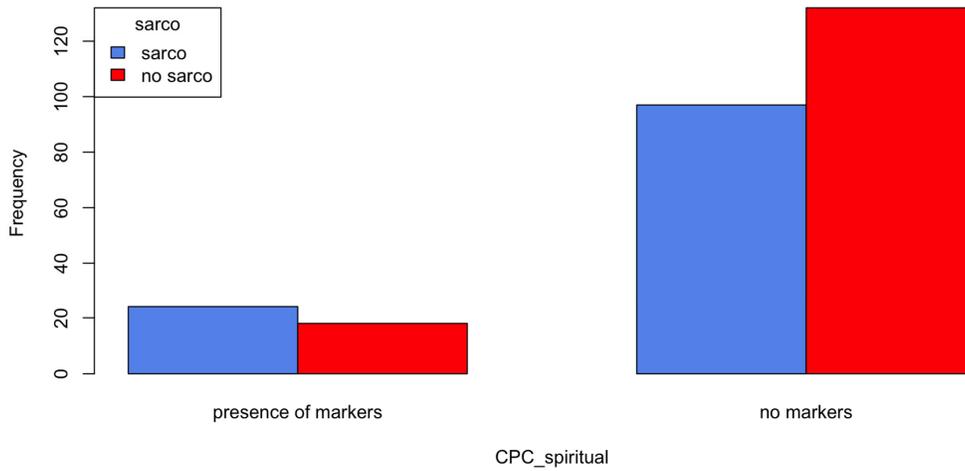


Notes: No strong evidence of a relationship.

sarco and CPC_spiritual bar graph

	1 or more checkmarks	No checkmarks	
sarco	24	97	121
No sarco	18	132	150
	42	229	271

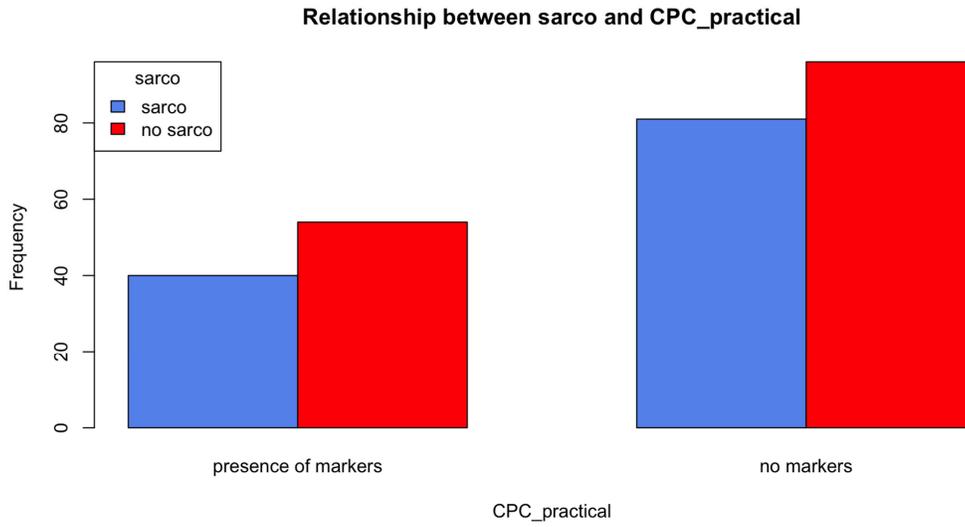
Relationship between sarco and CPC_spiritual



Notes: May not be a large enough spread to study (only 42 with spiritual concerns). However, among those with spiritual concerns, sarcopenia is more prevalent. In those without spiritual concerns, majority of individuals do not have sarcopenia.

sarco and CPC_practical bar graph

	1 or more checkmarks	No checkmarks	
sarco	40	81	121
No sarco	54	96	150
	94	177	271

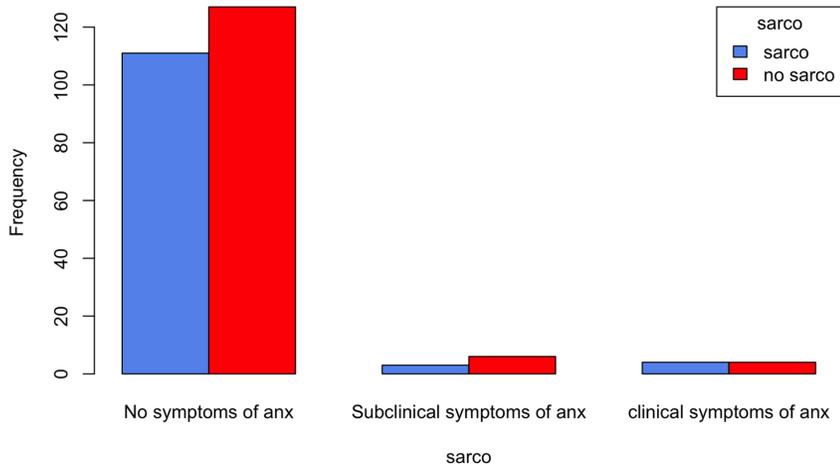


Notes: No evidence of a relationship.

sarco and anx bar graph

	No symptoms	subclinical symptoms	clinical symptoms	
sarco	111	3	4	118
No sarco	127	6	4	137
	238	9	8	255

Relationship between sarco and anx

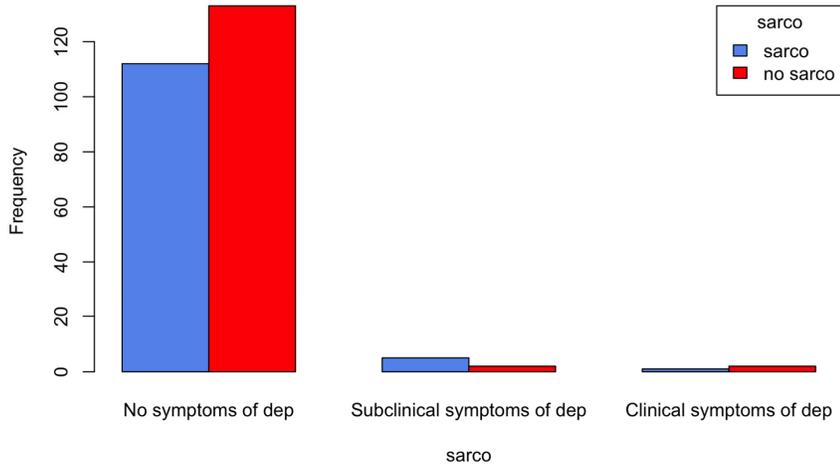


Notes: Most report no symptoms, so hard to study anything here (sparse cells a problem).

sarco and dep bar graph

	No symptoms	subclinical symptoms	clinical symptoms	
sarco	112	5	1	118
No sarco	133	2	2	137
	245	7	3	255

Relationship between sarco and dep

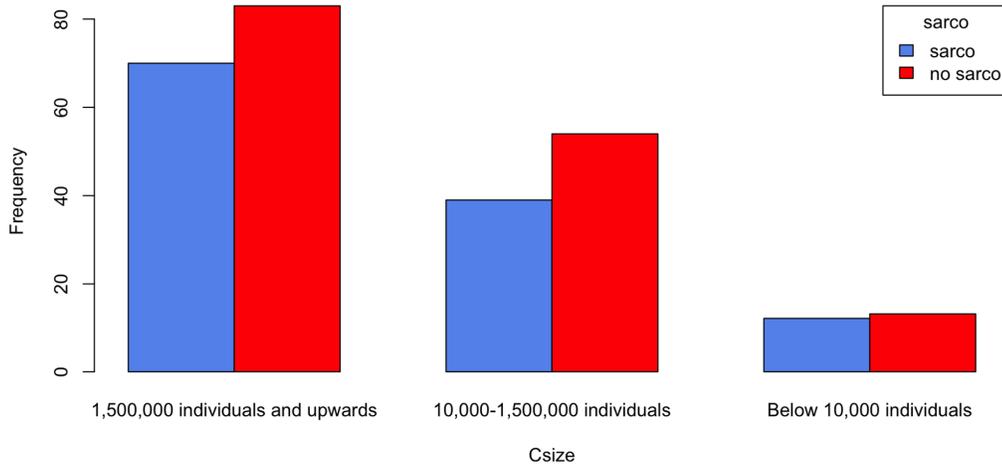


Notes: Most report no symptoms, so hard to study anything here (sparse cells a problem).

sarco and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
sarco	70	39	12	121
No sarco	83	54	13	150
	153	93	25	271

Relationship between sarco and Csize

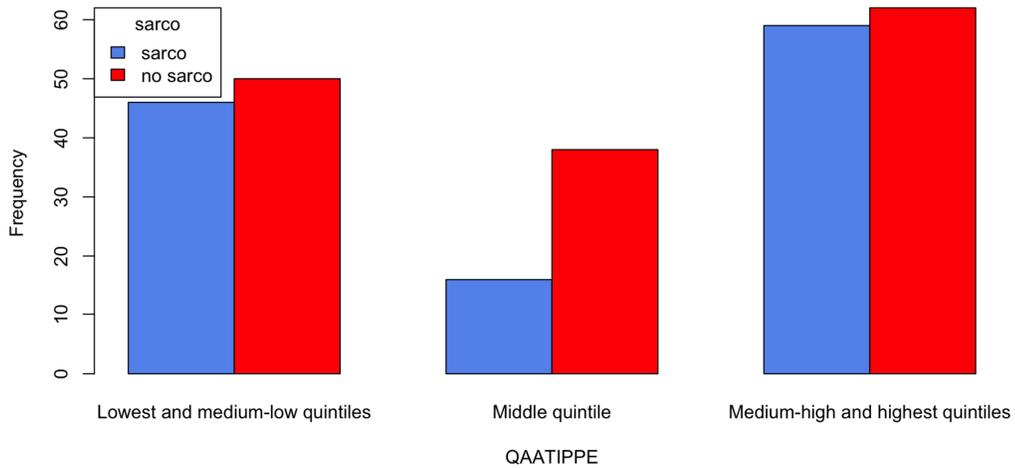


Notes: From looking at table and figure, no strong evidence of a relationship.

sarco and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
sarco	46	16	59	121
No sarco	50	38	62	150
	96	54	121	271

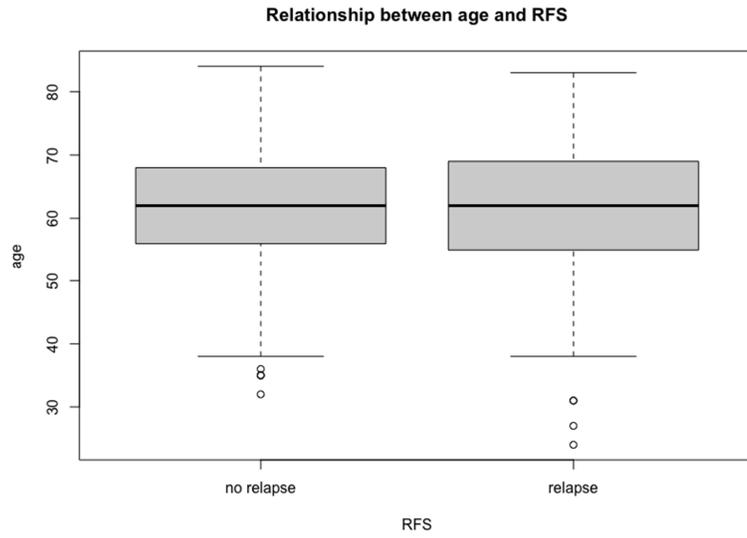
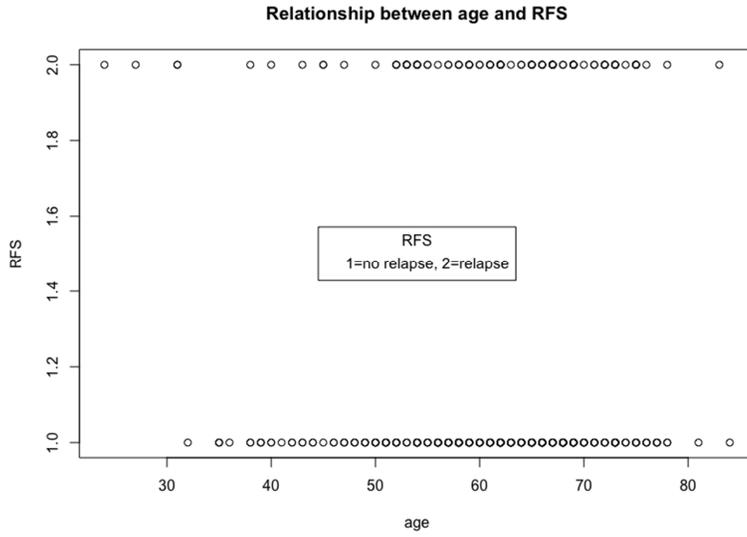
Relationship between sarco and QAATIPPE

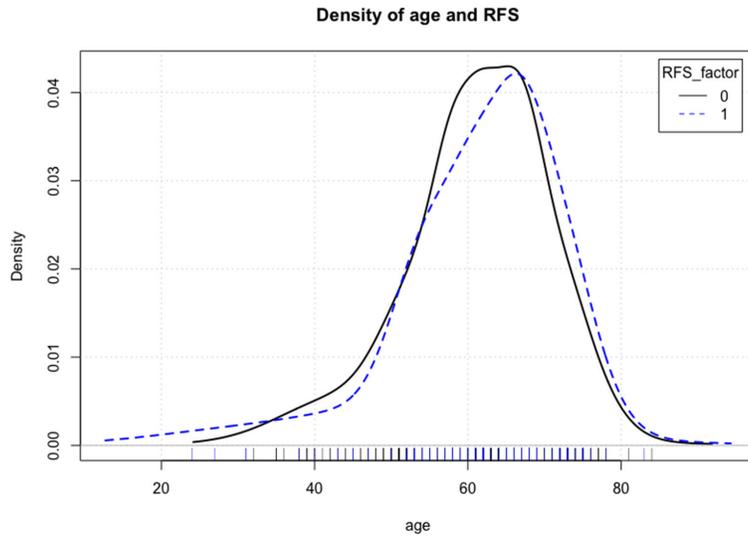


Notes: No strong evidence of relationship. More without sarcopenia in all income categories. Middle quintile has more of a gap between those with and without sarcopenia.

RFS and covariables

RFS and age

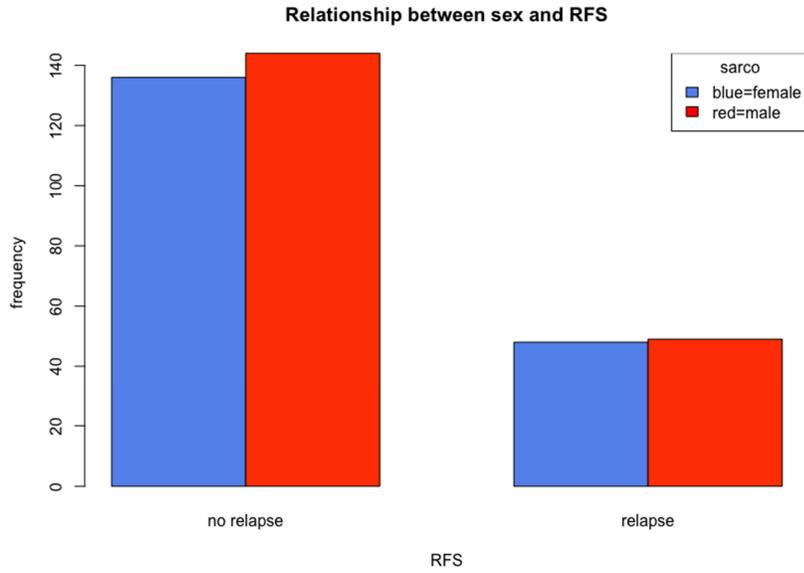




Notes: No strong evidence of a relationship (interestingly/not expected).

RFS and sex

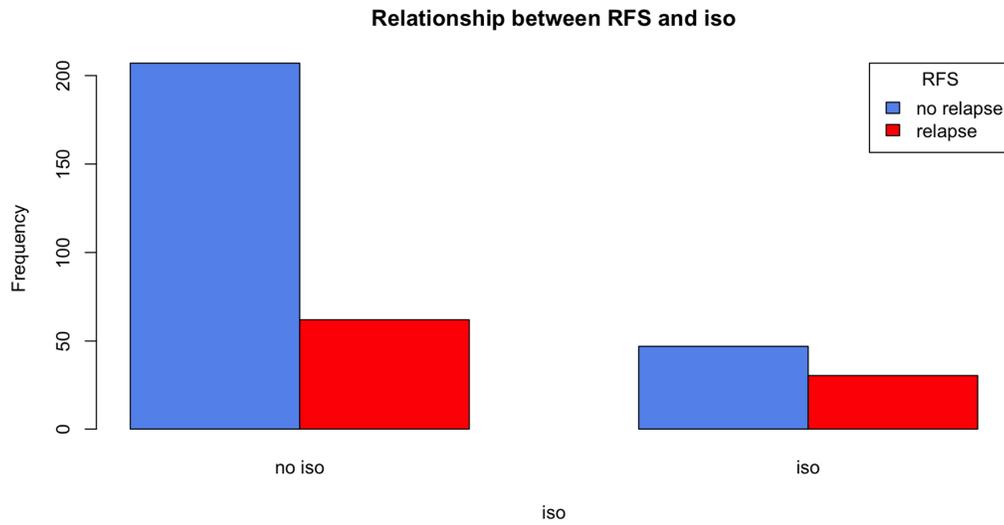
	No relapse	Relapse	
Female	136	48	184
Male	144	49	193
	280	97	377



Notes: No strong evidence of a relationship.

RFS and iso bar graph

	No iso	iso	
No relapse	207	47	254
relapse	62	30	92
	269	77	346

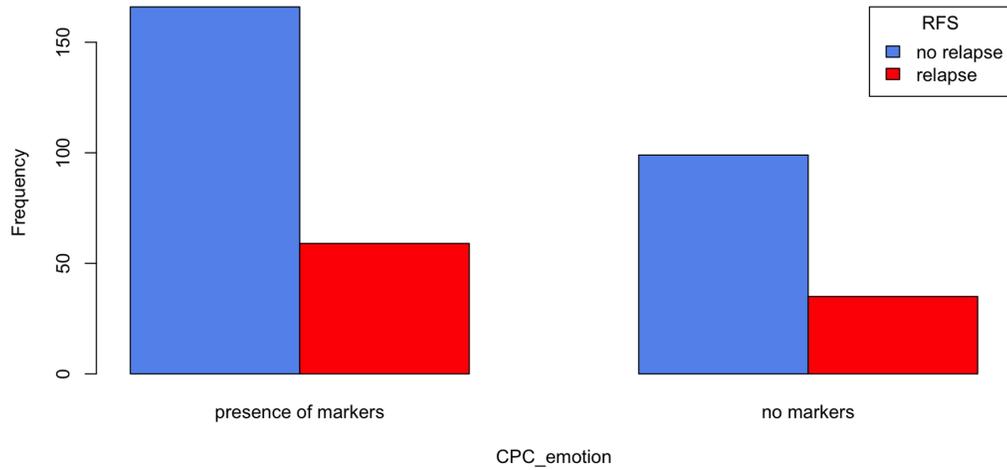


Notes: Most no do have markers of isolation or experience a relapse. No strong evidence of any association. However, more equal proportions in group with markers of isolation.

RFS and CPC_emotion bar graph

	1 or more checkmarks	No checkmarks	
No relapse	166	99	265
relapse	59	35	94
	225	134	359

Relationship between CPC_emotion and RFS

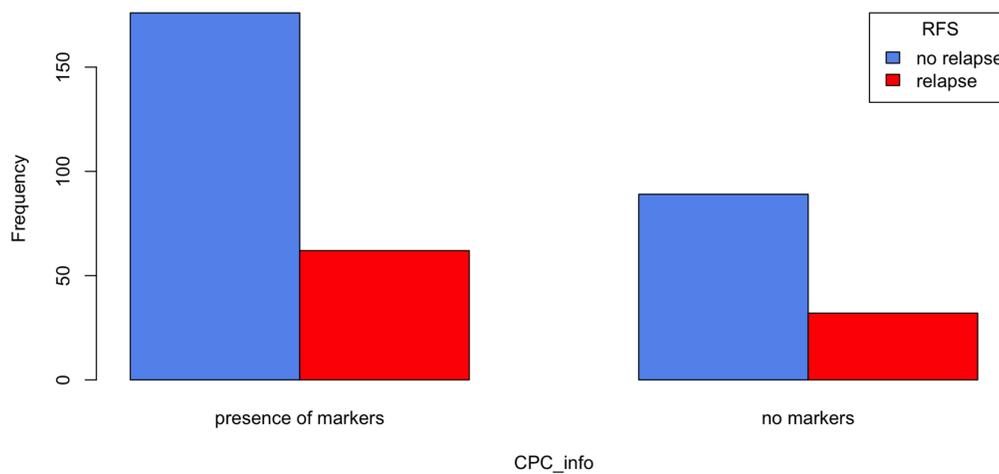


Notes: No strong evidence of a relationship.

RFS and CPC_info bar graph

	1 or more checkmarks	No checkmarks	
No relapse	176	89	265
relapse	62	32	94
	238	121	359

Relationship between CPC_info and RFS

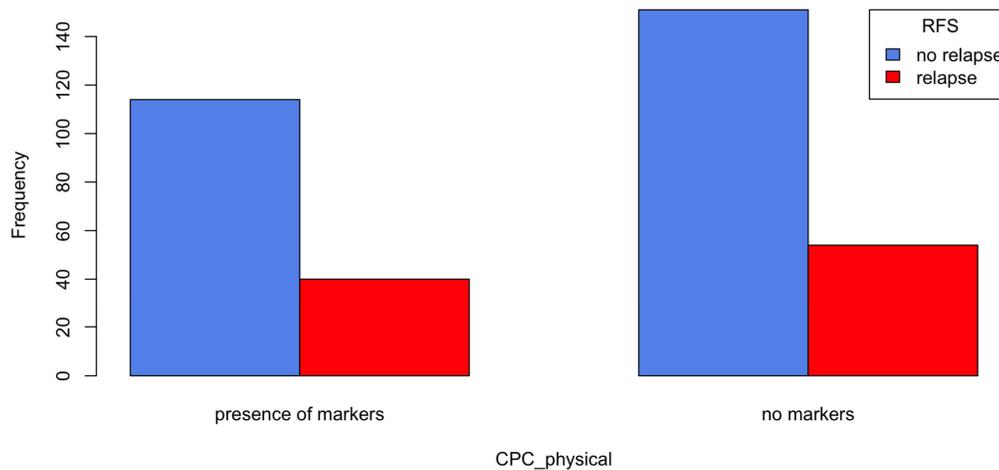


Notes: No strong evidence of a relationship.

RFS and CPC_physical bar graph

	1 or more checkmarks	No checkmarks	
No relapse	114	151	265
relapse	40	54	94
	154	205	359

Relationship between CPC_physical and RFS

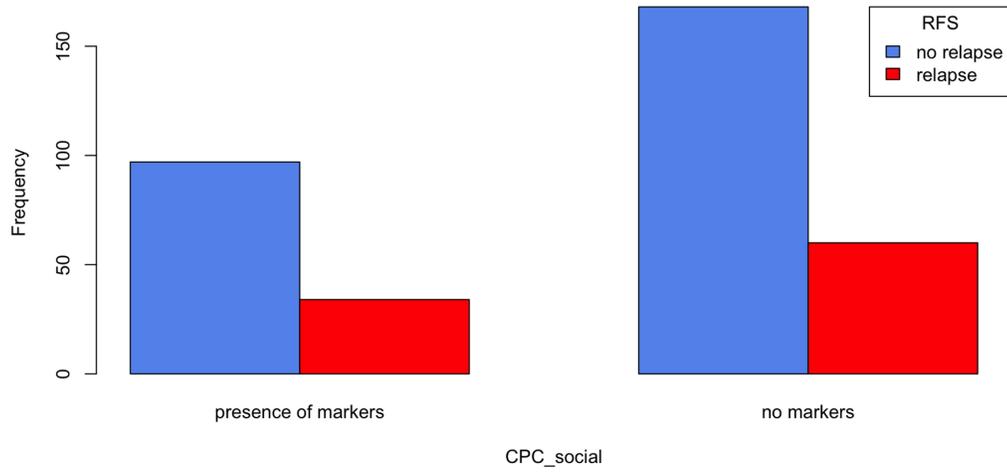


Notes: No evidence of relationship.

RFS and CPC_social bar graph

	1 or more checkmarks	No checkmarks	
No relapse	97	168	265
relapse	34	60	94
	131	228	359

Relationship between CPC_social and RFS

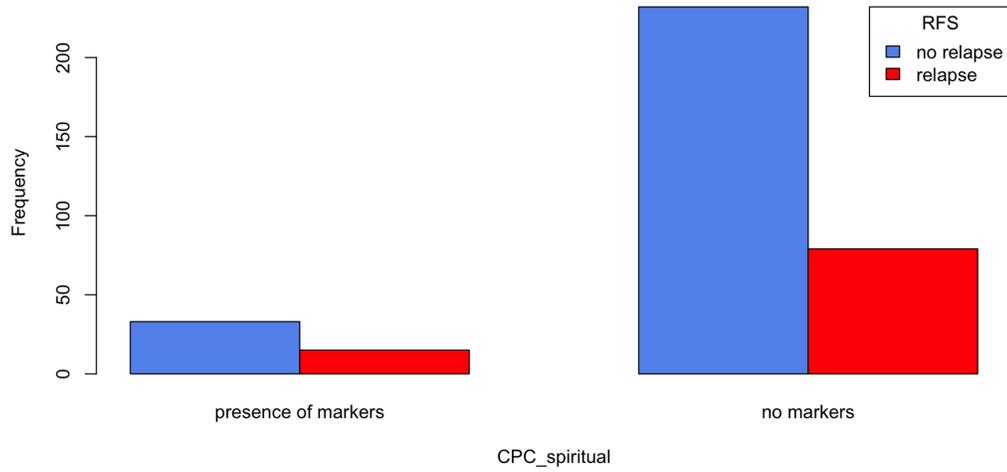


Notes: No strong evidence of a relationship.

RFS and CPC_spiritual bar graph

	1 or more checkmarks	No checkmarks	
No relapse	33	232	265
relapse	15	79	94
	48	311	359

Relationship between CPC_spiritual and RFS

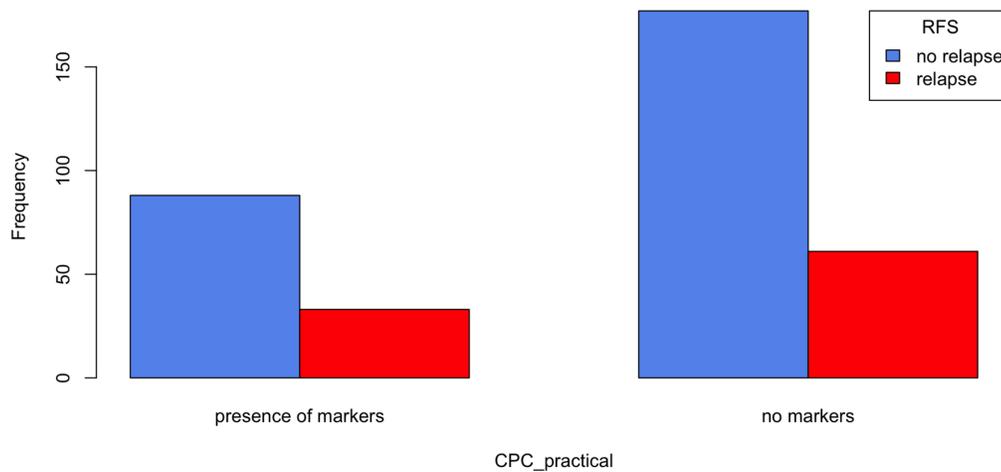


Notes: No strong evidence of a relationship.

RFS and CPC_practical bar graph

	1 or more checkmarks	No checkmarks	
No relapse	88	177	265
relapse	33	61	94
	121	238	359

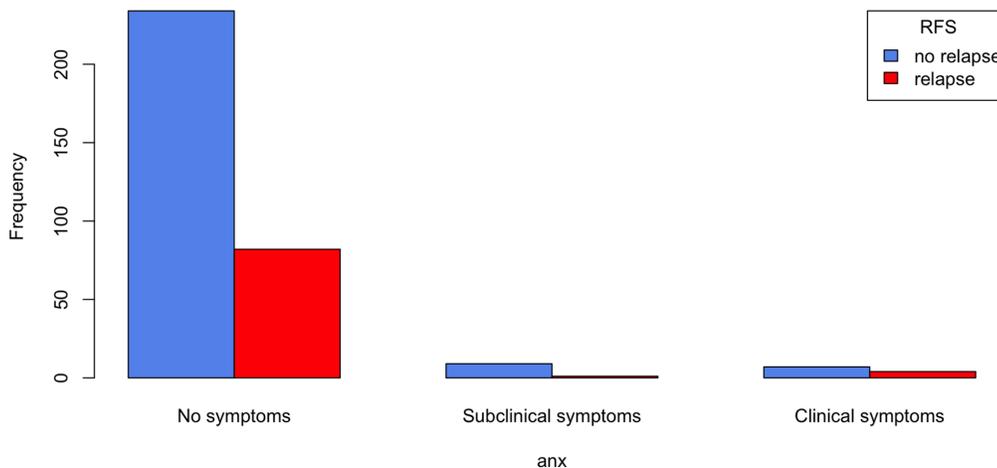
Relationship between CPC_practical and RFS



RFS and anx bar graph

	No symptoms	sublinical symptoms	clinical symptoms	
No relapse	234	9	7	250
relapse	82	1	4	87
	316	10	11	337

Relationship between RFS and anx

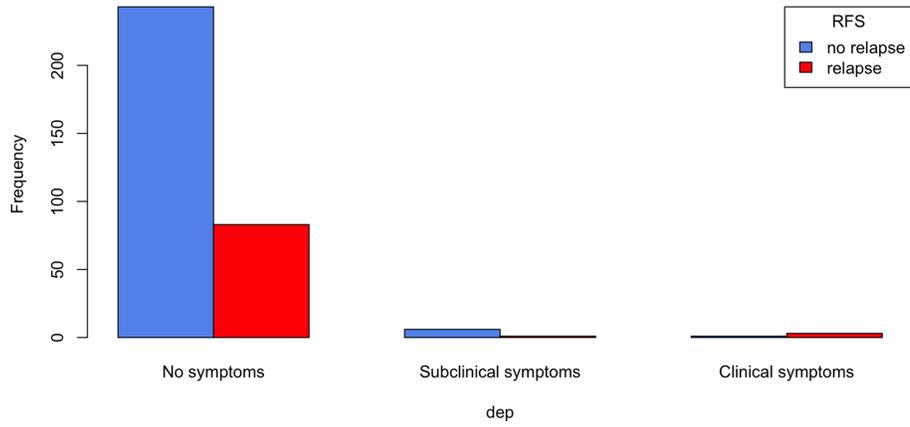


Notes: Sparse cells and no evidence of relationship.

RFS and dep bar graph

	No symptoms	subclinical symptoms	clinical symptoms	
No relapse	243	6	1	250
relapse	83	1	3	87
	326	7	4	337

Relationship between RFS and dep

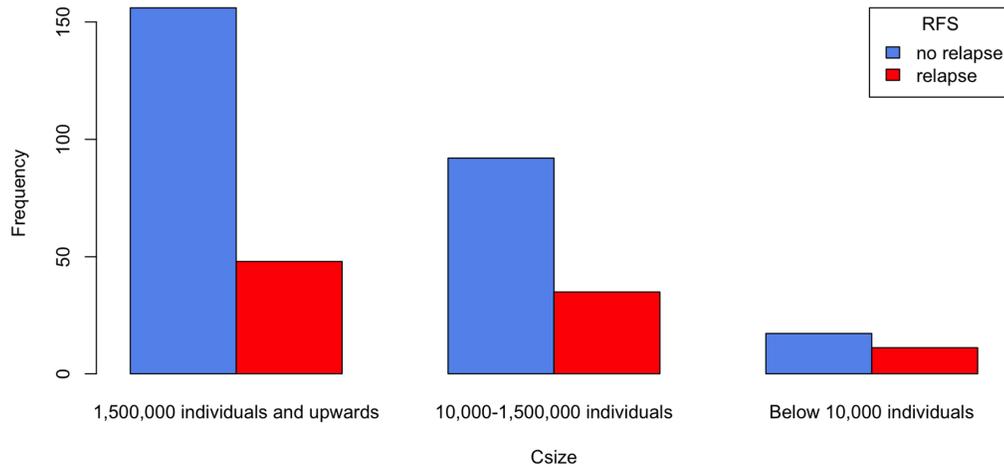


Notes: Sparse cells and no evidence of relationship.

RFS and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
No relapse	156	92	17	265
relapse	48	35	11	94
	204	127	28	359

Relationship between Csize and RFS

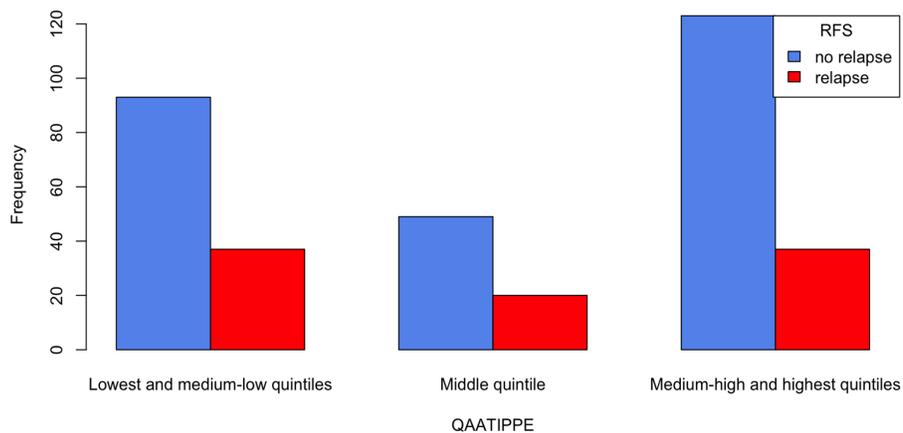


Notes: No evidence of relationship.

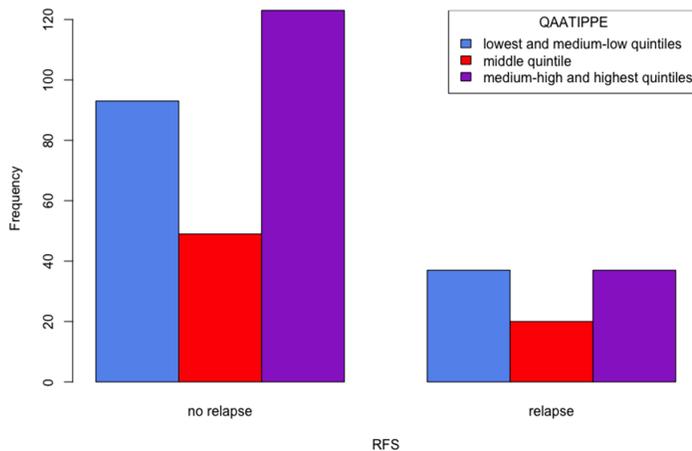
RFS and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
No relapse	93	49	123	265
relapse	37	20	37	94
	130	69	160	359

Relationship between QAATIPPE and RFS



Relationship between QAATIPPE and RFS

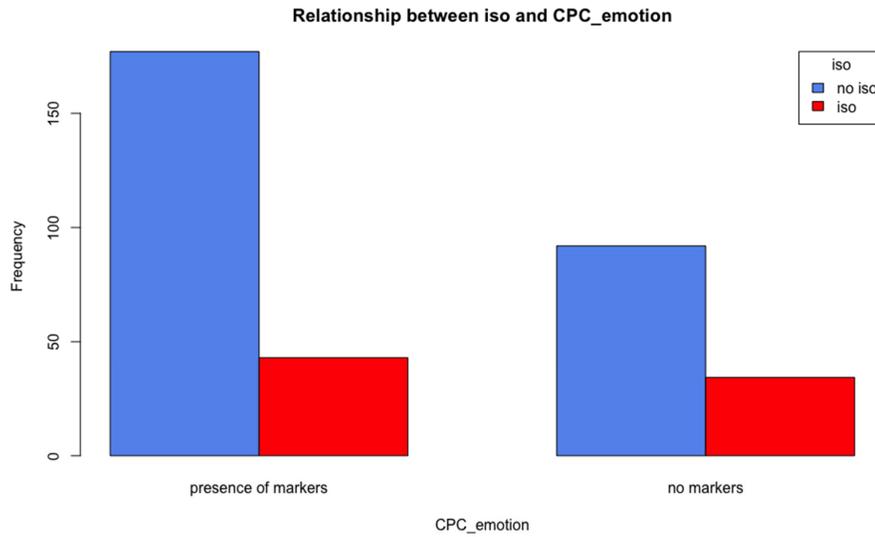


Notes: Potentially a disproportionate number with relapse in the lower grouping (considering they have less people in total).

Social and psychological covariables with each other

iso and CPC_emotion bar graph

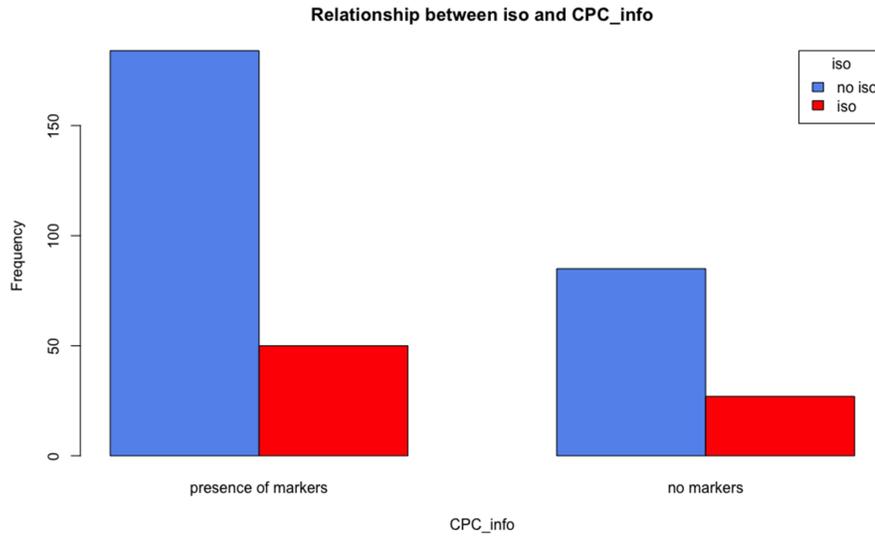
	1 or more checkmarks	No checkmarks	
No iso	177	92	269
iso	43	34	77
	220	126	346



Notes: No strong evidence of a relationship.

iso and CPC_info bar graph

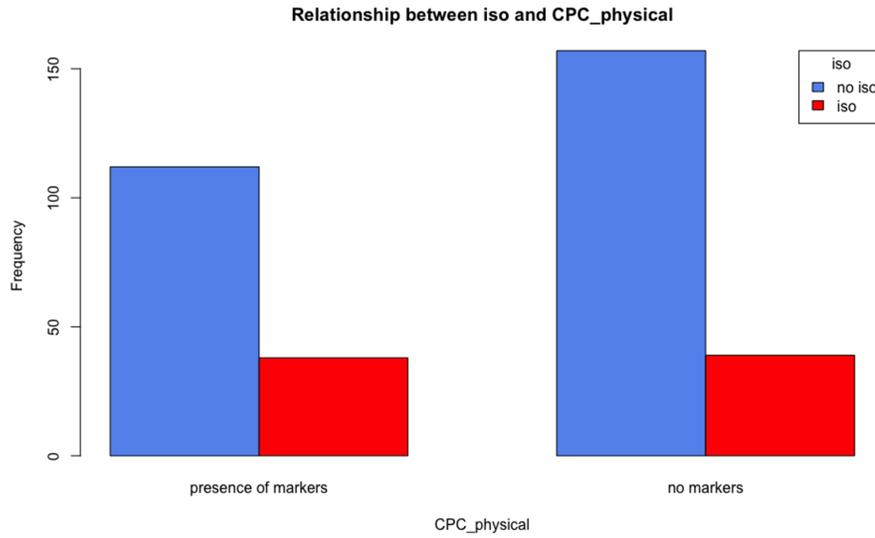
	1 or more checkmarks	No checkmarks	
No iso	184	85	269
iso	50	27	77
	234	112	346



Notes: No strong evidence of a relationship.

iso and CPC_physical bar graph

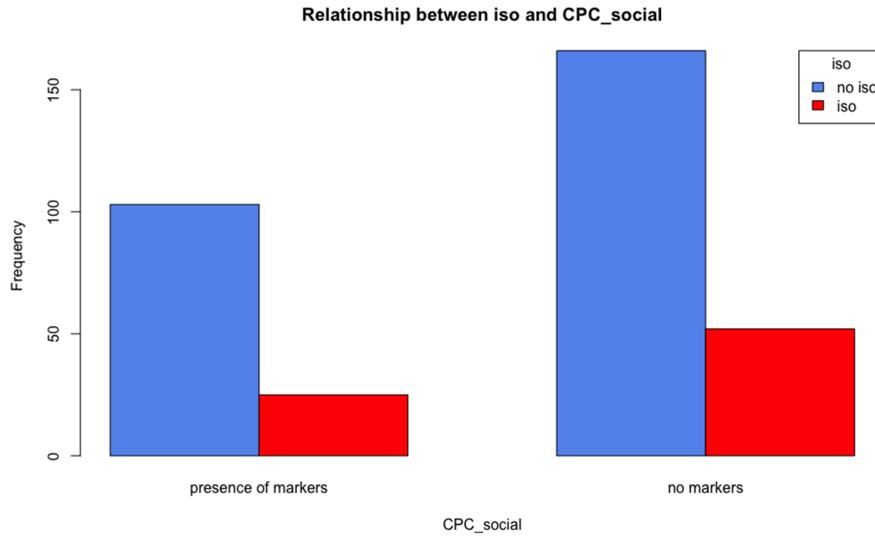
	1 or more checkmarks	No checkmarks	
No iso	112	157	269
iso	38	39	77
	150	196	346



Notes: Not strong evidence. However, almost equivalent amount with iso between those with and without physical concerns (even though there are more without physical concerns in total).

iso and CPC social bar graph

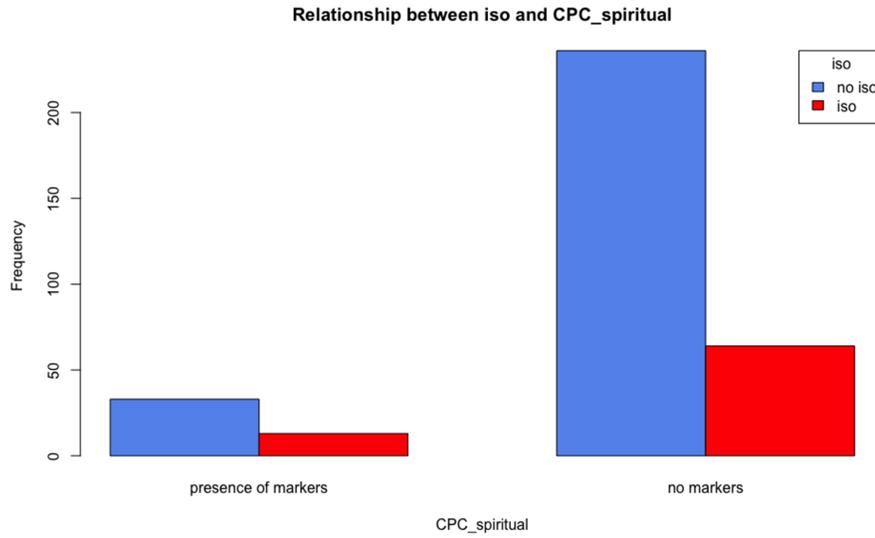
	1 or more checkmarks	No checkmarks	
No iso	103	166	269
iso	25	52	77
	128	218	346



Notes: No strong evidence of a relationship.

iso and CPC_spiritual bar graph

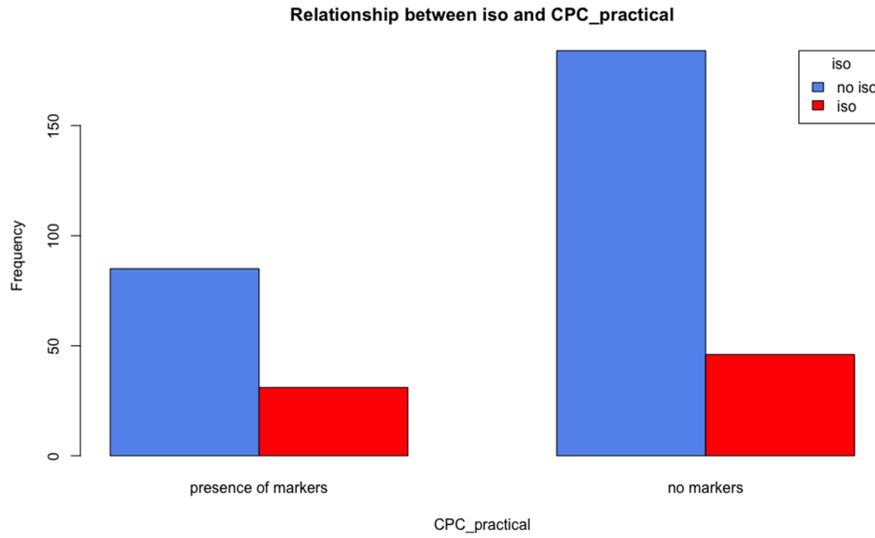
	1 or more checkmarks	No checkmarks	
No iso	33	236	269
iso	13	64	77
	46	300	346



Notes: No strong evidence of a relationship.

iso and CPC_practical bar graph

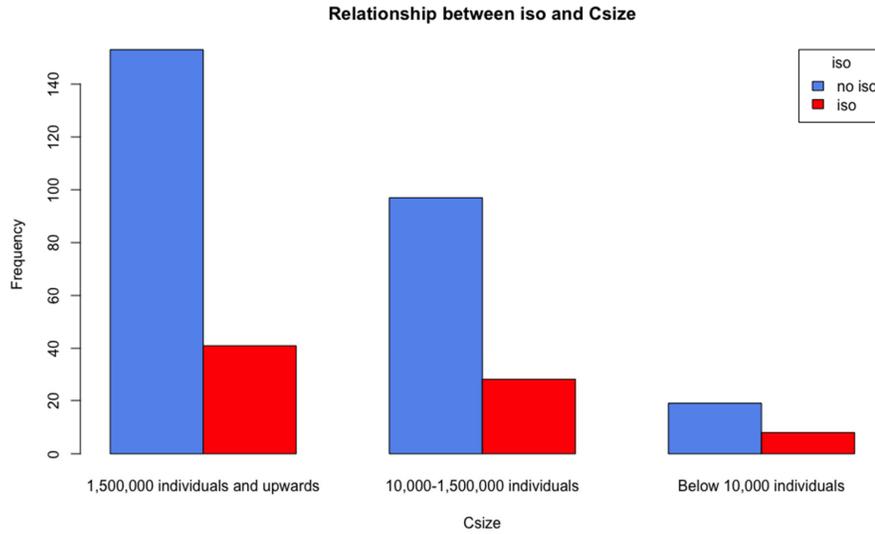
	1 or more checkmarks	No checkmarks	
No iso	85	184	269
iso	31	46	77
	116	230	346



Notes: No evidence of a relationship.

iso and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
No iso	79	56	134	269
iso	45	13	19	77
	124	69	153	346

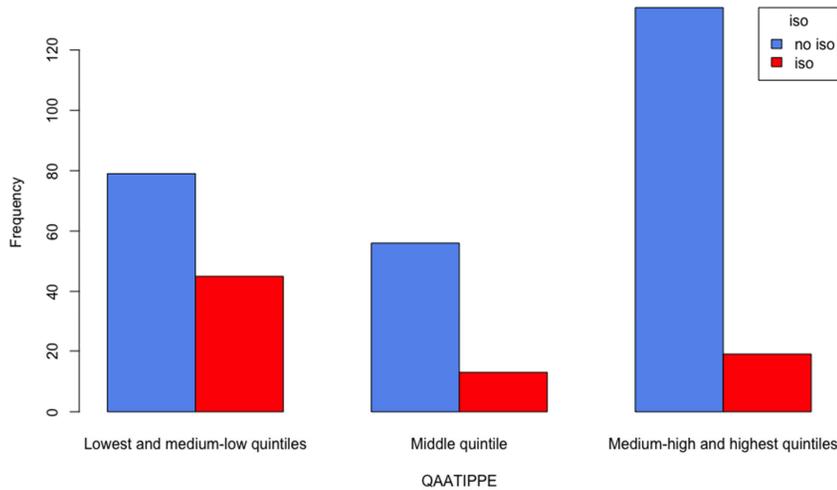


Notes: No strong evidence of a relationship.

iso and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
No iso	79	56	134	269
iso	45	13	19	77
	124	69	153	346

Relationship between iso and QAATIPPE



Notes: Interesting pattern, with a disproportionate number of people without markers of isolation in the medium-high to highest quintile group. Comparing the lowest group to the highest, the number of people with markers of isolation decreased but those without markers of isolation increased. In the low group, more than half had markers of isolation!

iso and anx bar graph

Notes: Collapsed anx to no symptoms and symptoms moving forward (no differentiation between subclinical and clinical symptoms, due to lack of individuals in these groupings). However, still sparse cells so can't study anything meaningful.

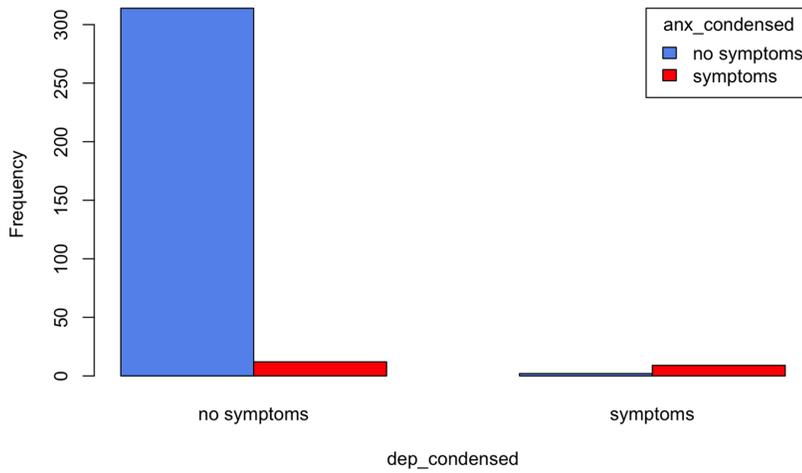
iso and dep bar graph

Notes: Collapsed dep to no symptoms and symptoms moving forward (no differentiation between subclinical and clinical symptoms, due to lack of individuals in these groupings). Still sparse cells so can't study anything meaningful.

anx and dep bar graph

	No symptoms (dep)	symptoms (dep)	
No symptoms (anx)	314	2	316
symptoms (anx)	12	9	21
	326	11	337

Relationship between anx_condensed and dep_condensed



Notes: Too sparse of data to study relationships. But there are more individuals with symptoms of anx in those with symptoms of depression (as expected).

anx and CPC emotion bar graph

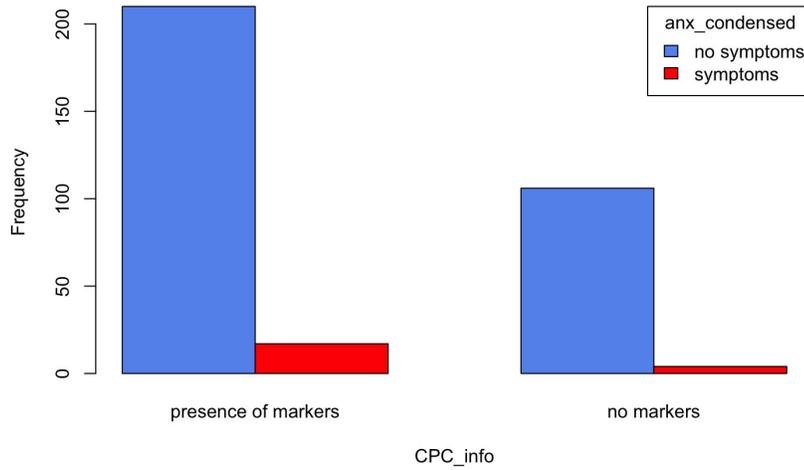
	1 or more checkmarks	No checkmarks	
No symptoms	192	124	316
symptoms	21	0	21
	213	124	337

Notes: 0 individuals in one group. Unable to study further relationships.

anx and CPC info bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	210	106	316
symptoms	17	4	21
	227	110	337

Relationship between anx_condensed and CPC_info

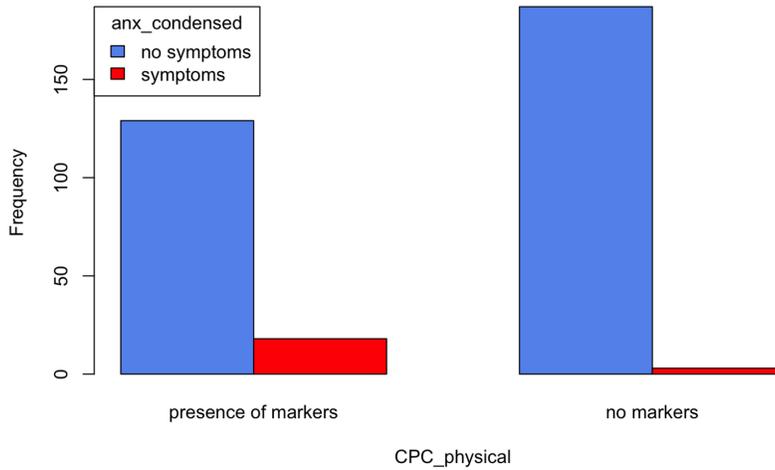


Notes: Still sparse cells and no evidence of relationship.

anx and CPC_physical bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	129	187	316
symptoms	18	3	21
	147	190	337

Relationship between anx_condensed and CPC_physical

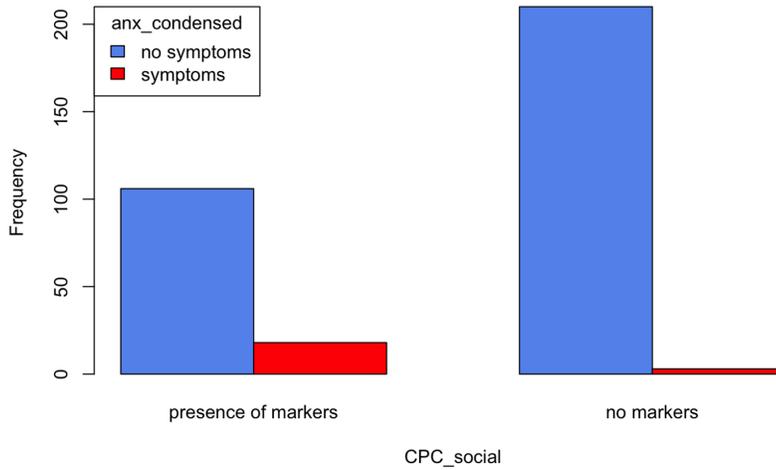


Notes: Not enough people to study relationship. But interestingly, when looking between groups of those with vs. without physical concerns, the number of individuals with symptoms of anxiety decreased, where are the number without symptoms increased.

anx and CPC social bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	106	210	316
symptoms	18	3	21
	124	213	337

Relationship between anx_condensed and CPC_social

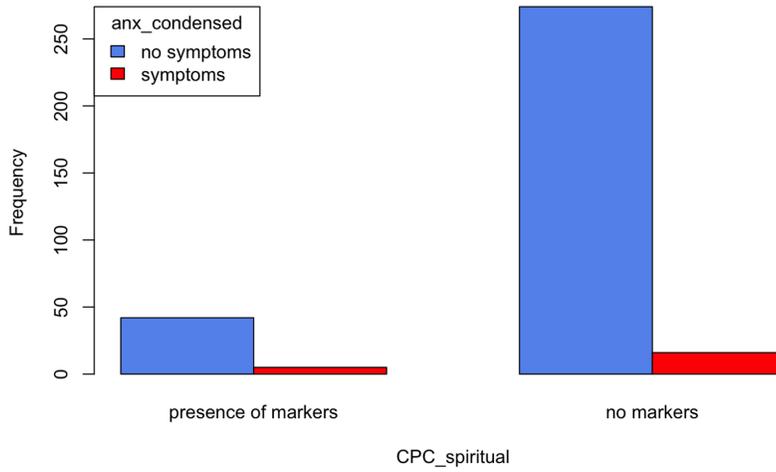


Notes: Not enough people to study relationship. But, similar to above findings with CPC_physical.

anx and CPC spiritual bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	42	274	316
symptoms	5	16	21
	47	290	337

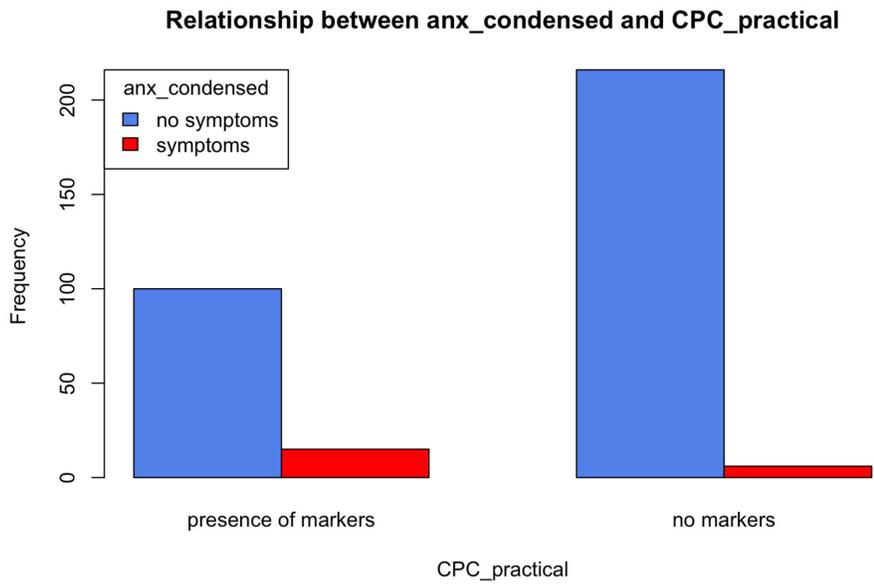
Relationship between anx_condensed and CPC_spiritual



Notes: Sparse cells and no strong evidence of a relationship.

anx and CPC practical bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	100	216	316
symptoms	15	6	21
	115	222	337

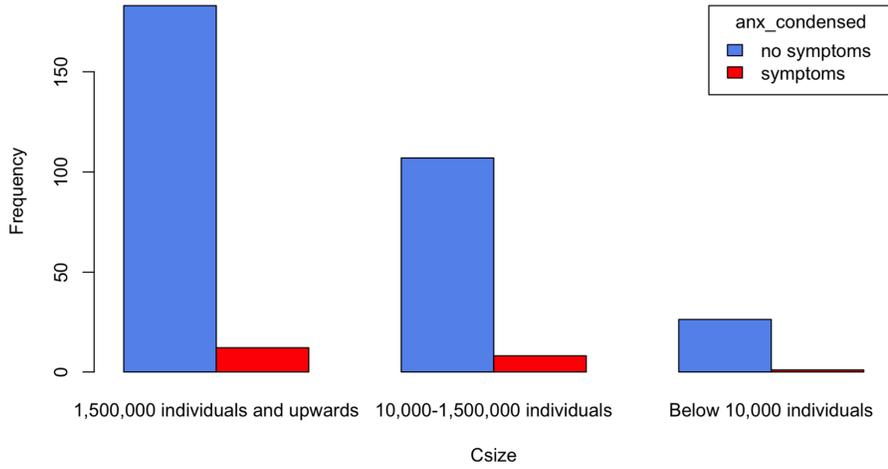


Notes: Between those with practical concerns and those without, the number of people with symptoms of anxiety decreases. However, the number of those without symptoms of anxiety (and the total number of individuals) increases.

anx and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
No symptoms	183	107	26	316
symptoms	12	8	1	21
	195	115	27	337

Relationship between anx_condensed and Csize

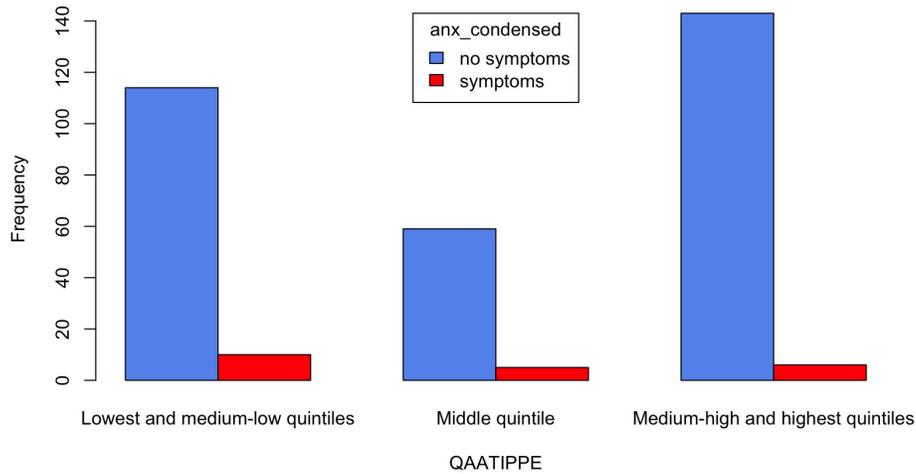


Notes: Decreased in the number of individuals in each group as you move to smaller community sizes. No strong evidence of relationship.

anx and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
No symptoms	114	59	143	316
symptoms	10	5	6	21
	124	64	149	337

Relationship between anx_condensed and QAATIPPE



Notes: No strong evidence of relationship. However, if you compare the lowest group with the highest, there are more individuals with symptoms of anxiety in the lowest group and less in the group with the highest income (even though the number with no symptoms and it total increases).

dep and CPC emotion bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	202	124	326
symptoms	11	0	11
	213	124	337

Notes: 0 cell. Unable to study further relationships.

dep and CPC info bar graph

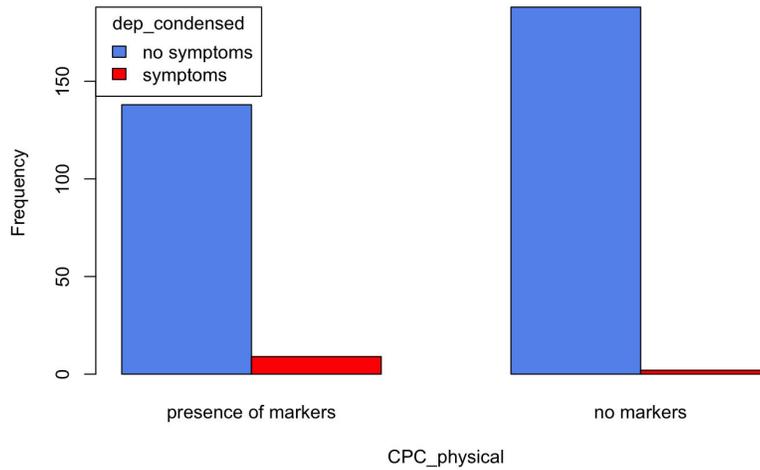
	1 or more checkmarks	No checkmarks	
No symptoms	216	110	326
symptoms	11	0	11
	227	110	337

Notes: 0 cells. Unable to study further relationships

dep and CPC physical bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	138	188	326
symptoms	9	2	11
	147	190	337

Relationship between dep_condensed and CPC_physical

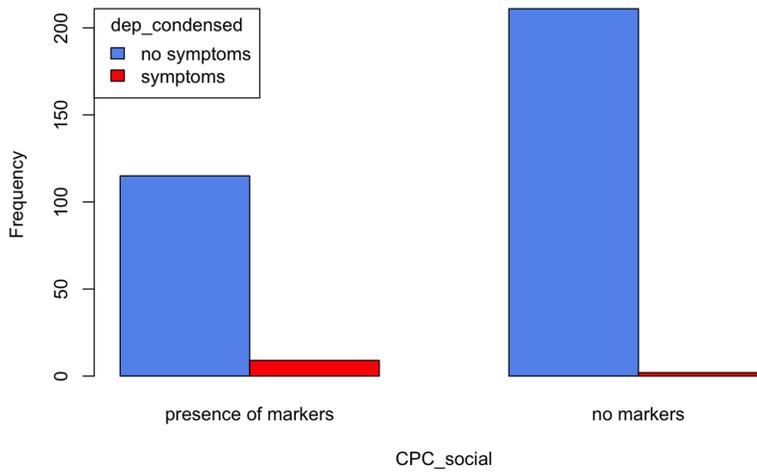


Notes: Not enough individuals to study relationships. However, comparing those with and without physical concerns, there is decrease in the number of individuals with symptoms of anxiety (even though there is an increase in the total number of individuals).

dep and CPC social bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	115	211	326
symptoms	9	2	11
	124	213	337

Relationship between dep_condensed and CPC_social

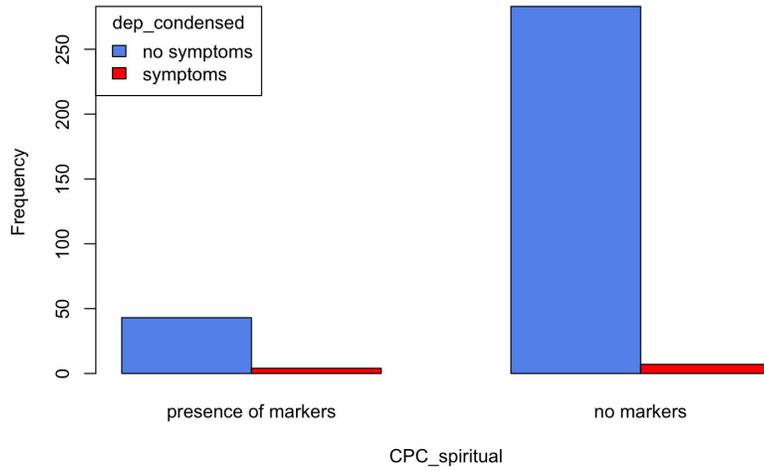


Notes: Not enough individuals to study relationship. However, similar trend as with CPC_physical above.

dep and CPC spiritual bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	43	283	326
symptoms	4	7	11
	47	290	337

Relationship between dep_condensed and CPC_spiritual

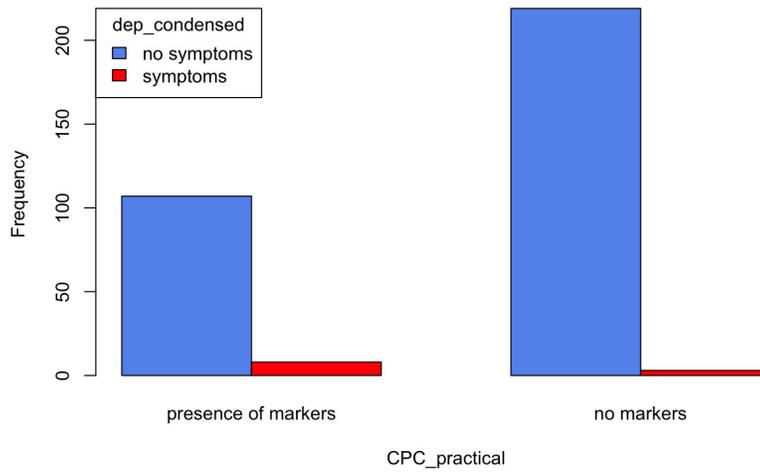


Notes: No strong evidence of relationship. However, similar amounts with symptoms of anx between both groups, even though significantly less individuals without spirituals concerns than with.

dep and CPC practical bar graph

	1 or more checkmarks	No checkmarks	
No symptoms	107	219	326
symptoms	8	3	11
	115	222	337

Relationship between dep_condensed and CPC_practical

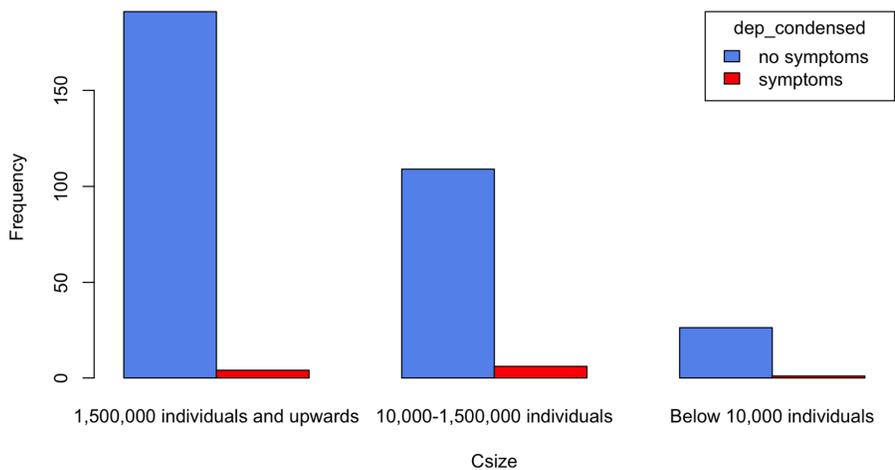


Notes: Not enough individuals to study relationship. However, similar trend as with CPC_social and CPC_physical above.

dep and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
No symptoms	191	109	26	326
symptoms	4	6	1	11
	195	115	27	337

Relationship between dep_condensed and Csize

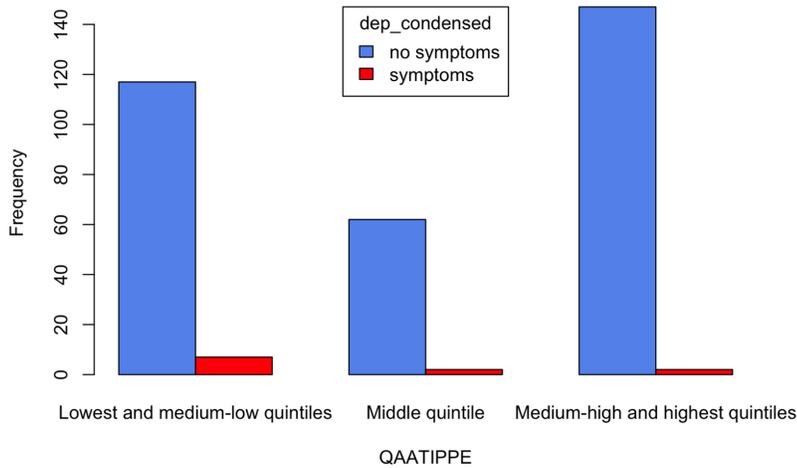


Notes: No strong evidence of a relationship.

dep and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
No symptoms	117	62	147	326
symptoms	7	2	2	11
	124	64	149	337

Relationship between dep_condensed and QAATIPPE

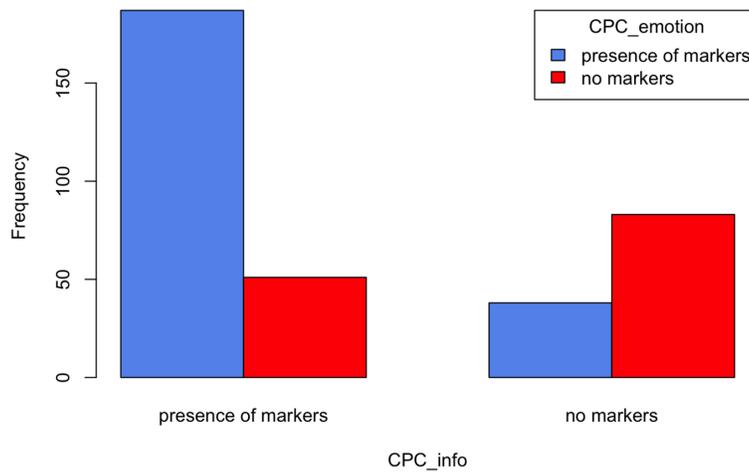


Notes: No strong evidence of relationship. However, if you compare the lowest group with the highest, there are more individuals with symptoms of dep in the lowest group and less in the group with the highest income (even though the number with no symptoms and it total increases).

CPC_emotion and CPC_info bar graph

	1 or more checkmarks (info)	No checkmarks (info)	
1 or more checkmarks (emotion)	187	38	225
No checkmarks (emotion)	51	83	134
	238	121	359

Relationship between CPC_emotion and CPC_info

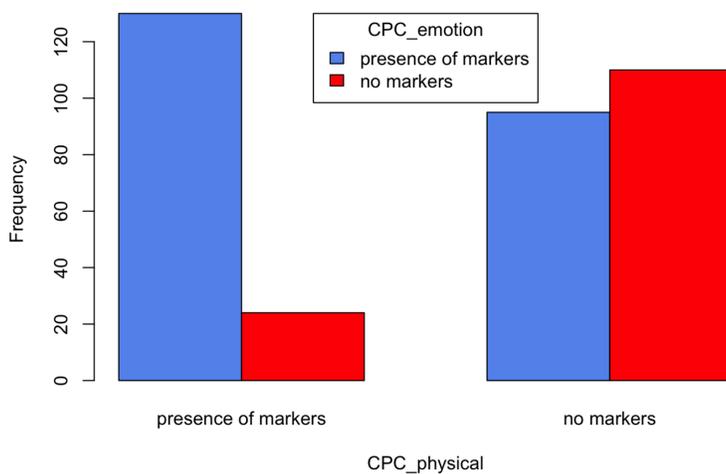


Notes: In those with informational concerns, there are more individuals with emotional concerns. In those without informational concerns, there are more individuals without emotional concerns. Could be relationship here.

CPC_emotion and CPC_physical bar graph

	1 or more checkmarks (physical)	No checkmarks (physical)	
1 or more checkmarks (emotion)	130	95	225
No checkmarks (emotion)	24	110	134
	154	205	359

Relationship between CPC_emotion and CPC_physical

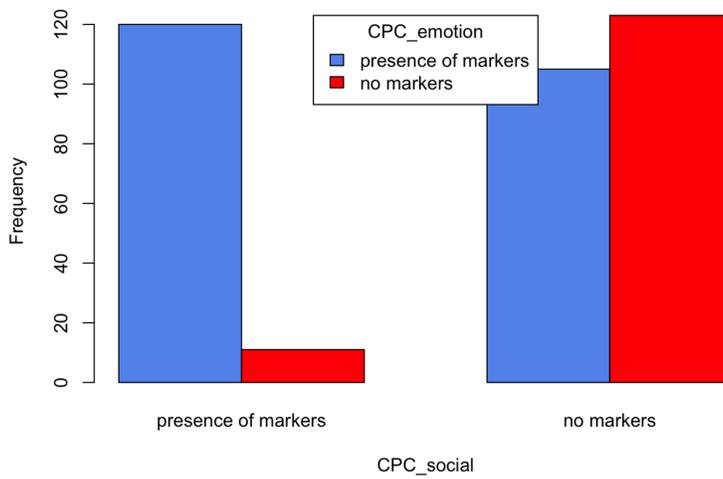


Notes: Similar trend to the above relationship. Could be relationship between these variables.

CPC_emotion and CPC_social bar graph

	1 or more checkmarks (social)	No checkmarks (social)	
1 or more checkmarks (emotion)	120	105	225
No checkmarks (emotion)	11	123	134
	131	228	359

Relationship between CPC_emotion and CPC_social

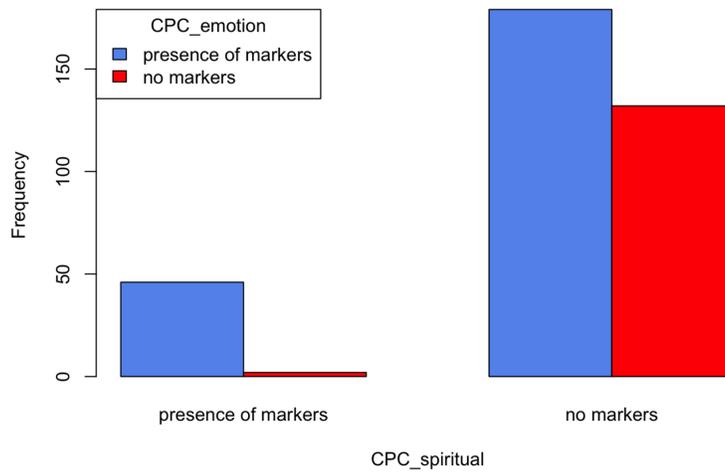


Notes: Like trends above. Could be a relationship between these variables.

CPC_emotion and CPC_spiritual bar graph

	1 or more checkmarks (spiritual)	No checkmarks (spiritual)	
1 or more checkmarks (emotion)	46	179	225
No checkmarks (emotion)	2	132	134
	48	311	359

Relationship between CPC_emotion and CPC_spiritual

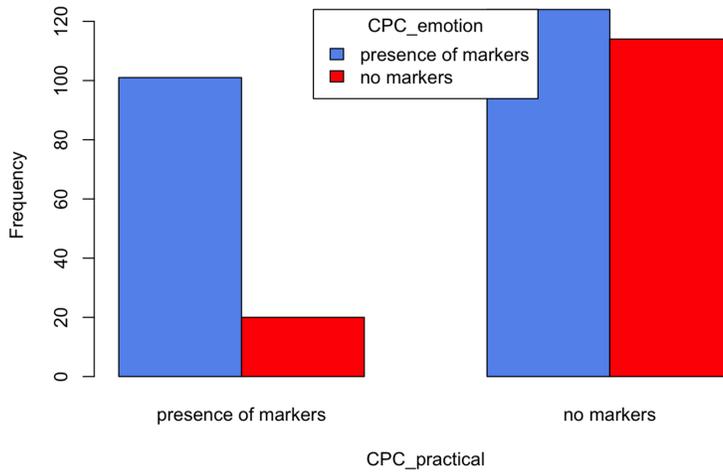


Notes: Sparse cell, so tough to decipher any sort of relationship here. However, there are more individuals with the emotional concerns in both groups.

CPC_emotion and CPC_practical bar graph

	1 or more checkmarks (practical)	No checkmarks (practical)	
1 or more checkmarks (emotion)	101	124	225
No checkmarks (emotion)	20	114	134
	121	238	359

Relationship between CPC_emotion and CPC_practical

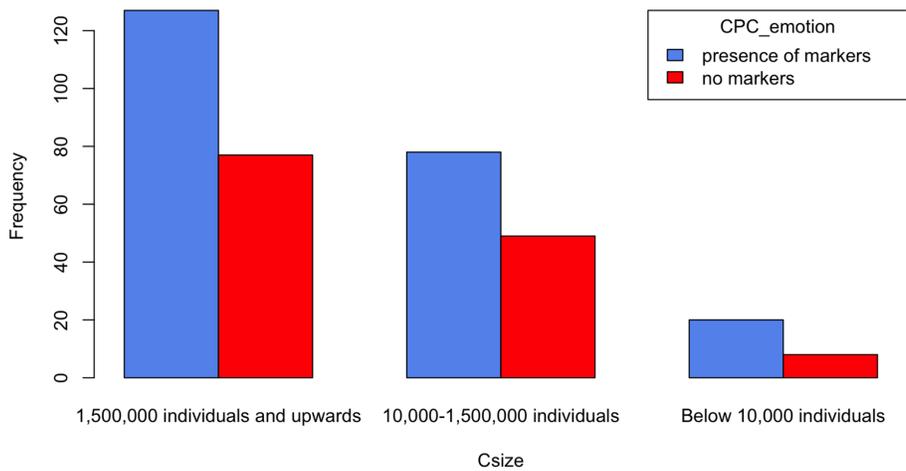


Notes: Unclear relationship. More individuals with emotional concerns in both groups. However, looking at proportions, only 17% of those with practical concerns do not have emotional concerns whereas 48% of those without practical concerns do not have emotional concerns.

CPC_emotion and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more checkmarks	127	78	20	225
No checkmarks	77	49	8	134
	204	127	28	359

Relationship between CPC_emotion and Csize

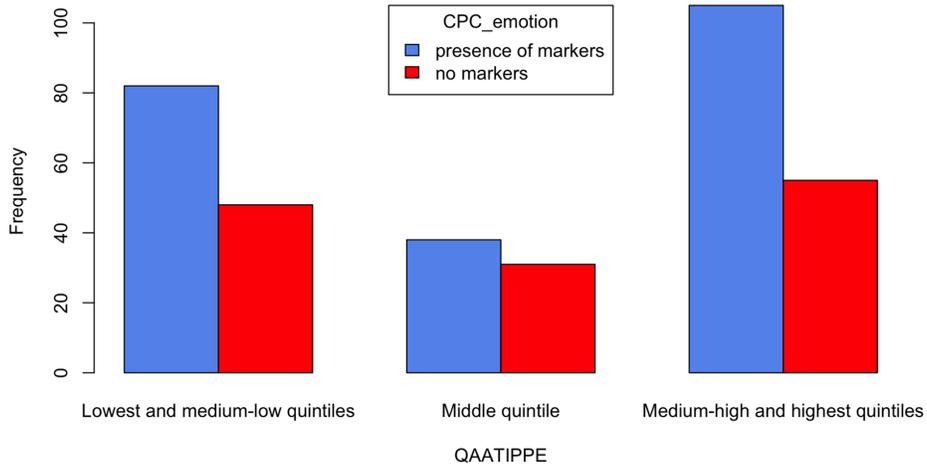


Notes: No strong evidence of a relationship.

CPC emotion and QAATIPPE

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	82	38	105	225
No checkmarks	48	31	55	134
	130	69	160	359

Relationship between CPC_emotion and QAATIPPE

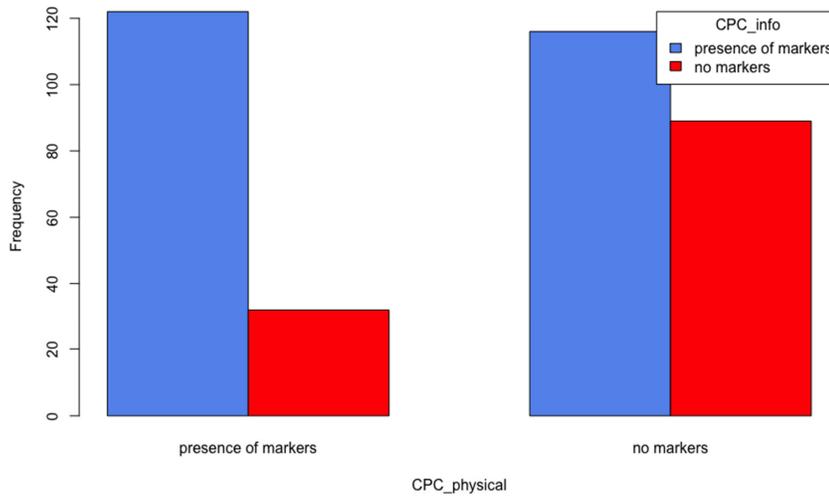


Notes: Not strong evidence. However, there does seem to be a disproportionate number of individuals in the higher income grouping that have emotional concerns.

CPC_info and CPC_physical bar graph

	1 or more checkmarks (physical)	No checkmarks (physical)	
1 or more checkmarks (info)	122	116	238
No checkmarks (info)	32	89	121
	154	205	359

Relationship between CPC_info and CPC_physical

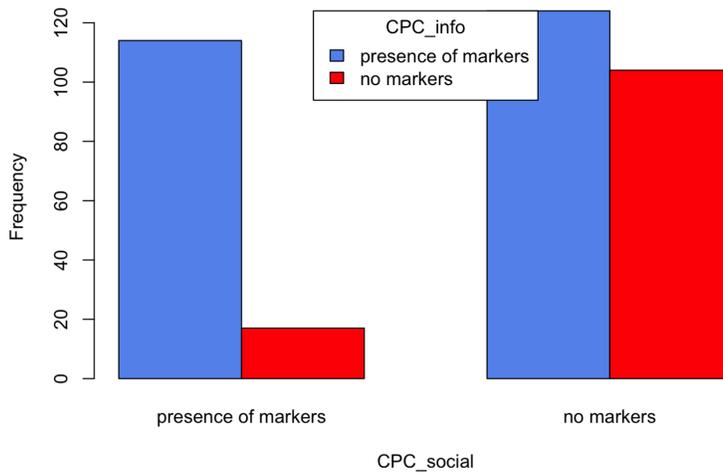


Notes: More without the informational concerns in both groups of physical concerns. However, in those with physical concerns, only 21% had informational concerns vs. in those without physical concerns, 43% had informational concerns.

CPC_info and CPC_social bar graph

	1 or more checkmarks (social)	No checkmarks (social)	
1 or more checkmarks (info)	114	124	238
No checkmarks (info)	17	104	121
	131	225	359

Relationship between CPC_info and CPC_social

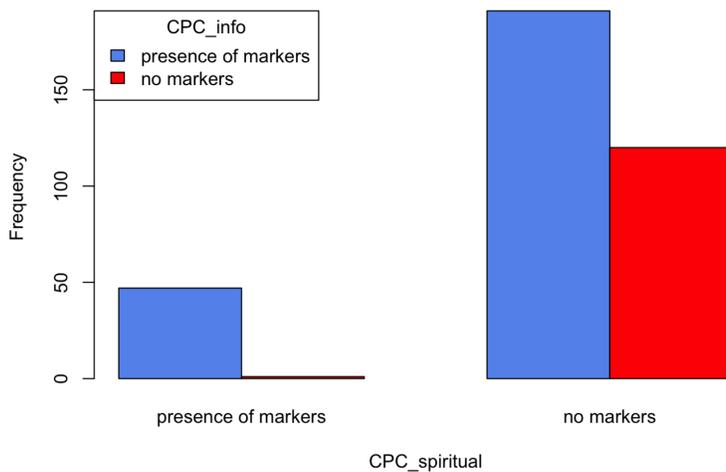


Notes: More with informational concerns in both groups. However, proportions are different again. Only small amount of those with social concerns do not have informational concerns, whereas closer to half of those without social concerns do not have information concerns.

CPC_info and CPC_spiritual bar graph

	1 or more checkmarks (spiritual)	No checkmarks (spiritual)	
1 or more checkmarks (info)	47	191	238
No checkmarks (info)	1	120	121
	48	311	359

Relationship between CPC_info and CPC_spiritual

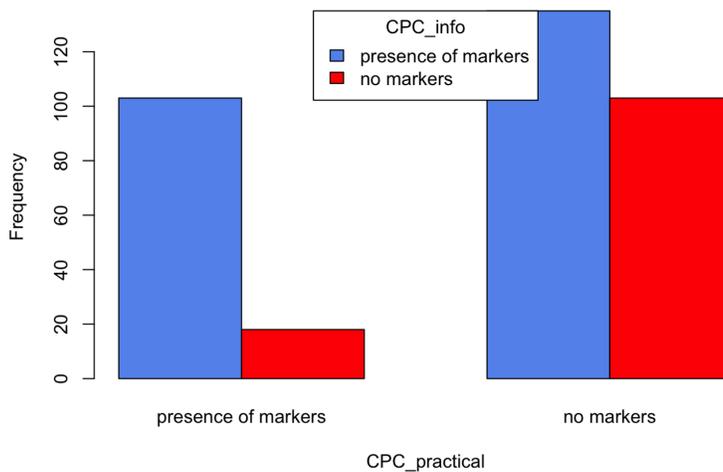


Notes: Sparse cells, so can't comment on relationship much. No evidence of any relationship though.

CPC_info and CPC_practical bar graph

	1 or more checkmarks (practical)	No checkmarks (practical)	
1 or more checkmarks (info)	103	135	238
No checkmarks (info)	18	103	121
	121	238	359

Relationship between CPC_info and CPC_practical

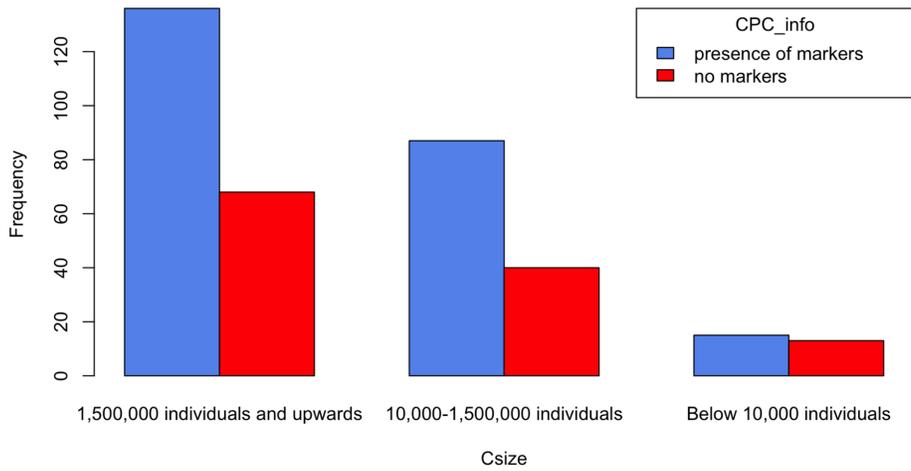


Notes: No strong evidence, but proportions different. In those with practical concerns, a small amount have informational concerns. This proportion grows in those without practical concerns. However, in both groups, there are more individuals with informational concerns.

CPC info and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more checkmarks	136	87	15	238
No checkmarks	68	40	13	121
	204	127	28	359

Relationship between CPC_info and Csize

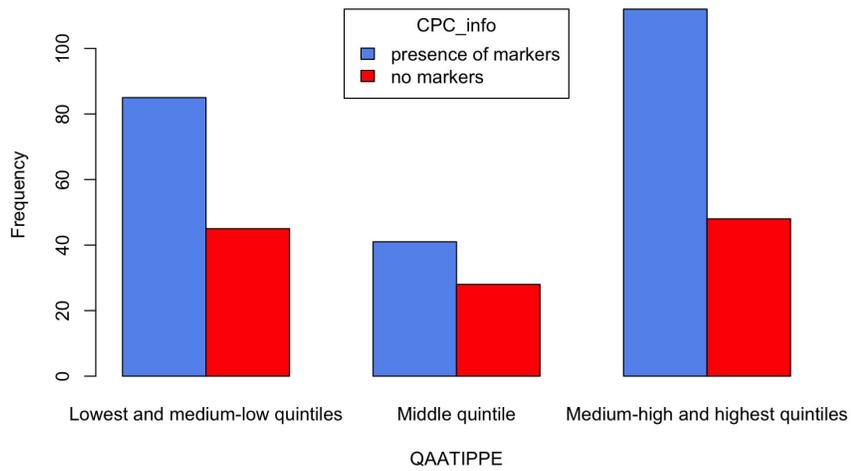


Notes: More with informational concerns in all groups. However, no strong evidence of any relationships.

CPC info and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	85	41	112	238
No checkmarks	45	28	48	121
	130	69	160	359

Relationship between CPC_info and QAATIPPE

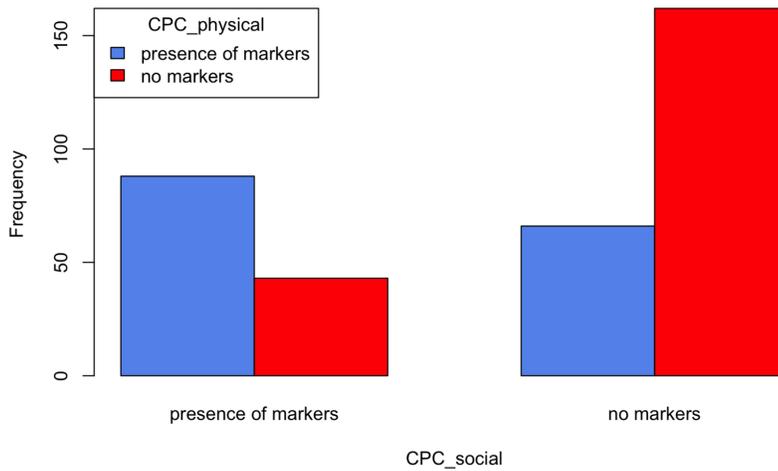


Notes: No strong evidence of any relationship. There are potentially a smaller proportion of individuals without informational concerns in the highest grouping, but likely not strong relationship.

CPC_physical and CPC_social bar graph

	1 or more checkmarks (social)	No checkmarks (social)	
1 or more checkmarks (physical)	88	66	154
No checkmarks (physical)	43	162	205
	131	228	359

Relationship between CPC_physical and CPC_social

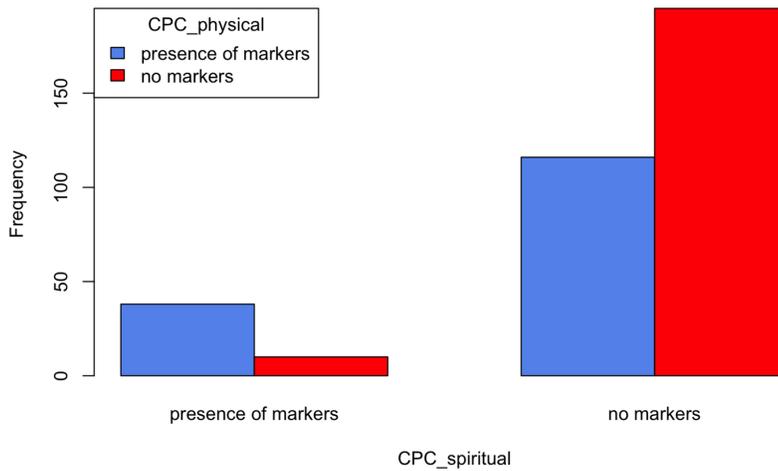


Notes: Potential relationship. In the group with social concerns, more also have physical concerns. In group without social concerns, there are more that also do not have physical concerns.

CPC_physical and CPC_spiritual bar graph

	1 or more checkmarks (spiritual)	No checkmarks (spiritual)	
1 or more checkmarks (physical)	38	116	154
No checkmarks (physical)	10	195	205
	48	311	359

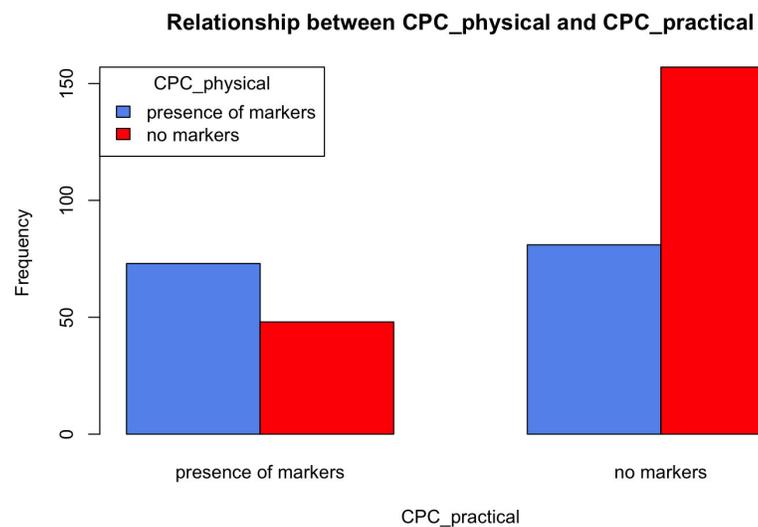
Relationship between CPC_physical and CPC_spiritual



Notes: Less people to study, but potential relationship. In group with spiritual concerns, more also have physical concerns. In group without spiritual concerns, more are also missing indicators of physical concerns.

CPC_physical and CPC_practical bar graph

	1 or more checkmarks (practical)	No checkmarks (practical)	
1 or more checkmarks (physical)	73	81	154
No checkmarks (physical)	48	157	205
	121	138	359

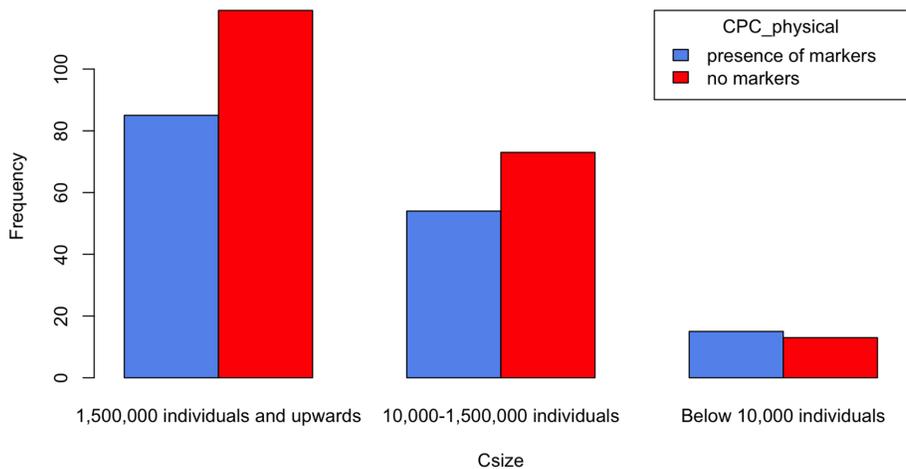


Notes: Similar to above. More with practical concerns also have physical concerns. Most without practical concerns are also missing indicators of physical concerns.

CPC_physical and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more checkmarks	85	54	15	154
No checkmarks	119	73	13	205
	204	127	28	359

Relationship between CPC_physical and Csize

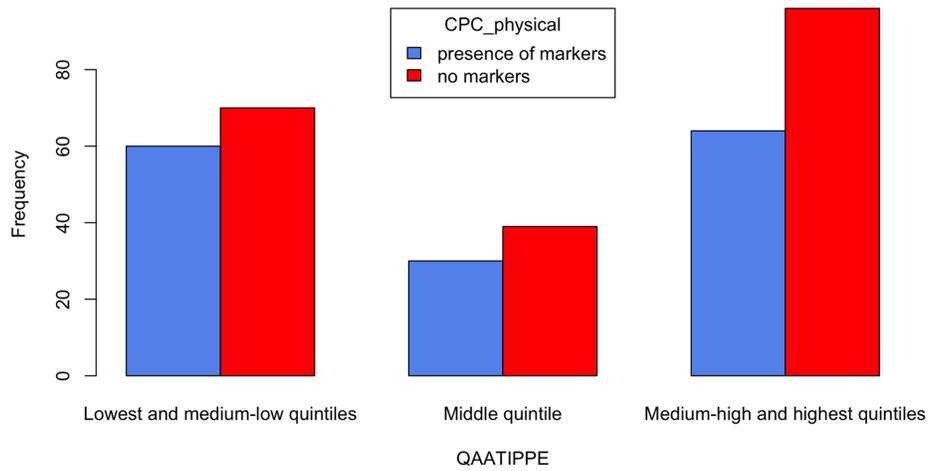


Notes: No strong evidence of relationship. However, in the smallest community size, there are more individuals with physical concerns than without (opposite to other groups). This is a very small number, so can't know for sure.

CPC_physical and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	60	30	64	154
No checkmarks	70	39	96	205
	130	69	160	359

Relationship between CPC_physical and QAATIPPE

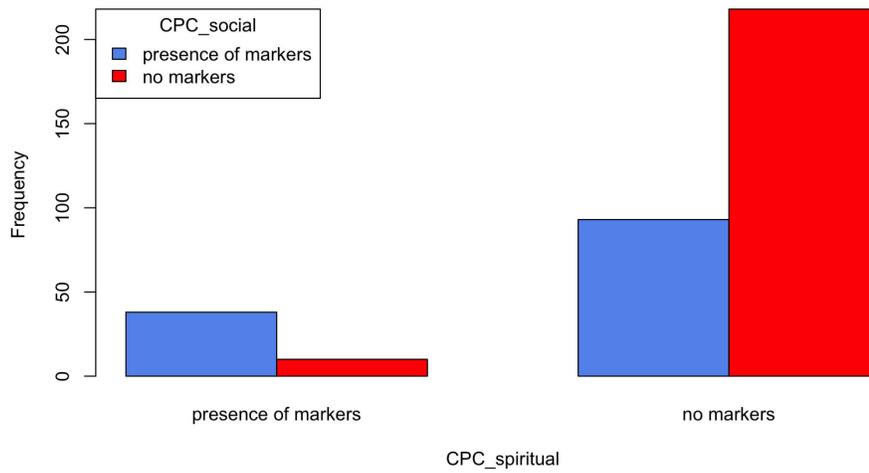


Notes: No evidence of relationship. All groups have more without physical concerns and proportions are similar.

CPC social and CPC spiritual bar graph

	1 or more checkmarks (spiritual)	No checkmarks (spiritual)	
1 or more checkmarks (social)	38	93	131
No checkmarks (social)	10	218	228
	48	311	359

Relationship between CPC_social and CPC_spiritual

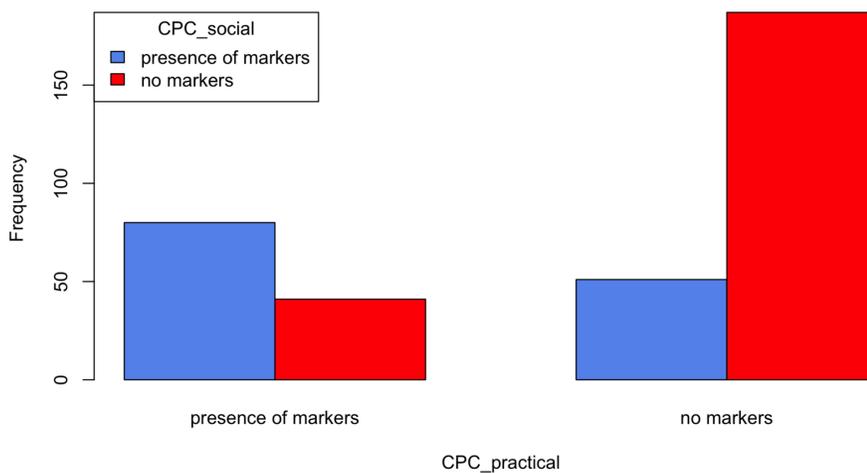


Notes: Not many individuals to study, but majority with spiritual concerns also have social concerns. Majority without spiritual concerns are also lacking in social concerns.

CPC_social and CPC_practical bar graph

	1 or more checkmarks (practical)	No checkmarks (practical)	
1 or more checkmarks (social)	80	51	131
No checkmarks (social)	41	187	228
	121	238	359

Relationship between CPC_social and CPC_practical

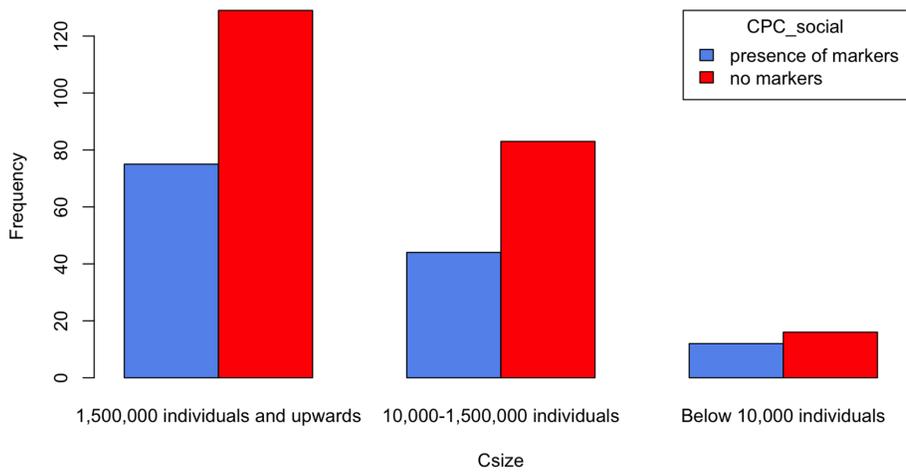


Notes: Potential relationship. Majority with practical concerns also have social concerns. Majority without practical concerns also do not have social concerns.

CPC social and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more checkmarks	75	44	12	131
No checkmarks	129	83	16	228
	204	127	28	359

Relationship between CPC_social and Csize

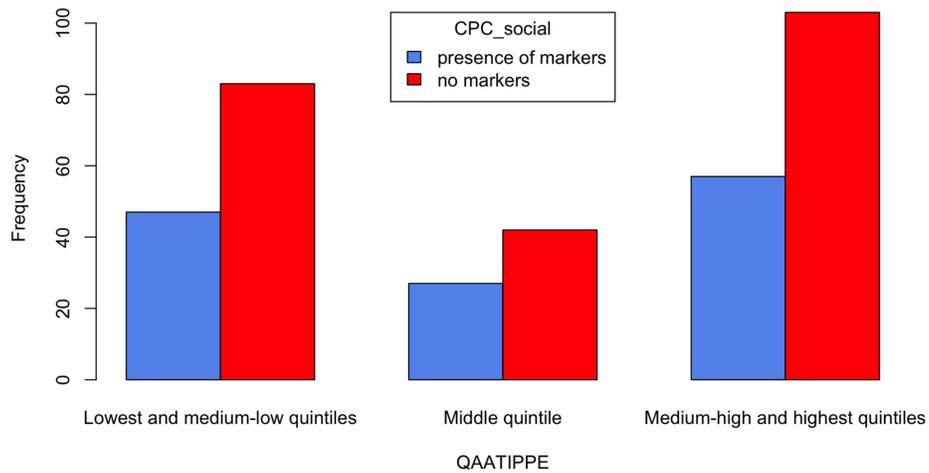


Notes: No strong evidence of relationship. More without social concerns in all groups and similar proportions.

CPC social and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	47	27	57	131
No checkmarks	83	42	103	228
	130	69	160	359

Relationship between CPC_social and QAATIPPE

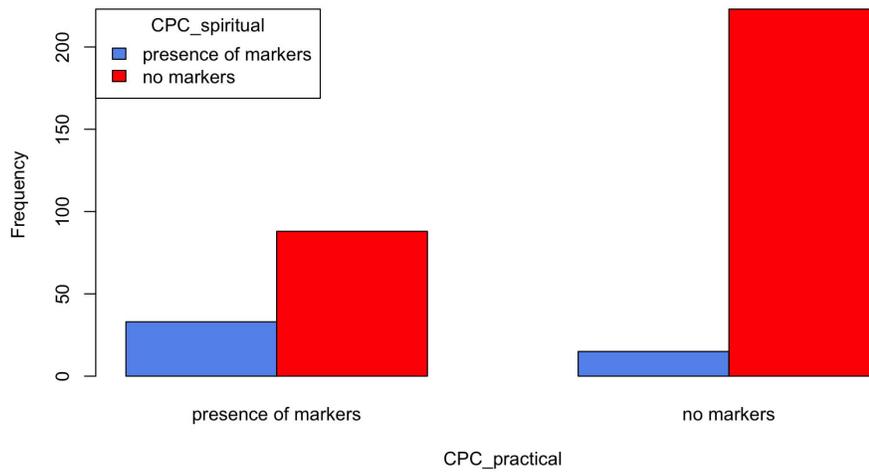


Notes: No strong evidence of relationship. More without social concerns in all groups and similar proportions.

CPC_spiritual and CPC_practical bar graph

	1 or more checkmarks (practical)	No checkmarks (practical)	
1 or more checkmarks (spiritual)	33	15	48
No checkmarks (spiritual)	88	223	311
	121	238	359

Relationship between CPC_spiritual and CPC_practical

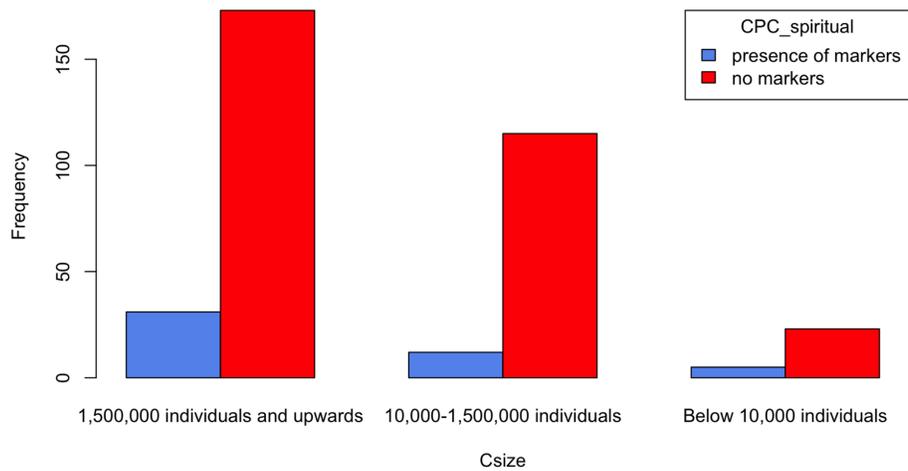


Notes: No strong evidence of relationship. More without practical concerns overall. Potentially different proportions, with a smaller proportion having physical concerns in those without practical concerns (as compared to those with), but this is minor.

CPC spiritual and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more checkmarks	31	12	5	48
No checkmarks	173	115	23	311
	204	127	28	359

Relationship between CPC_spiritual and Csize

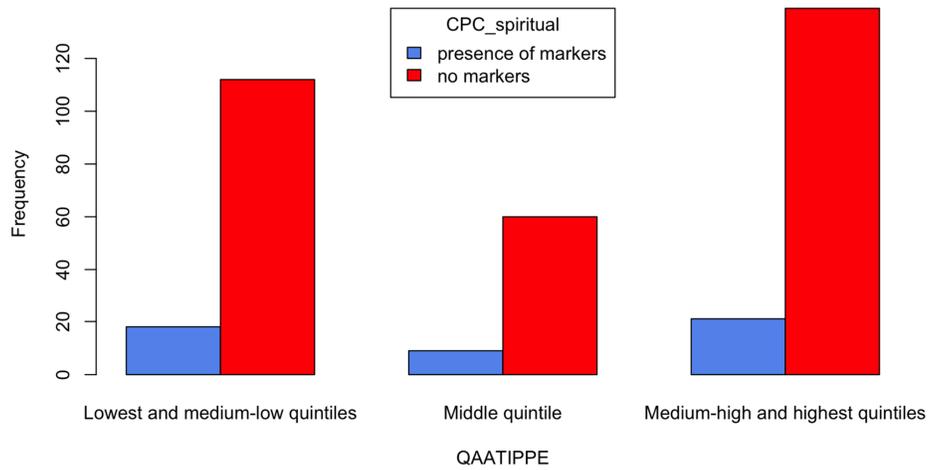


Notes: No strong evidence of relationship. Small proportion of individuals with markers of spiritual concerns in all groups.

CPC_spiritual and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	18	9	21	48
No checkmarks	112	60	139	311
	130	69	160	359

Relationship between CPC_spiritual and QAATIPPE

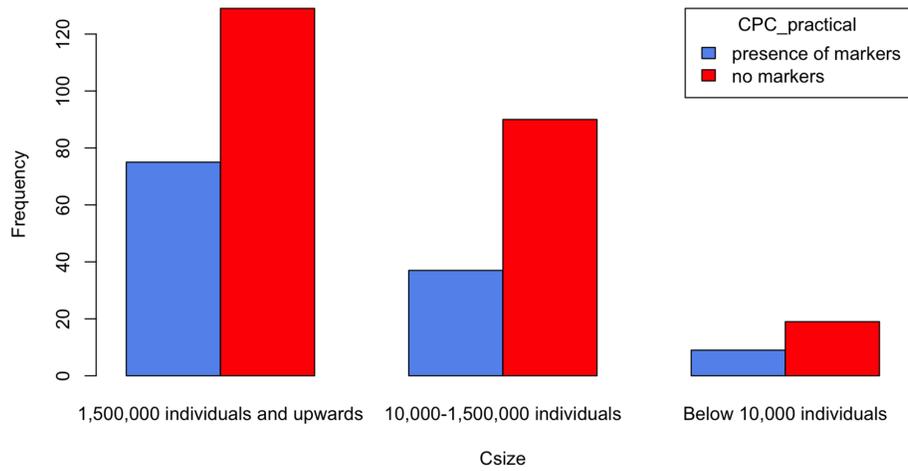


Notes: No strong evidence of relationship. Small proportion with spiritual concerns across all groups.

CPC practical and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more checkmarks	75	37	9	121
No checkmarks	129	90	19	238
	204	127	28	359

Relationship between CPC_practical and Csize

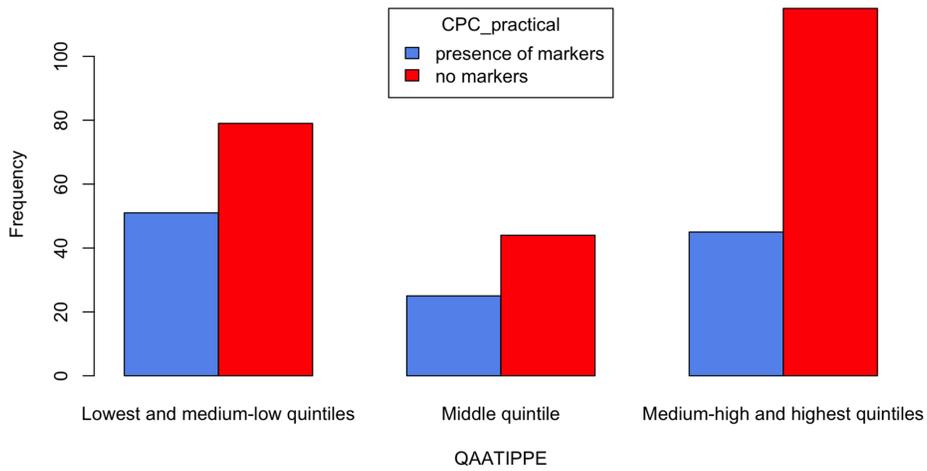


Notes: No strong evidence of relationship. More individuals without practical concerns in all groups and very similar looking proportions.

CPC practical and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	51	25	45	121
No checkmarks	79	44	115	238
	130	69	160	359

Relationship between CPC_practical and QAATIPPE

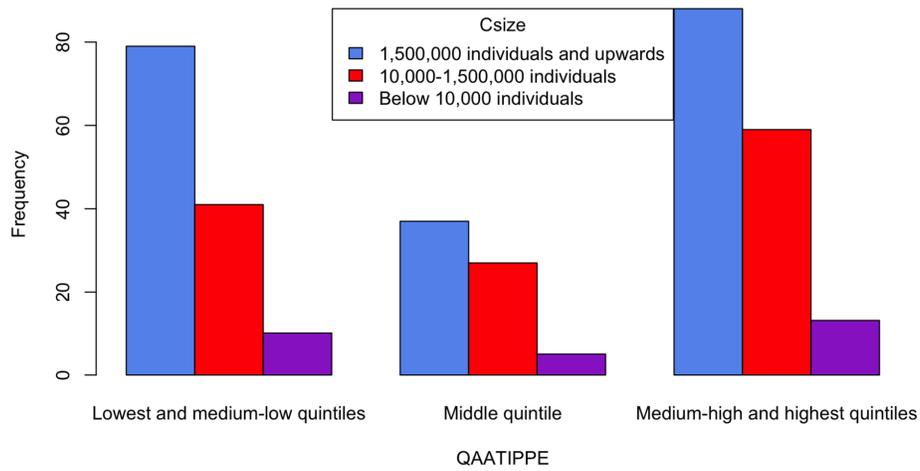


Notes: No strong evidence of relationship. More without practical concerns in all groups. Slightly different proportions (i.e., higher proportion of those with practical concerns in the lower income group) but likely not significant.

Csize and QAATIPPE bar graph

	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1,500,000 individuals and upwards	79	37	88	204
10,000-1,500,000 individuals	41	27	59	127
Below 10,000 individuals	10	5	13	28
	130	69	160	359

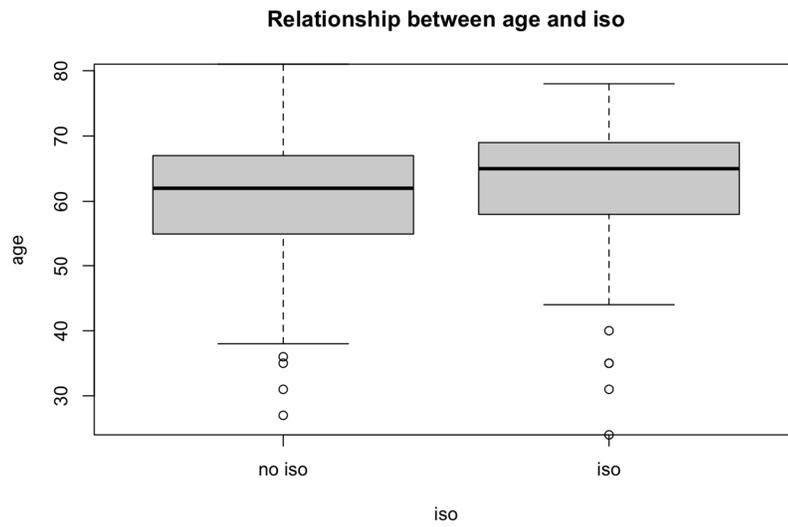
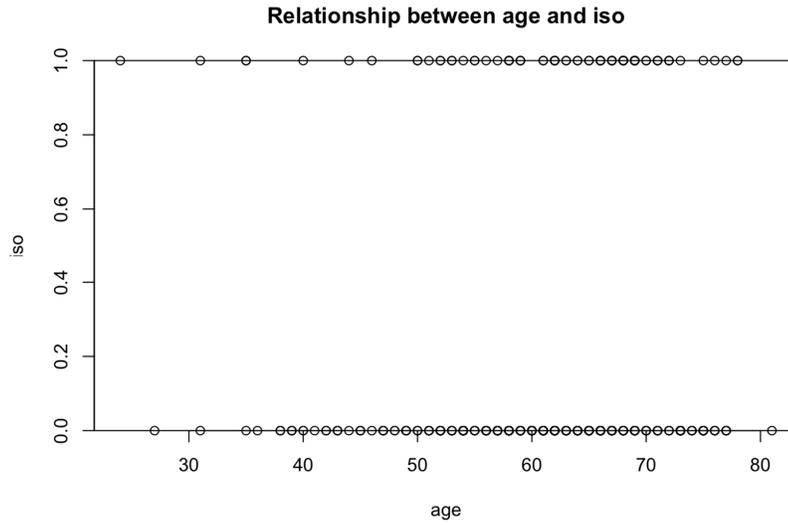
Relationship between Csize and QAATIPPE

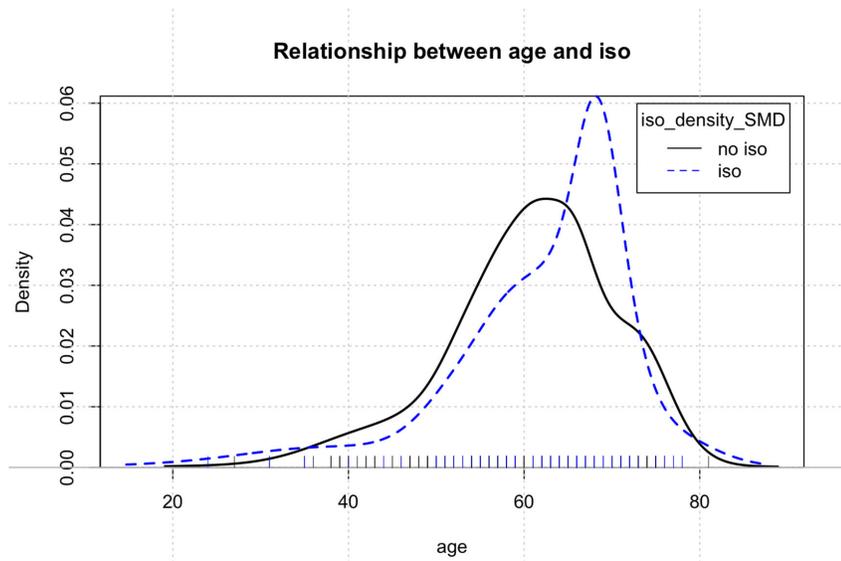


Notes: No strong evidence of relationship. Most are from larger community sizes in all groups. Similar proportions across groups as well.

Age and social/psychological covariables

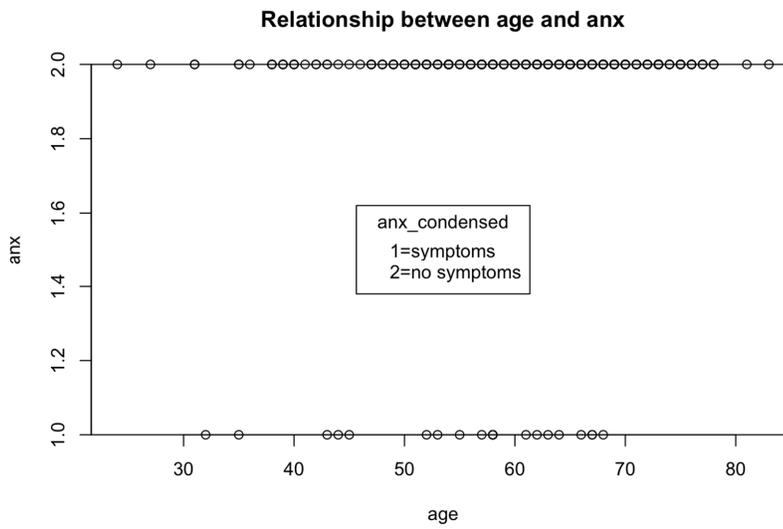
age and iso

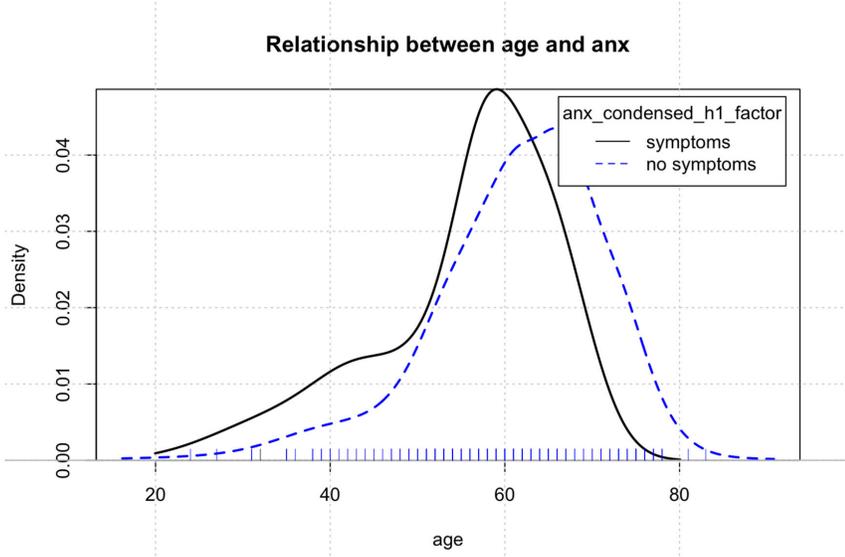
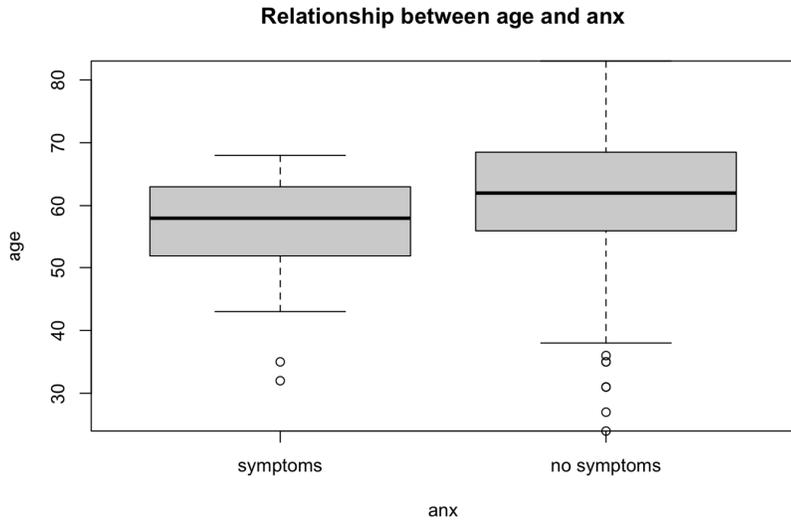




Notes: Not a strong relationship (lots of overlap) but appears those with iso might also be older (as expected, it asks if you live alone etc.)

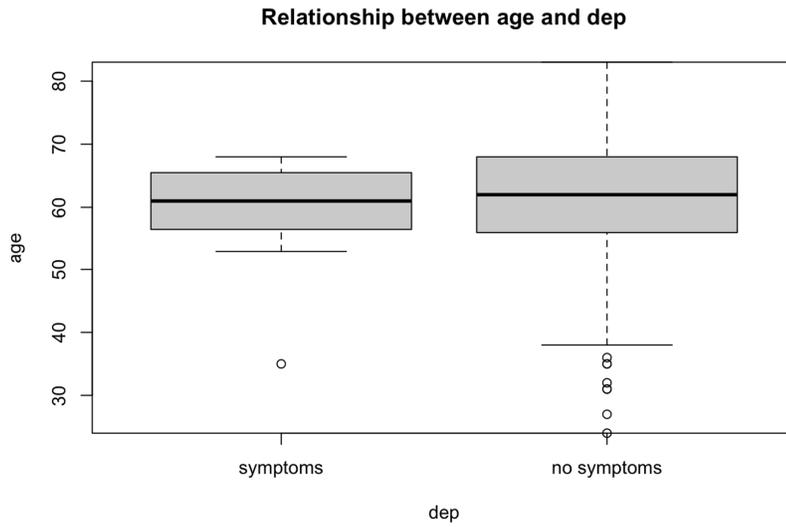
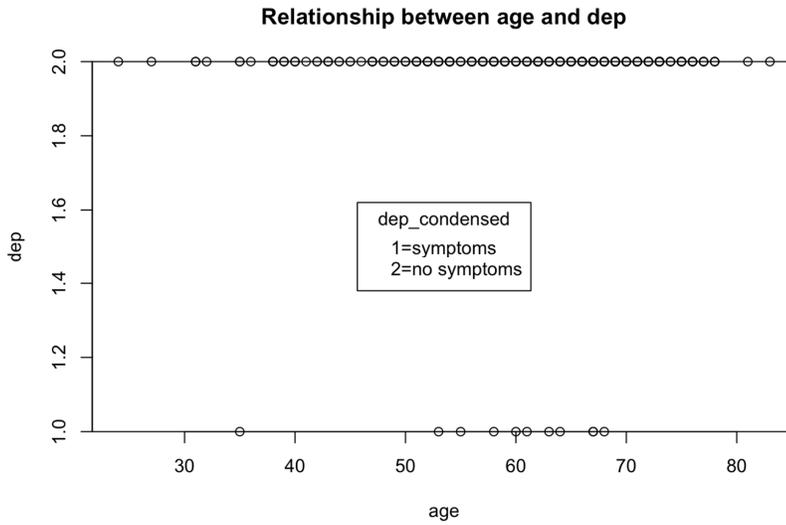
age and anx

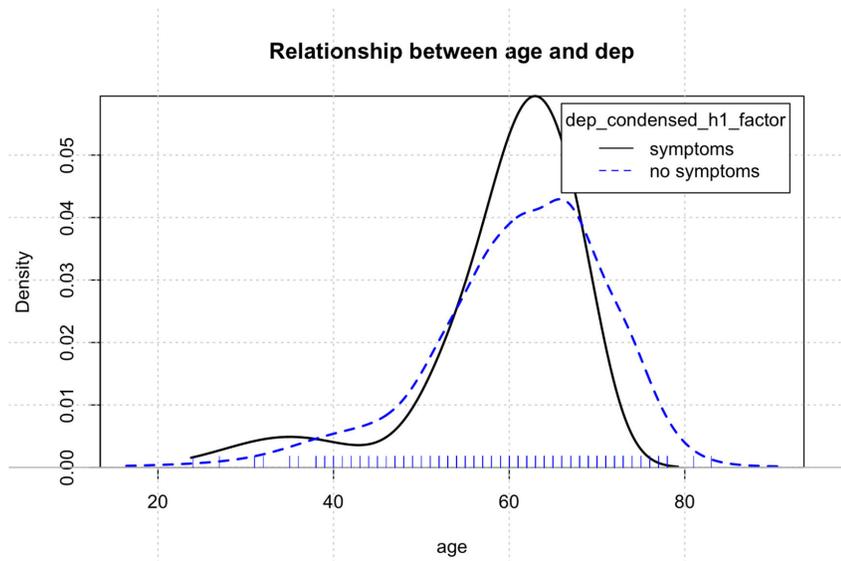




Notes: Potential that those with symptoms of anx are younger. However, there is not many individuals in that group so hard to study.

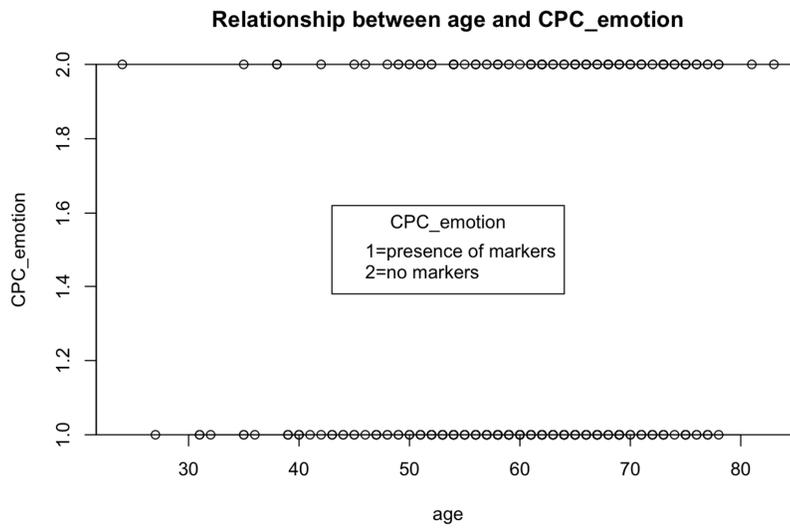
age and dep

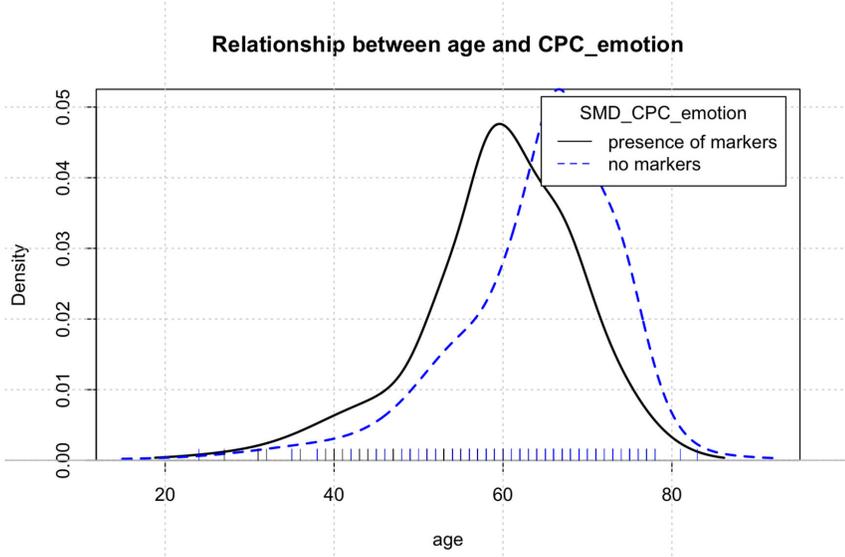
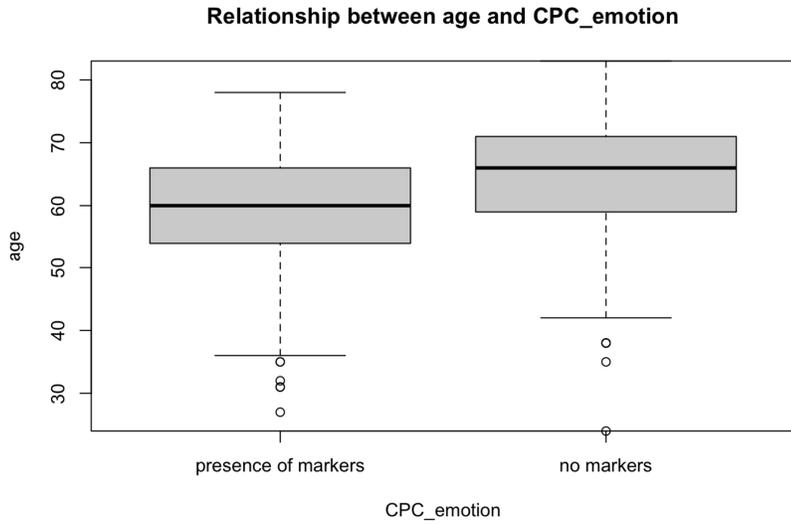




Notes: Not enough people with symptoms of dep to study but no evidence of relationship regardless.

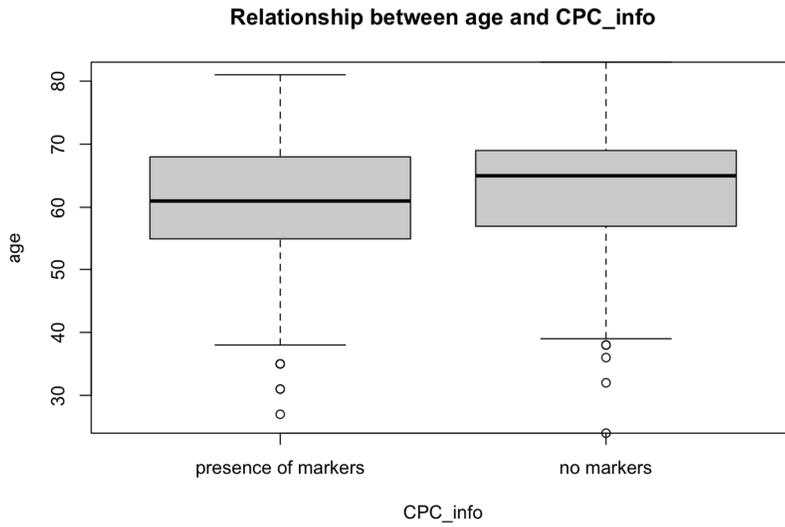
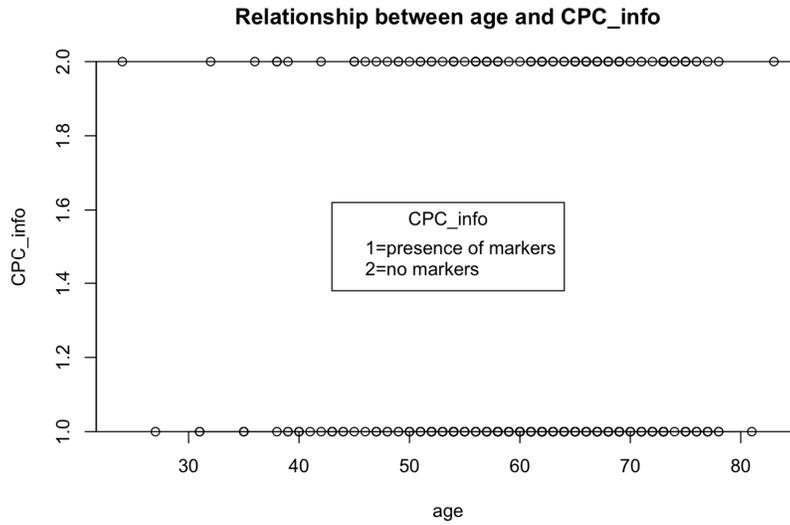
age and CPC_emotion

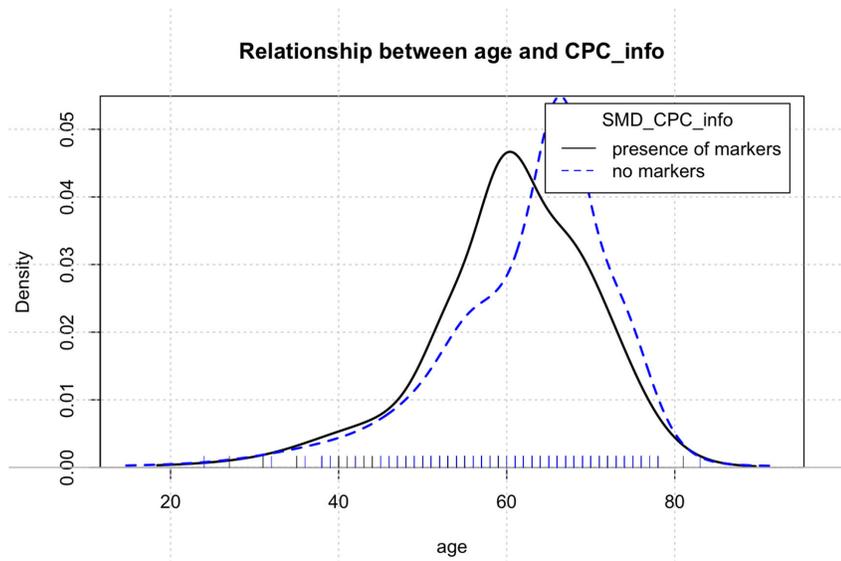




Notes: Seems like younger patients have more emotional concerns. Still overlap/likely not strong relationship.

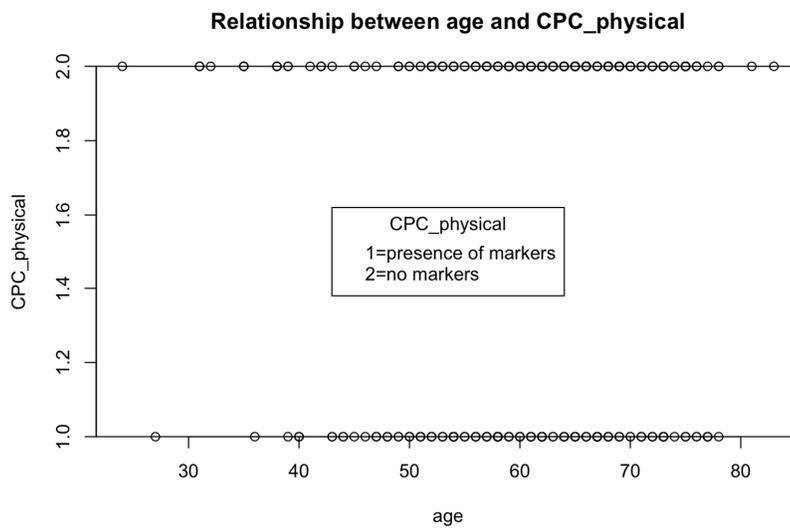
age and CPC_info

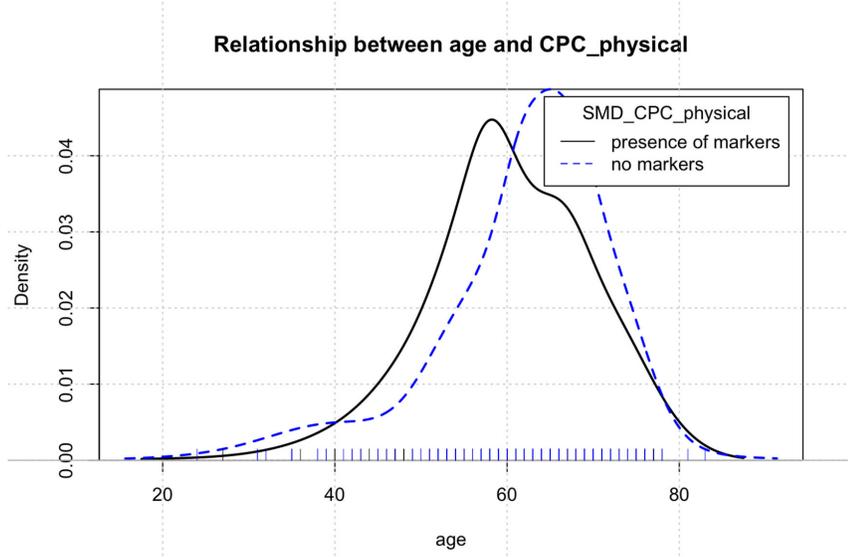
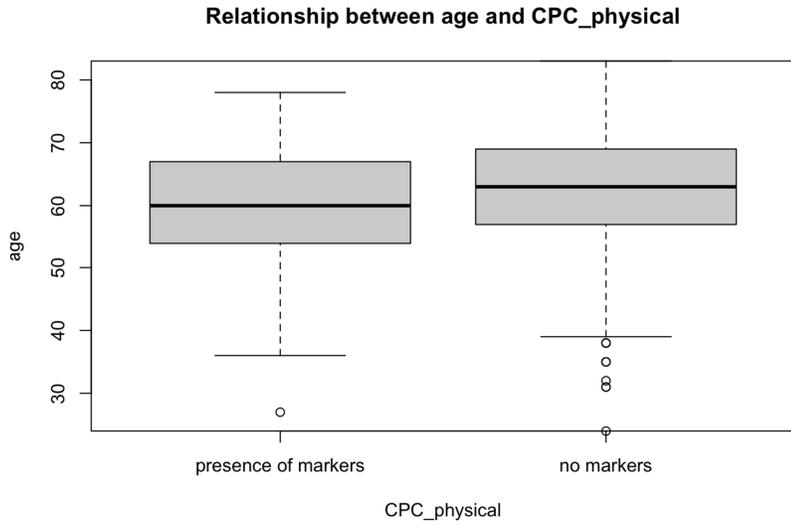




Notes: Overlap but appears that these with informational concerns are younger.

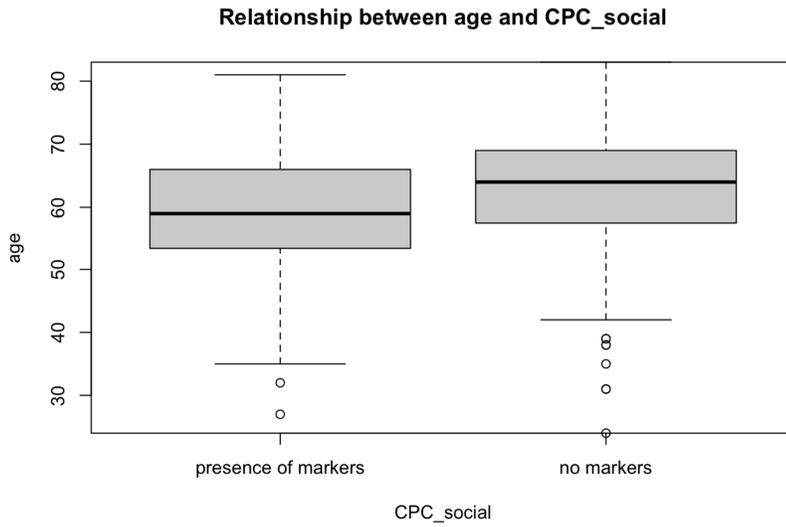
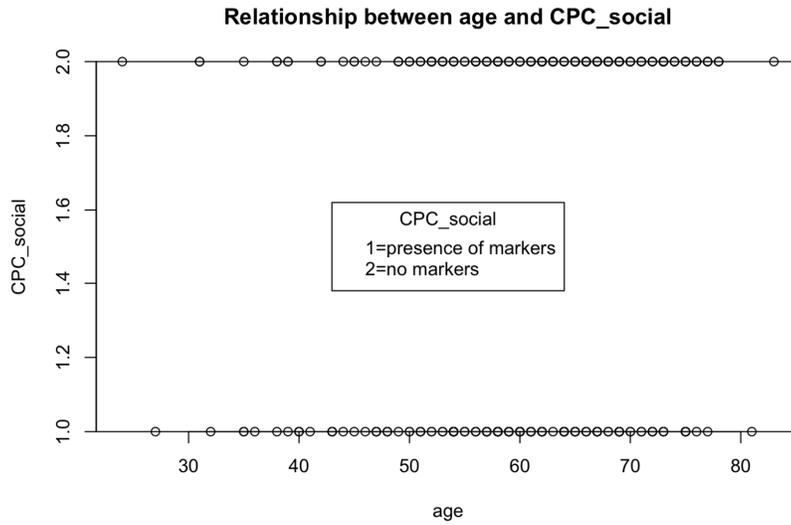
age and CPC_physical

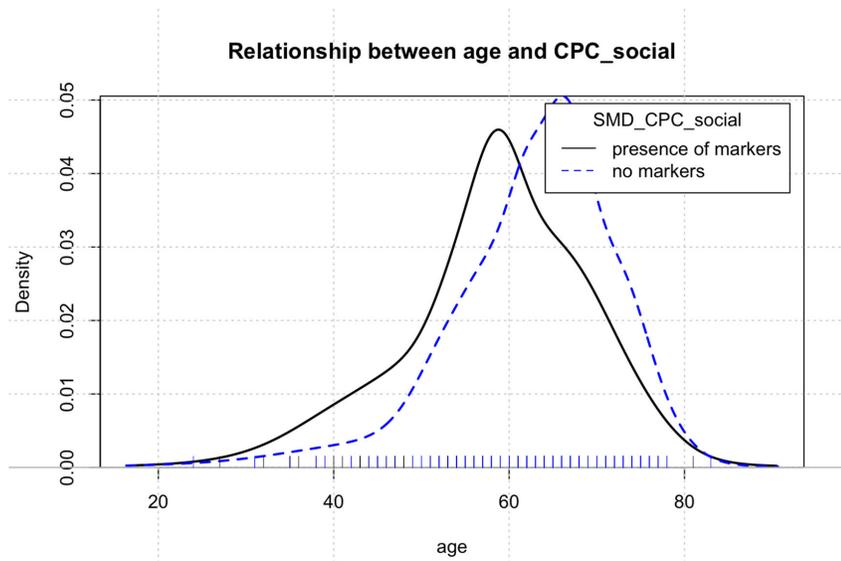




Notes: Very slight but appears that those who are younger may more likely have physical concerns.

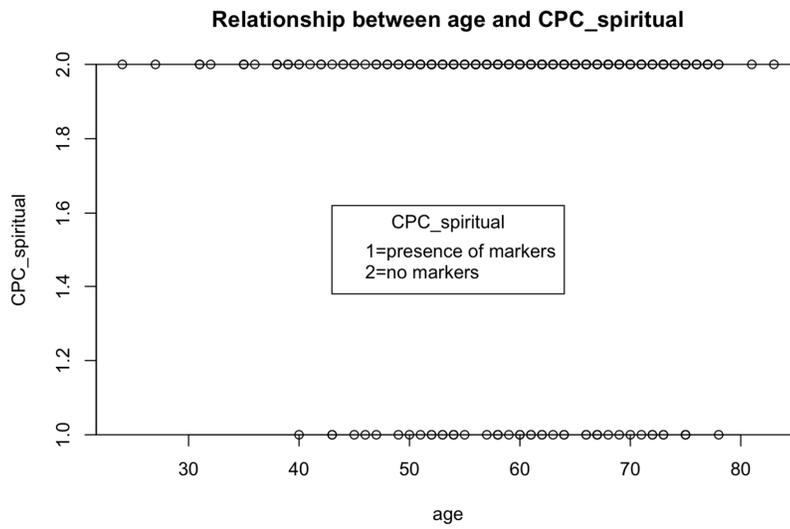
age and CPC_social

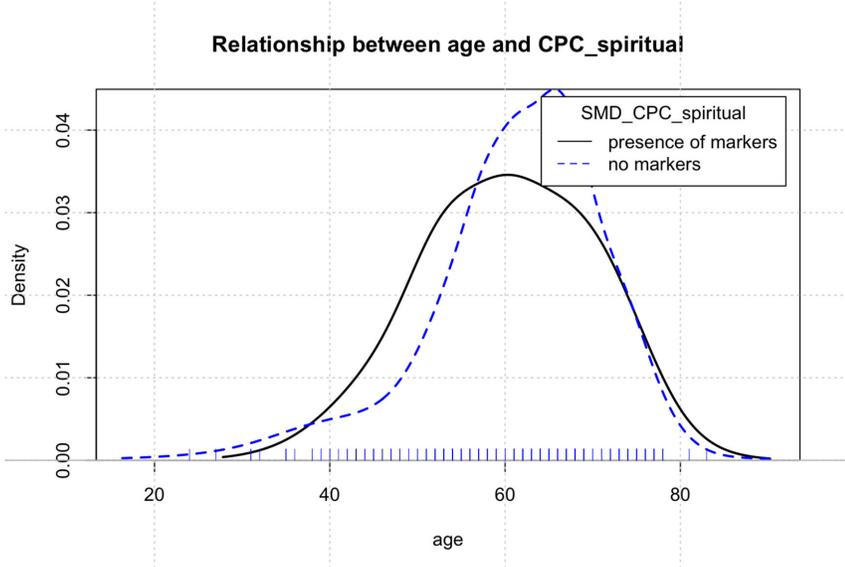
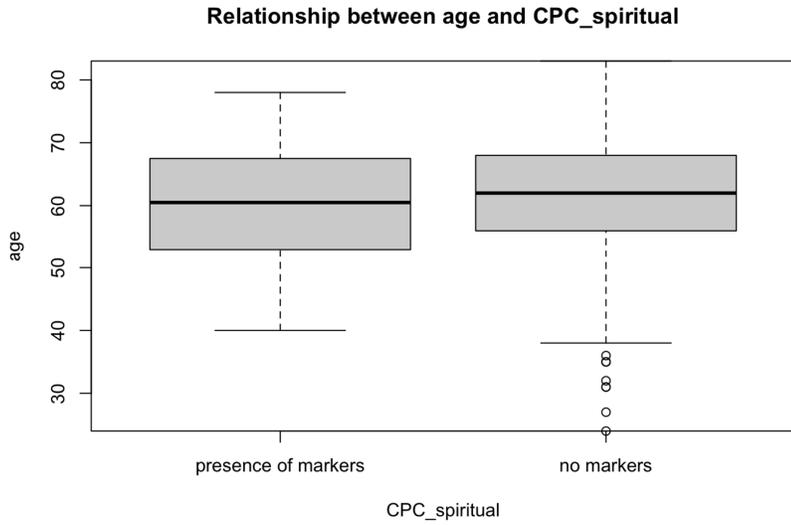




Notes: Again, those that are younger more readily have social concerns. This is interesting, as those that were older were more likely to be isolated.

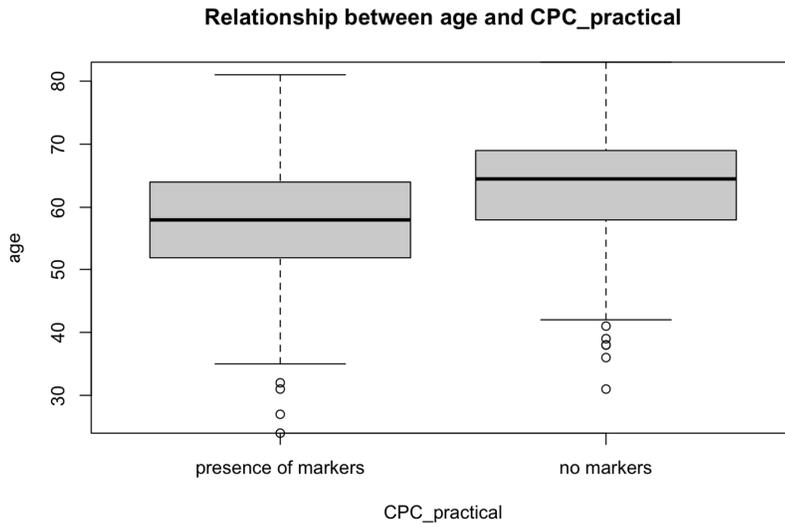
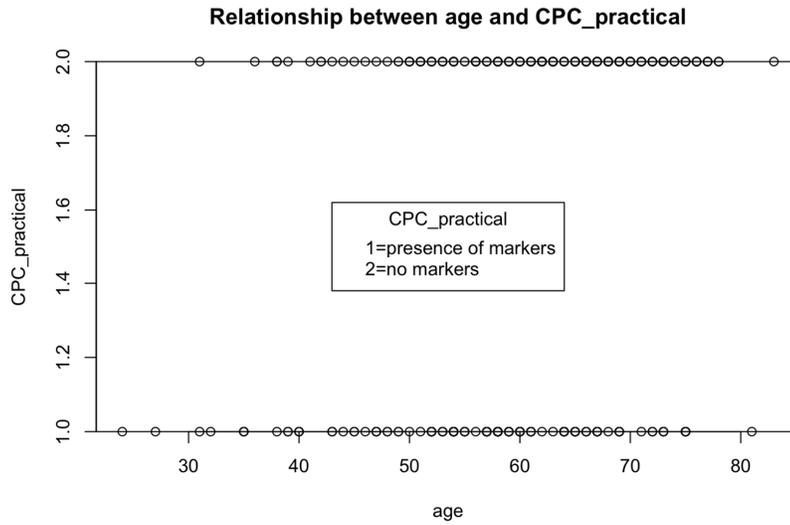
age and CPC_spiritual

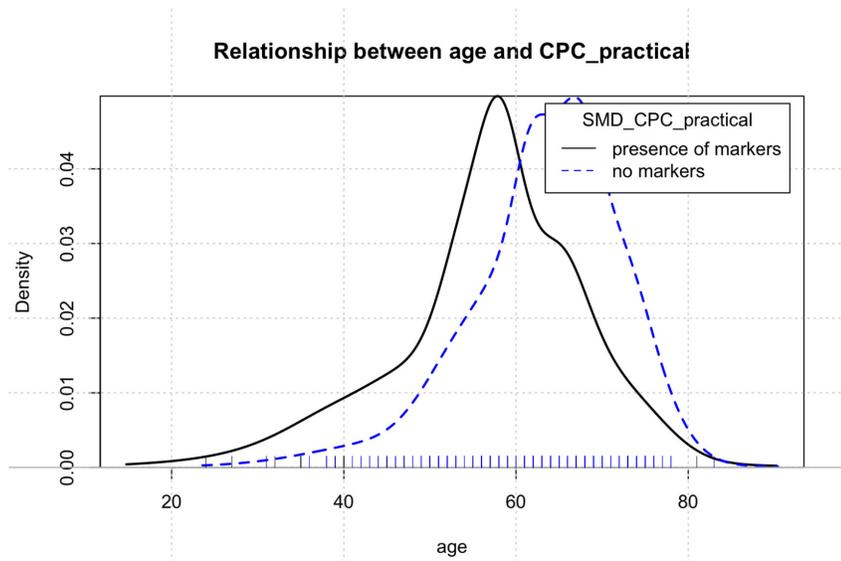




Notes: No strong evidence of relationship.

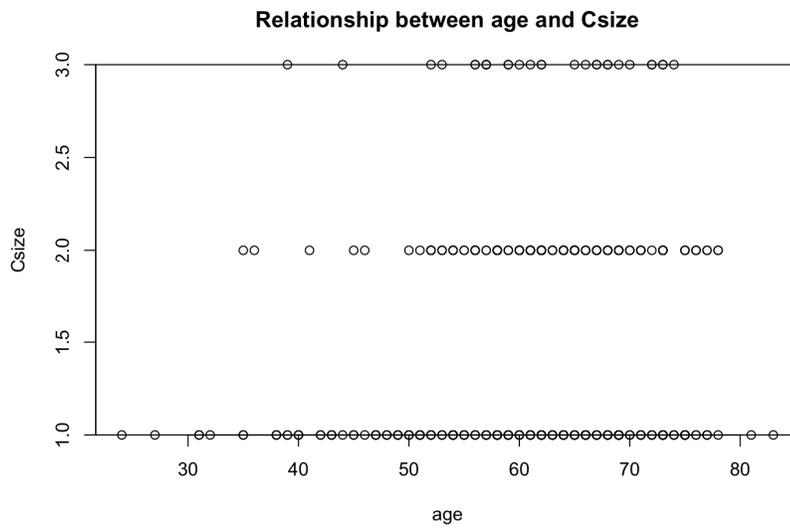
age and CPC_practical



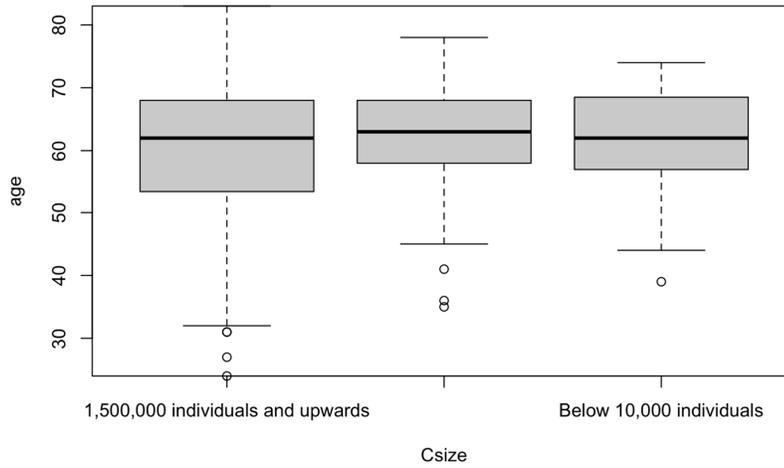


Notes: Those that are younger more readily report practical concerns. This is one of the more prominent relationships seen.

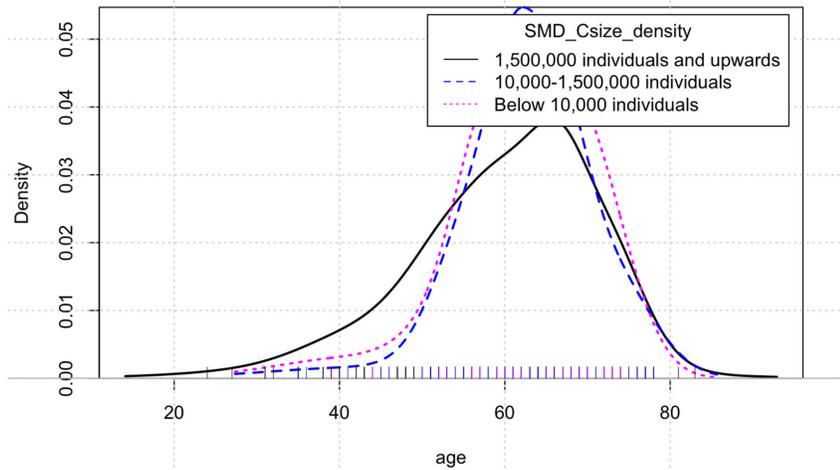
age and Csize



Relationship between age and Csize

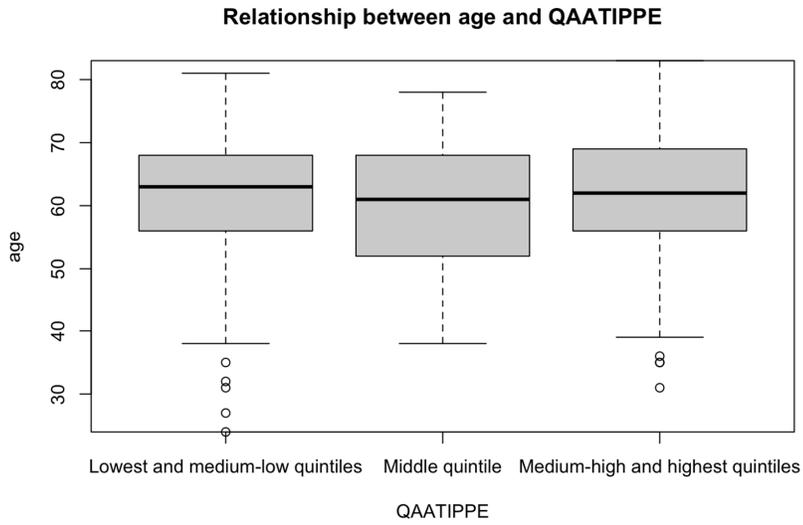
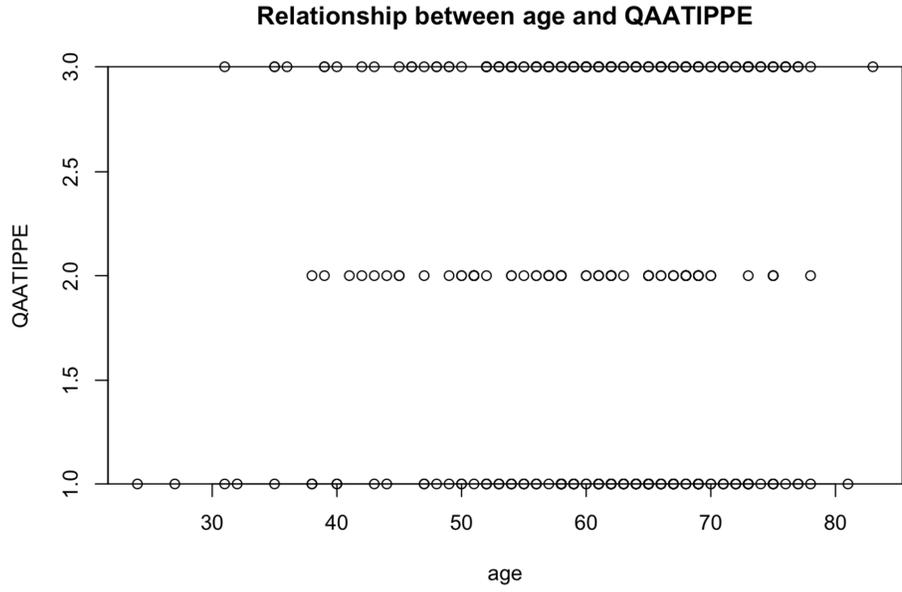


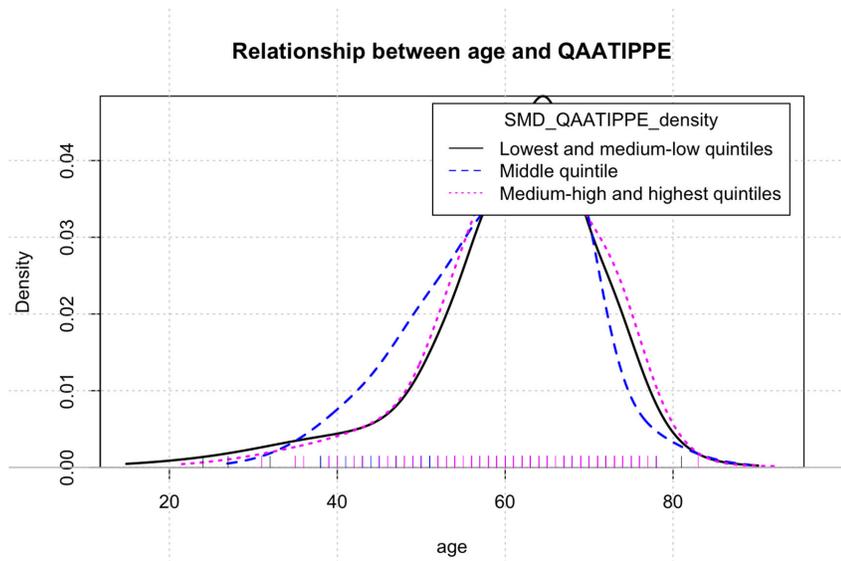
Relationship between age and Csize



Notes: No strong evidence of a relationship. Those in the lower age range more in cities, but this group just has a wider range (not median).

age and QAATIPPE



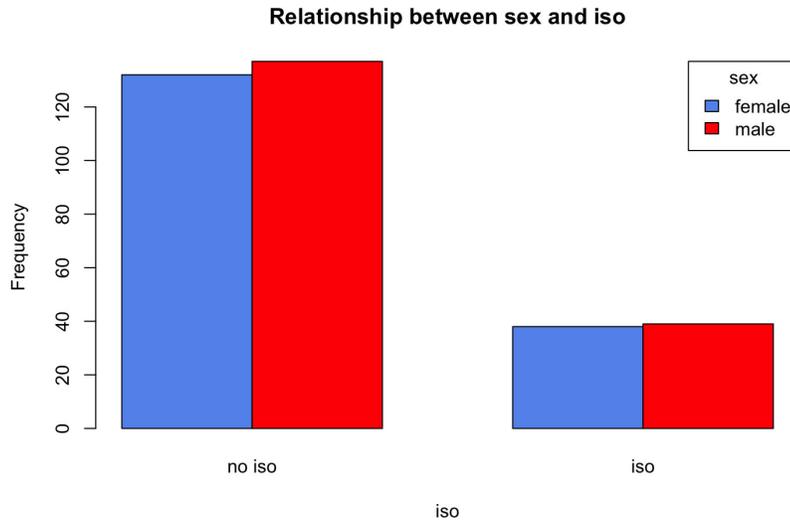


Notes: Potential shift when looking at middle quintile vs. both low and high groups. Middle quintile appears younger, then low and high appear to be skewed older. Middle grouping also just has less people.

Sex and social/psychological covariables

sex and iso bar graph

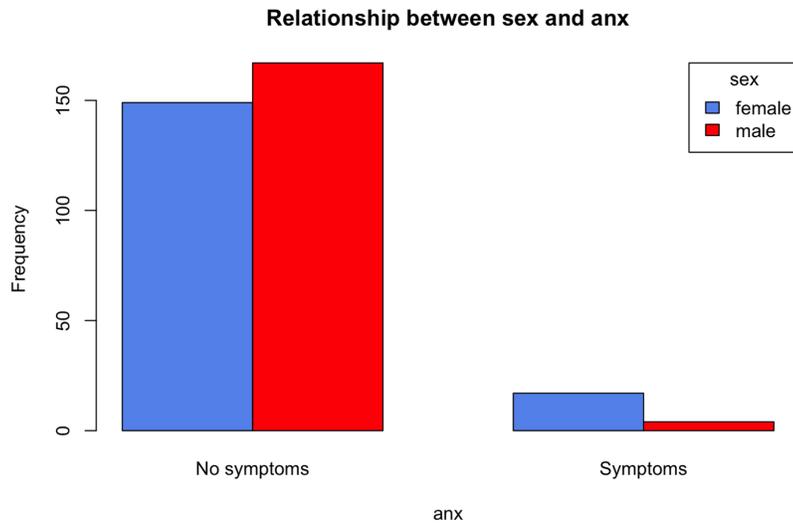
	No iso	iso	
female	132	38	170
male	137	39	176
	269	77	346



Notes: No strong evidence of relationship.

sex and anx bar graph

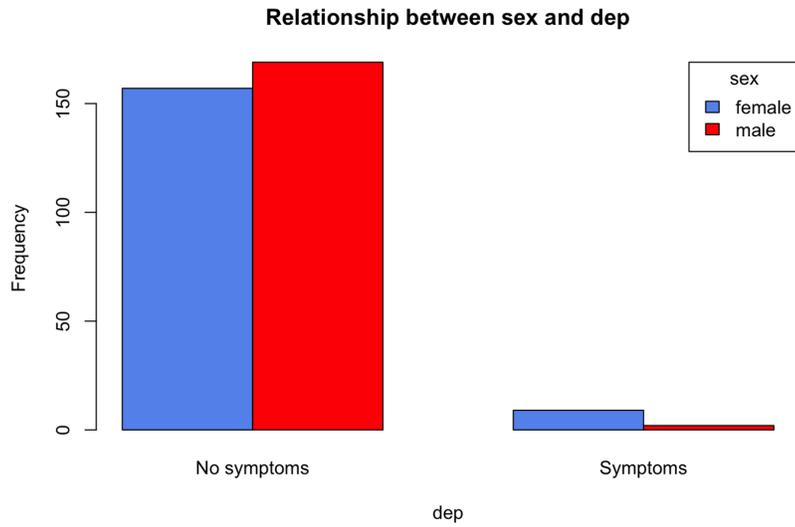
	No symptoms	symptoms	
female	149	17	166
male	167	4	171
	316	21	337



Notes: Sparse cells so likely can't study relationship. However, in those without symptoms, there are more males and in those with symptoms, there are more females.

sex and dep bar graph

	No symptoms	symptoms	
female	157	9	166
male	169	2	171
	326	11	337

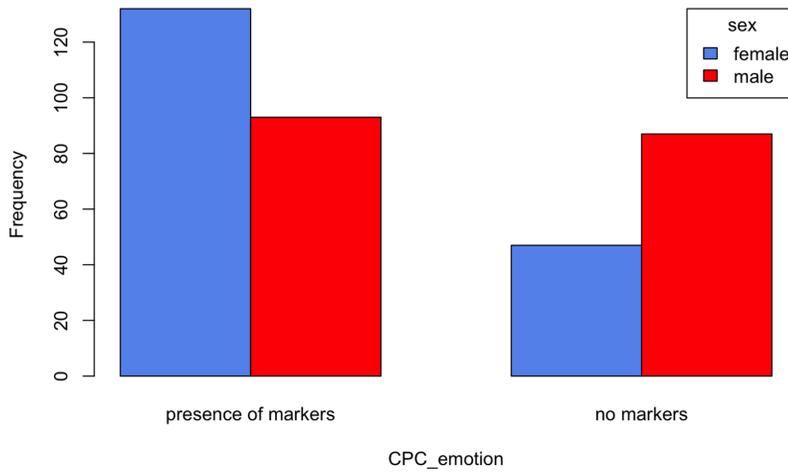


Notes: Same as above comments with anx.

sex and CPC_emotion bar graph

	1 or more checkmarks	No checkmarks	
female	132	47	179
male	93	87	180
	225	134	359

Relationship between CPC_emotion and sex

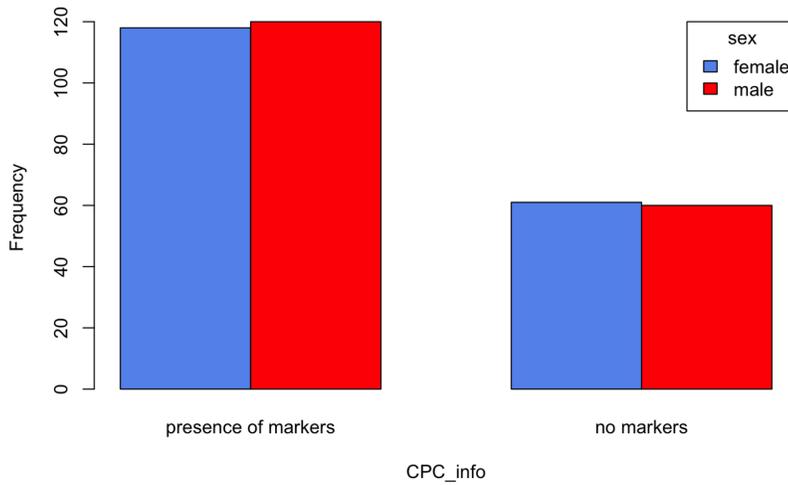


Notes: Potential for relationship here. In those with emotional concerns, there are more females. In those without emotional concerns, there are more males.

sex and CPC_info bar graph

	1 or more checkmarks	No checkmarks	
female	118	61	179
male	120	60	180
	238	121	359

Relationship between CPC_info and sex

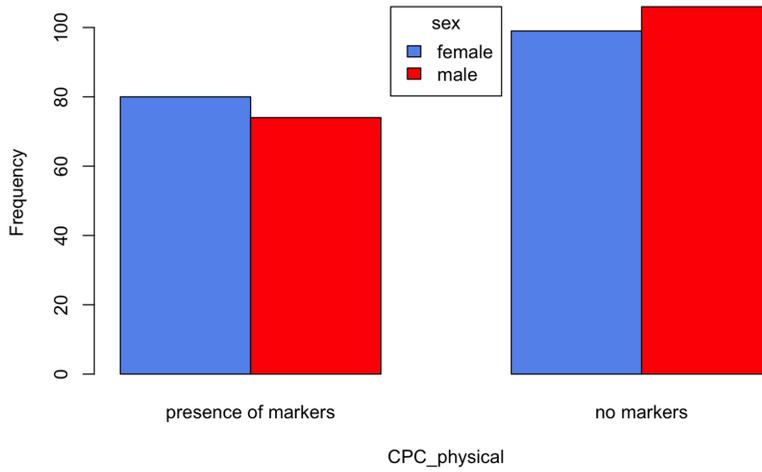


Notes: No evidence of relationship. Very equal amounts of each male and females between groups.

sex and CPC_physical bar graph

	1 or more checkmarks	No checkmarks	
female	80	99	179
male	74	106	180
	154	205	359

Relationship between CPC_physical and sex

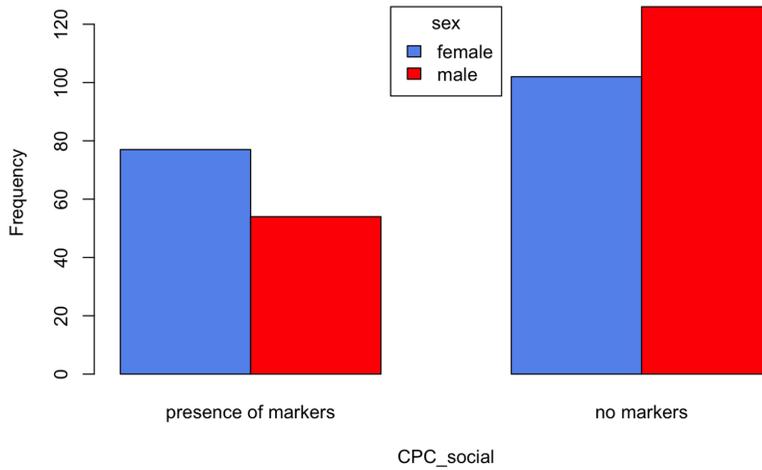


Notes: Likely not strong relationship (almost half and half). However, there are more females in the group with physical concerns and more males in the groups without physical concerns.

sex and CPC_social bar graph

	1 or more checkmarks	No checkmarks	
female	77	102	179
male	54	126	180
	131	228	359

Relationship between CPC_social and sex

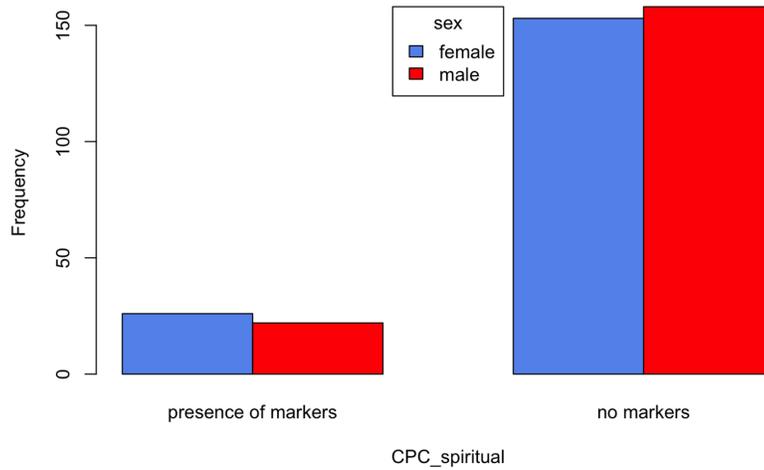


Notes: Potential relationship. More females in the group with social concerns and more males in the group without social concerns.

sex and CPC_spiritual bar graph

	1 or more checkmarks	No checkmarks	
female	26	153	179
male	22	158	180
	48	311	359

Relationship between CPC_spiritual and sex

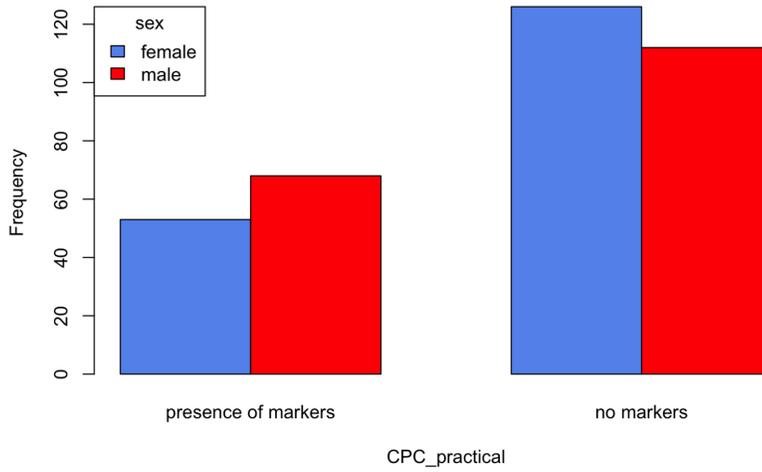


Notes: No strong evidence of relationship. However, slightly more females in those that report spiritual concerns and slightly more males in the group that do not report spiritual concerns.

sex and CPC_practical bar graph

	1 or more checkmarks	No checkmarks	
female	53	126	179
male	68	112	180
	121	238	359

Relationship between CPC_practical and sex

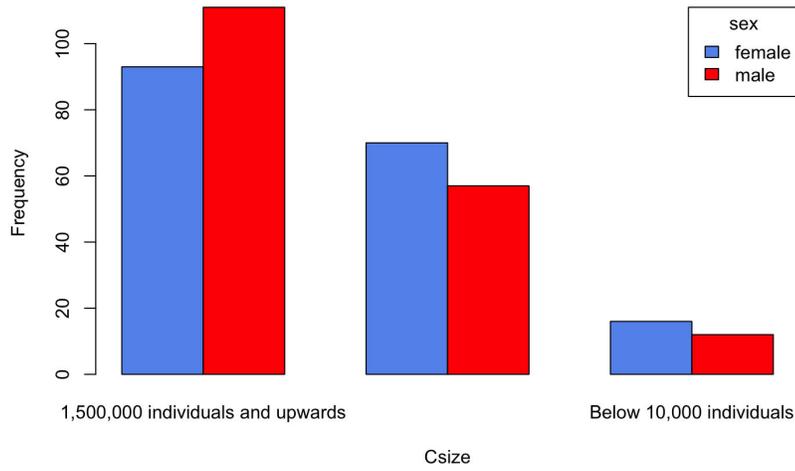


Notes: Not strong relationship. However, in those that report practical concerns, there are more males. In those that do not report practical concerns, there are more females.

sex and Csize bar graph

	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
female	93	70	16	179
male	111	57	12	180
	204	127	28	359

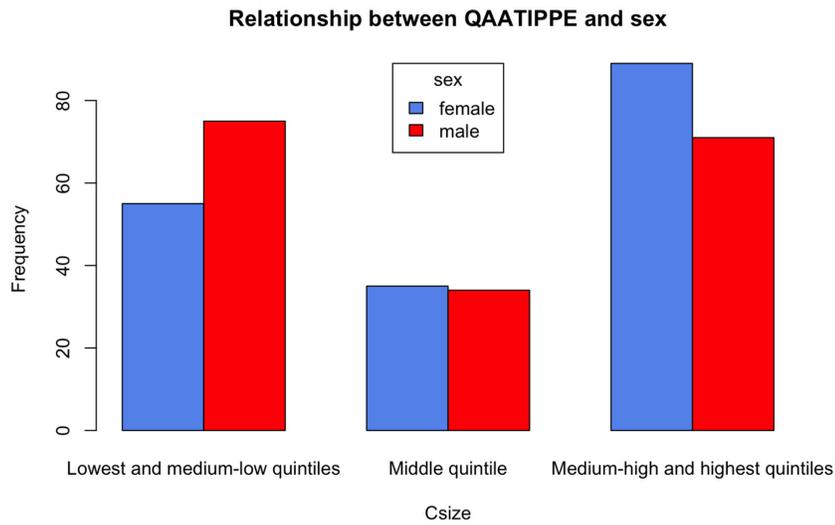
Relationship between Csize and sex



Notes: Interestingly, there are more males in larger cities. In the other two groups there are more females.

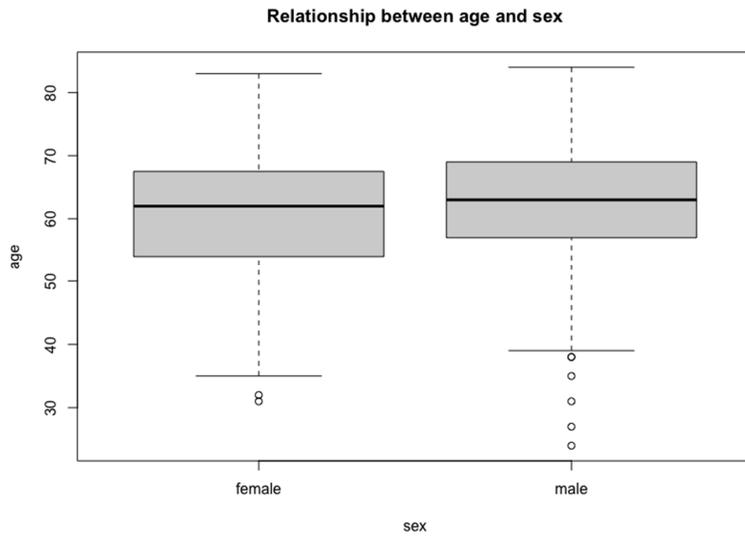
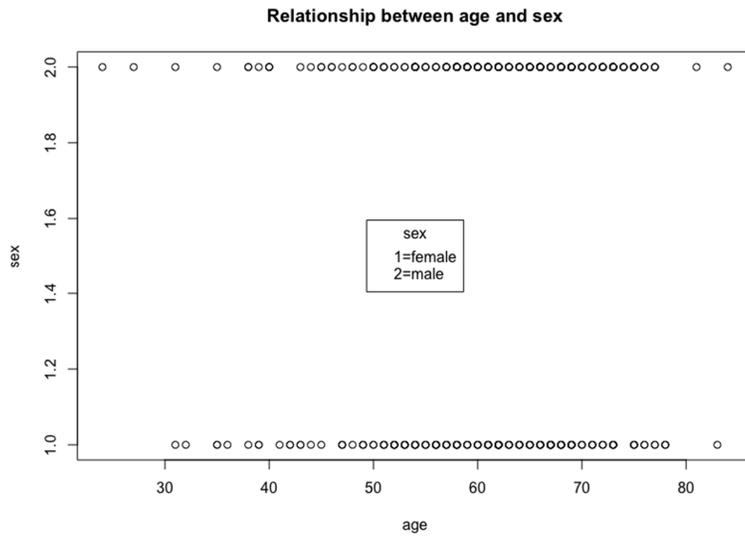
sex and QAATIPPE bar graph

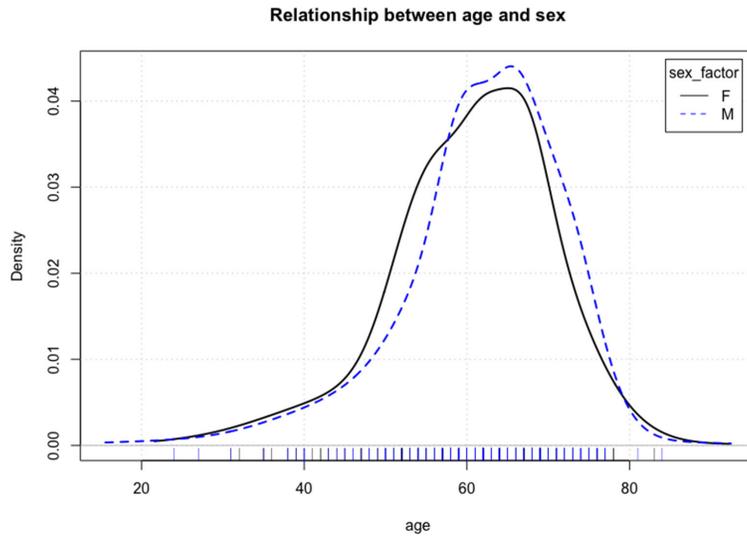
	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more checkmarks	55	35	89	179
No checkmarks	75	34	71	180
	130	69	160	359



Notes: Interestingly, in the lower income group there are more males. In the higher income group, there are more females.

Age and sex





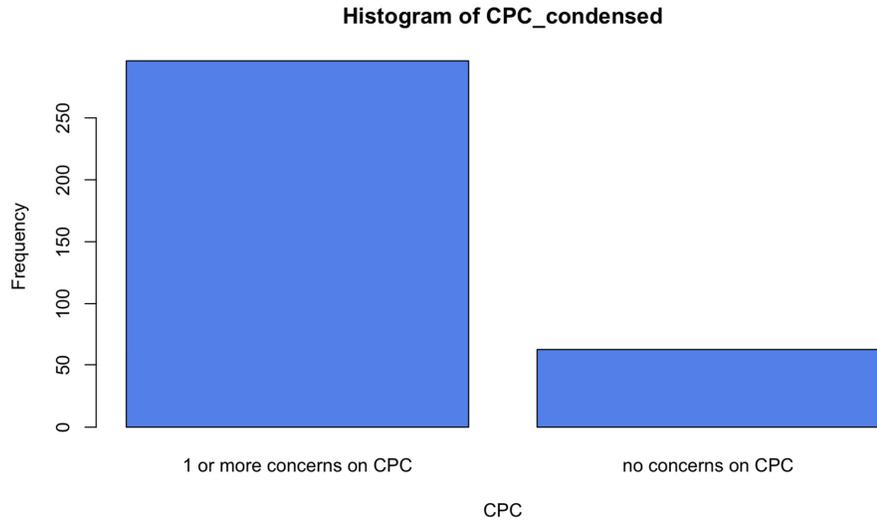
Notes: No strong evidence of relationship. However, potential that females are slightly younger.

CPC (entire checklist, defined as no checkmarks in any domains or checkmarks in 1 or more domains):

Distribution

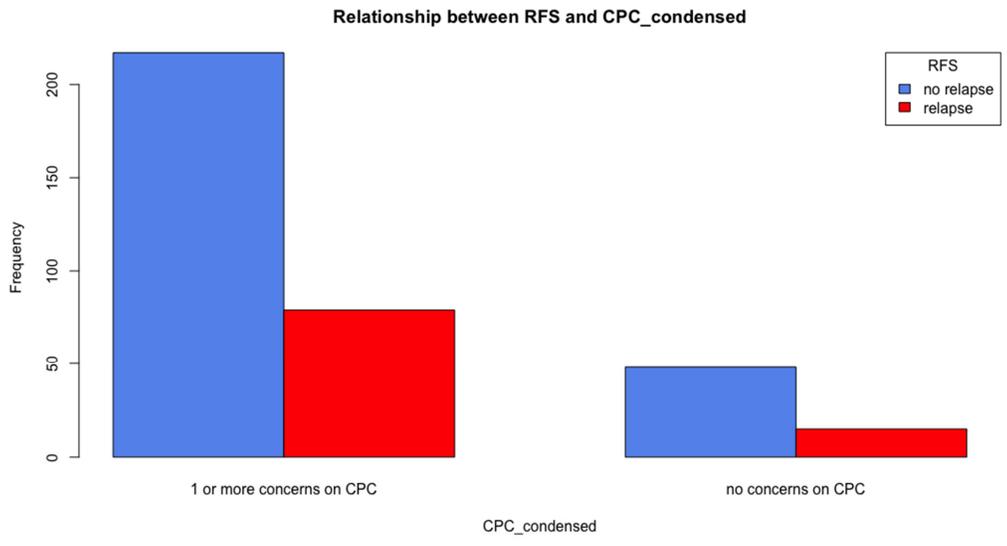
1 or more concerns on CPC: 296

No concerns: 63



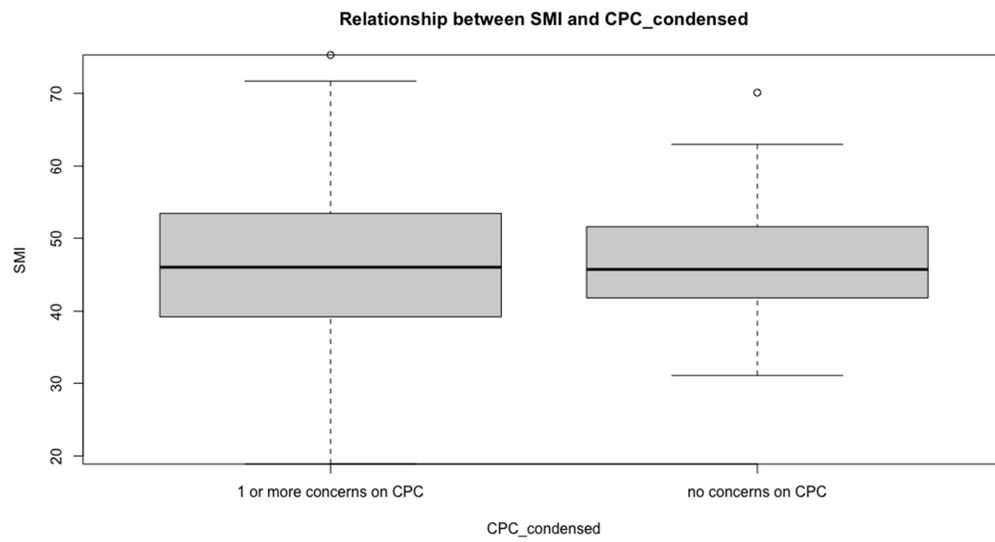
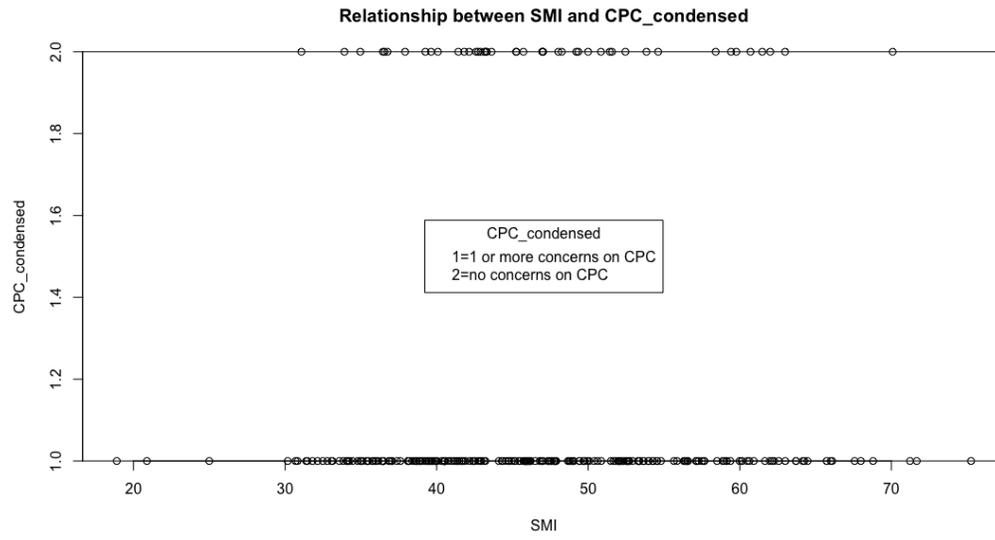
CPC condensed and RFS bar graph

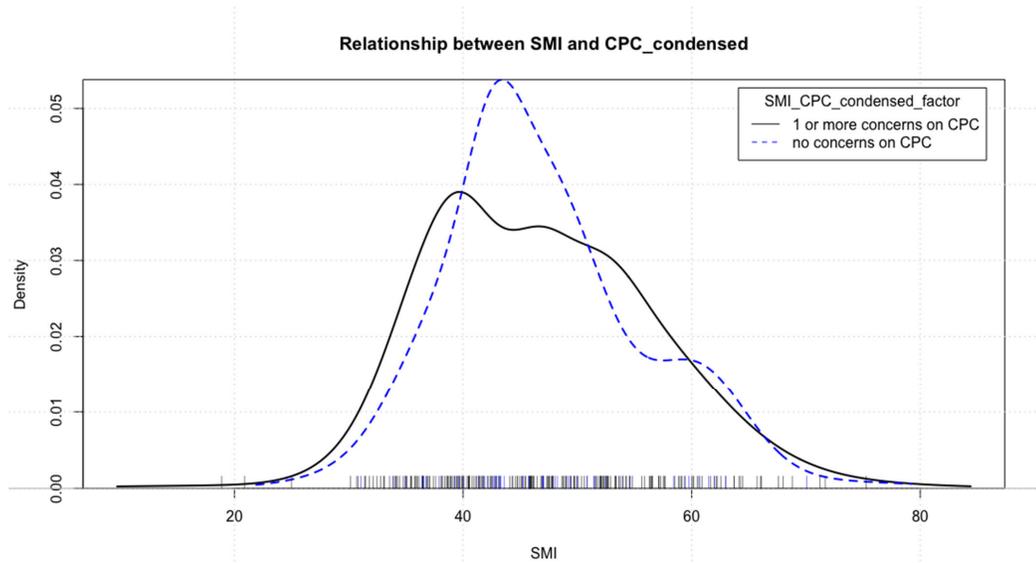
	1 or more concerns on CPC	no concerns on CPC
No relapse	217	48
relapse	79	15



Notes: No strong evidence of a relationship.

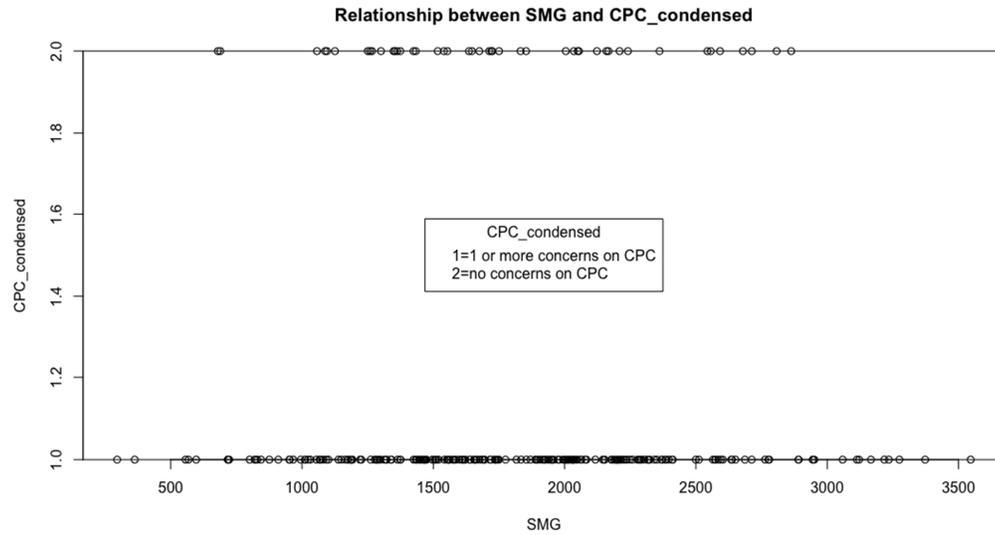
CPC_condensed and SMI

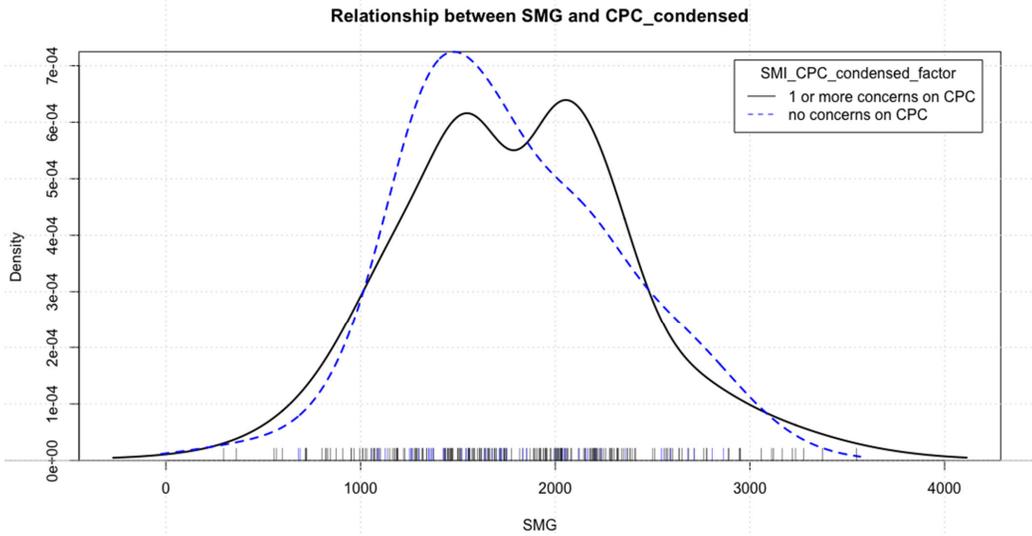
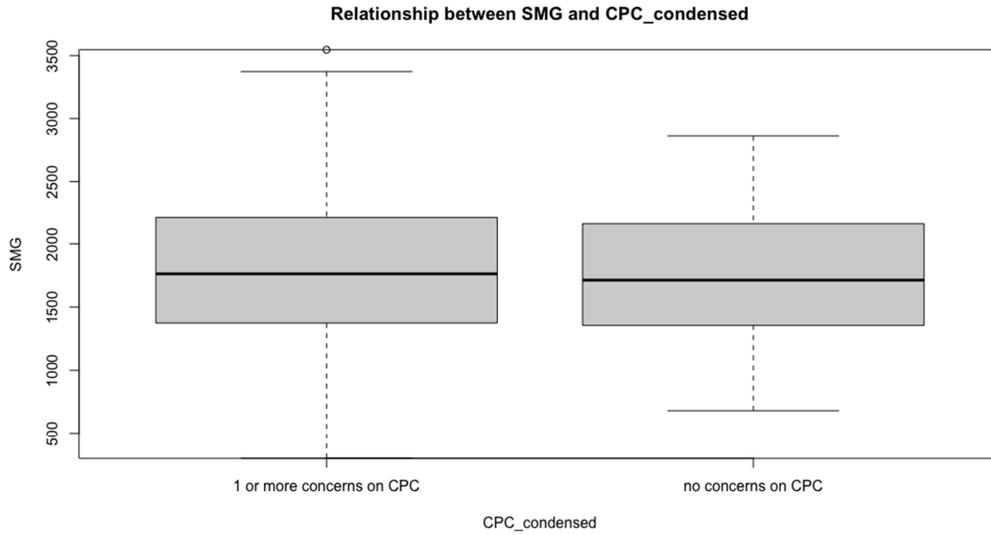




Notes: No strong evidence of a relationship. Potentially a slight shift to lower SMI's in the group with 1 or more concerns on CPC but this group also has more data points/a larger range.

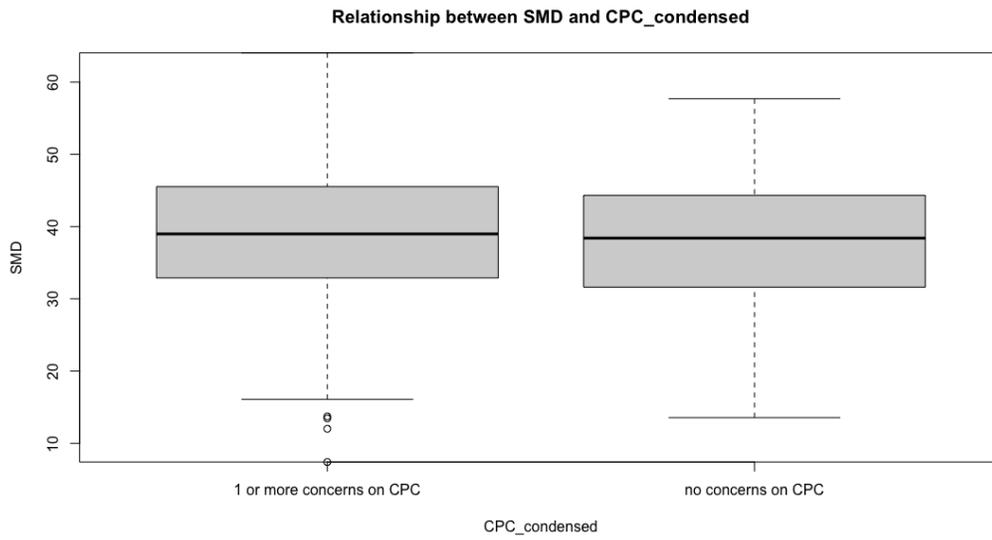
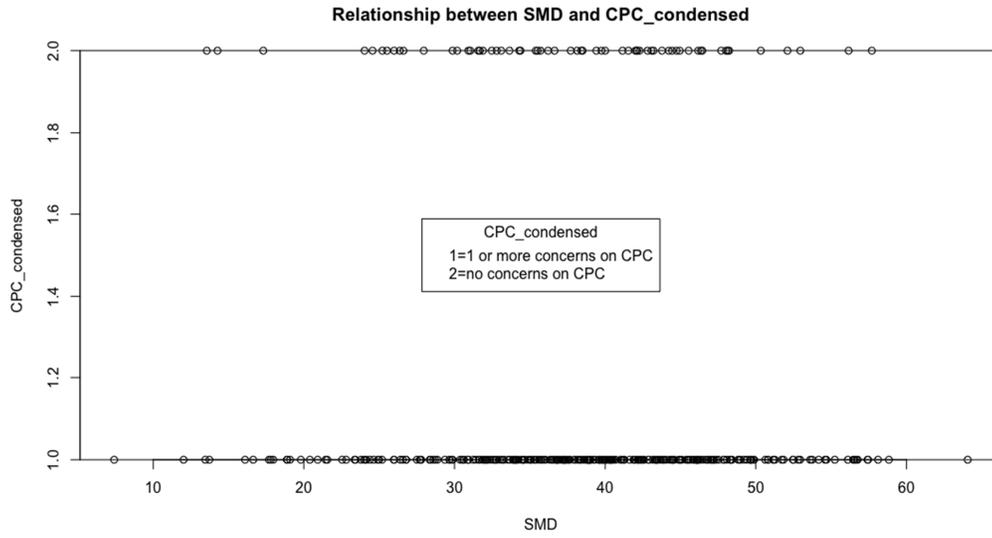
CPC_condensed and SMG

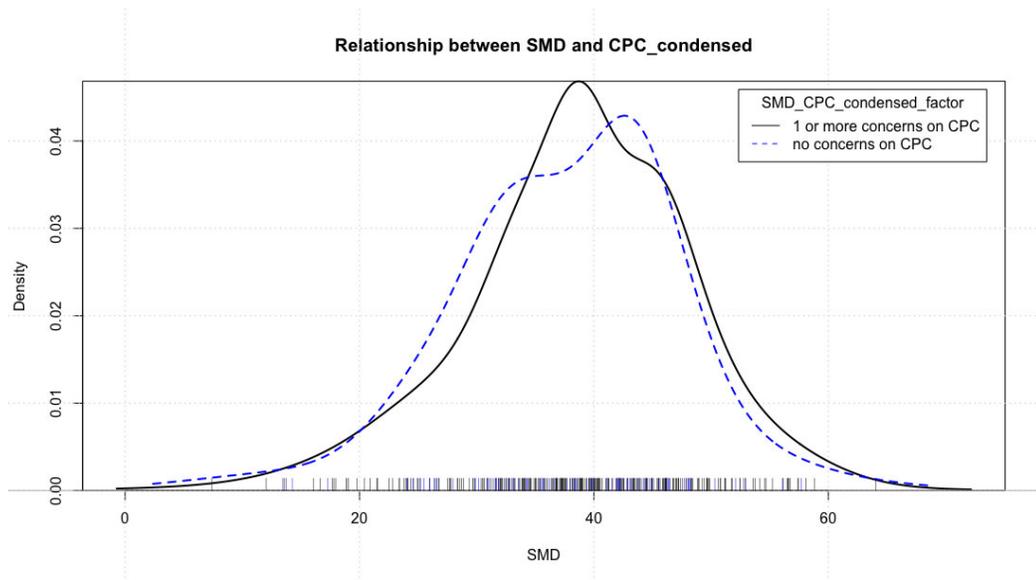




Notes: No strong evidence of relationship.

CPC_condensed and SMD

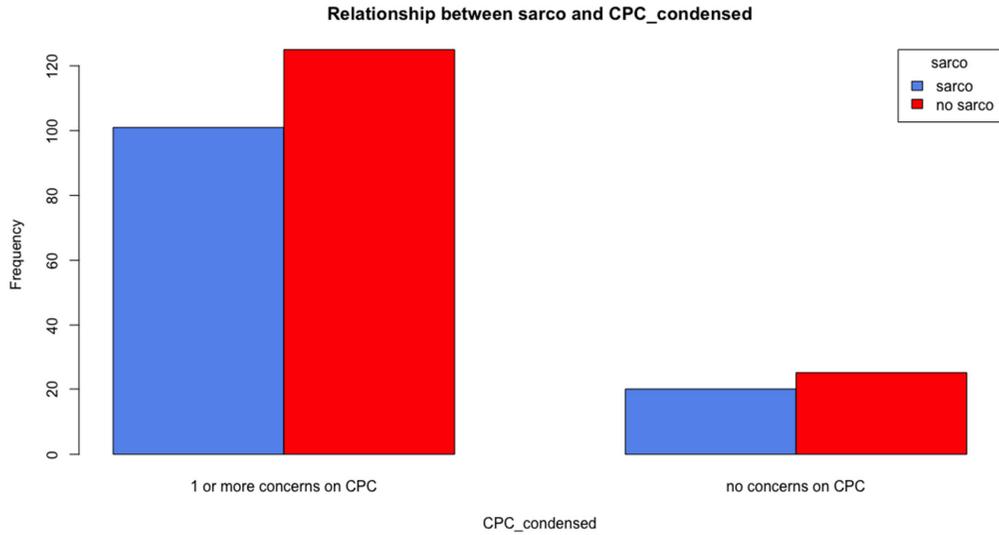




Notes: No strong evidence of a relationship.

CPC condensed and sarco bar graph

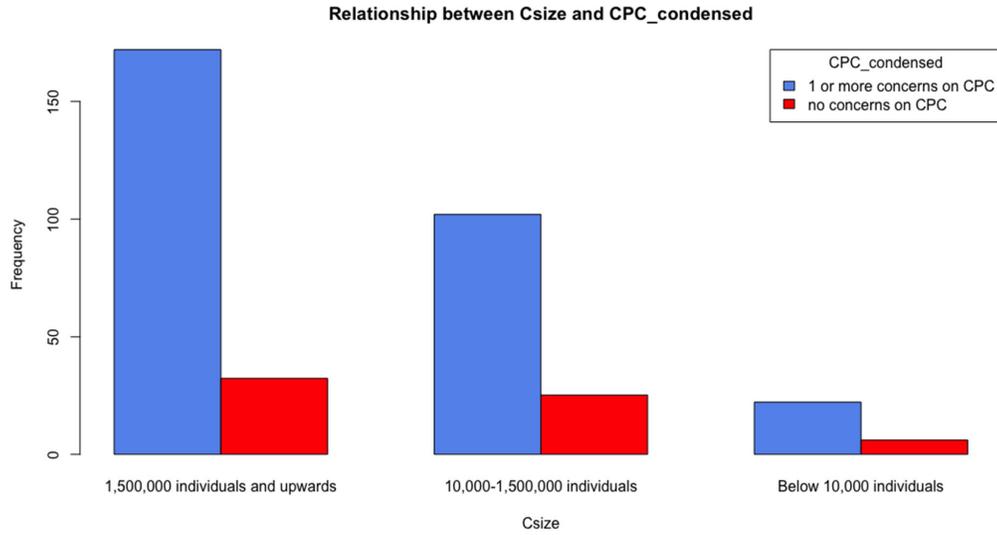
	1 or more concerns on CPC	no concerns on CPC	
sarco	101	20	121
no sarco	125	25	150
	226	45	271



Notes: No strong evidence of relationship. Similar proportions in both groups.

CPC condensed and Csize bar graph

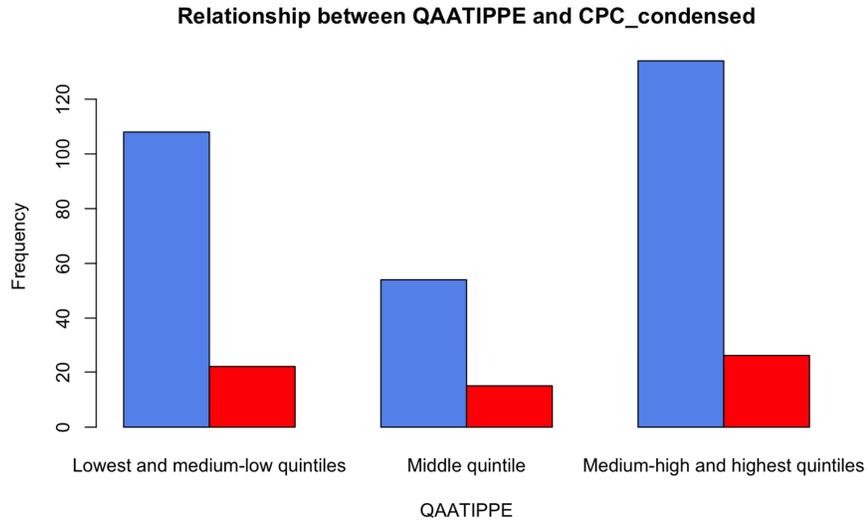
	1,500,000 individuals and upwards	10,000-1,500,000 individuals	Below 10,000 individuals	
1 or more concerns on CPC	172	102	22	296
no concerns on CPC	32	25	6	63
	204	127	28	359



Notes: No evidence of relationship.

CPC condensed and QAATIPPE

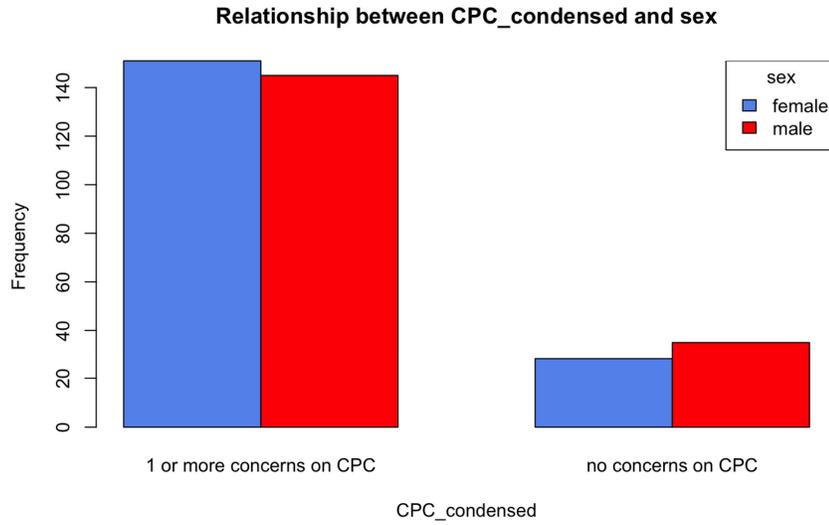
	Lowest and medium-low quintile	Middle quintile	Medium-high and highest quintile	
1 or more concerns on CPC	108	54	134	296
no concerns on CPC	22	15	26	63
	130	69	160	359



Notes: No strong evidence of a relationship.

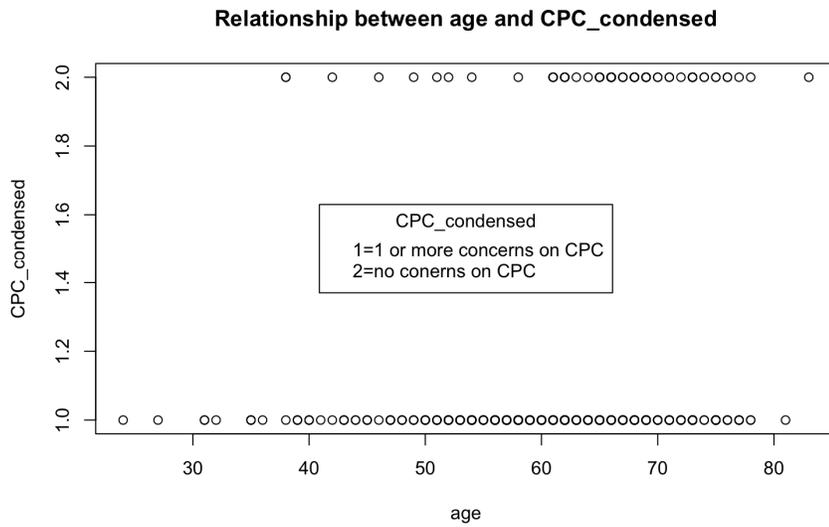
CPC condensed and sex

	1 or more concerns on CPC	no concerns on CPC	
Female	151	28	179
Male	145	35	180
	296	63	359

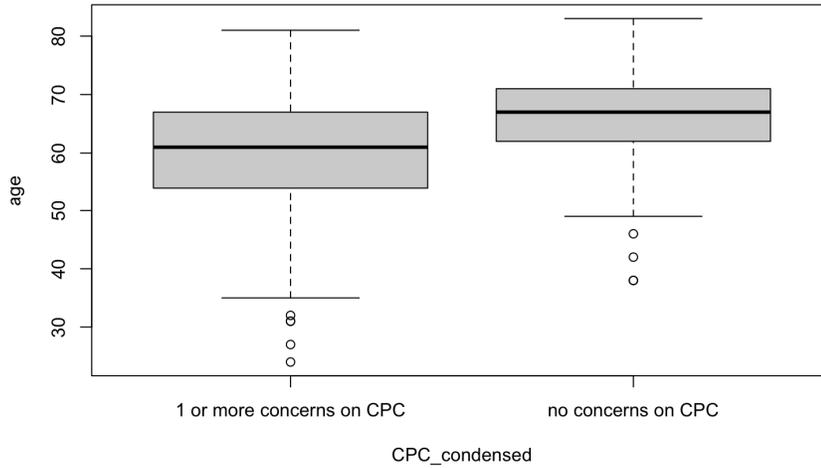


Notes: There are more females than males in the group that report 1 or more concerns on CPC. There are more males than females in the group that do not report concerns. However, this difference is very slight and do not predict a strong relationship.

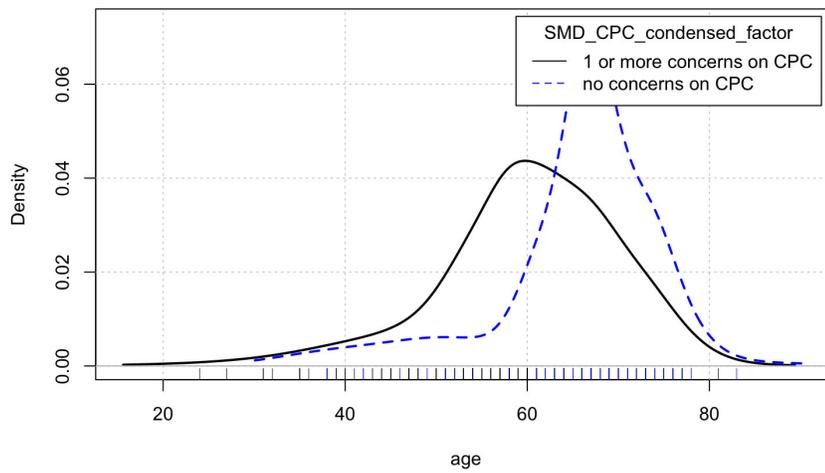
CPC_condensed and age



Relationship between age and CPC_condensed



Relationship between age and CPC_condensed

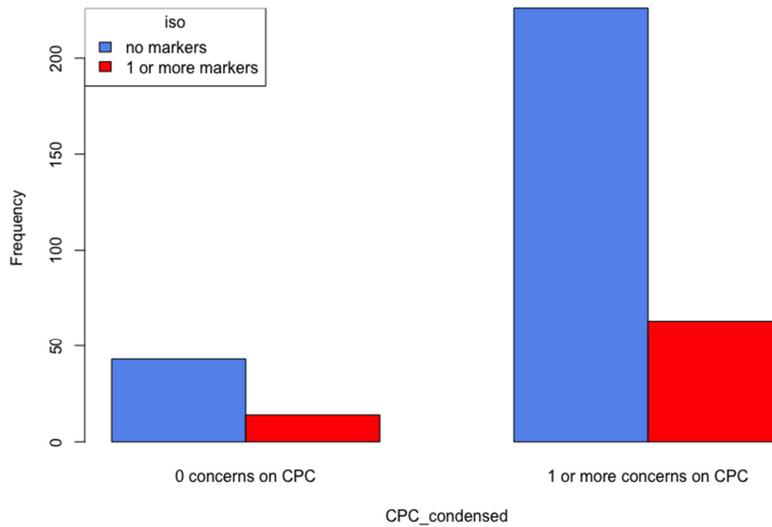


Notes: In those that report one of more concerns, the age tends to be younger. There is still quite an overlap though so don't predict a significant relationship.

CPC condensed and iso

	no more concerns on CPC	1 or more concerns on CPC	
No markers	43	226	269
One or more markers	14	63	77
	57	289	346

Relationship between iso and CPC_condensed



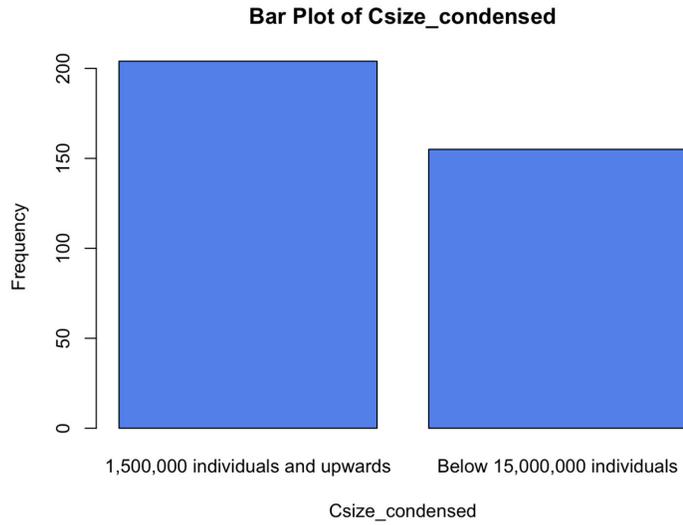
Notes: No strong evidence of a relationship.

Csize (condensed to city larger than 1,500,000 and smaller as groups)

Distribution

1,500,000 individuals and upwards: 204

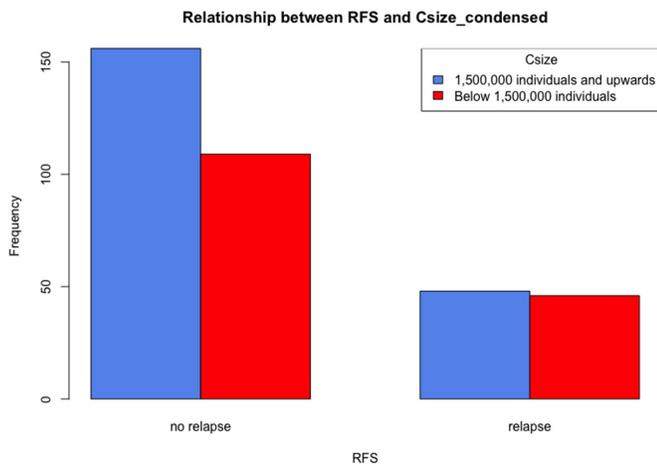
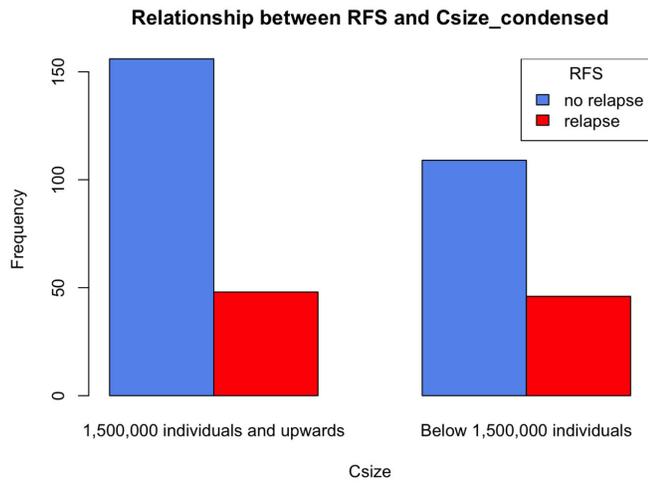
Below 1,500,000 individuals: 155



Notes: More in the higher group (accounting for Vancouver) vs. the rest of the BC populations (Kelowna and Victoria both below this number).

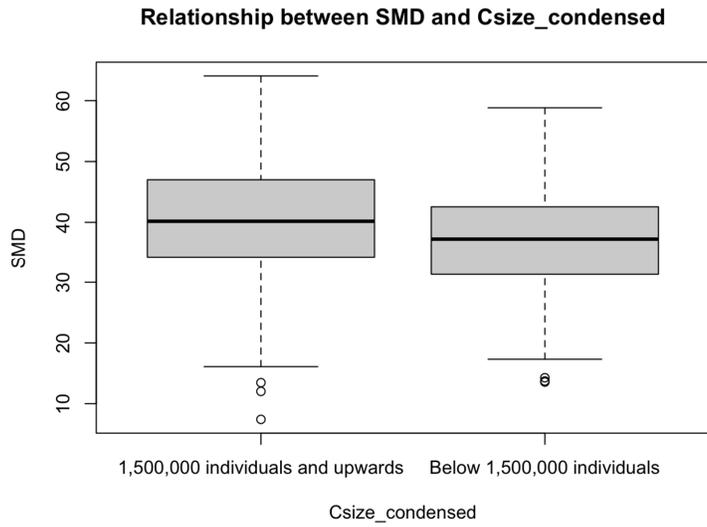
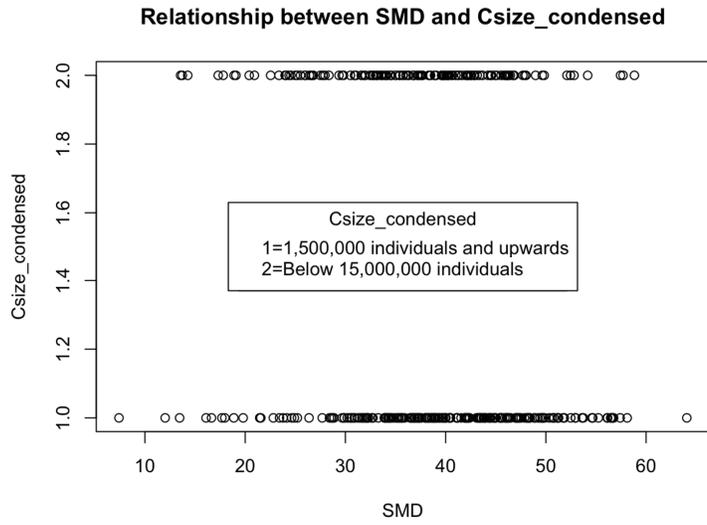
Csize_condensed and RFS bar graph

	1,500,000 individuals and upwards	Below 1,500,000 individuals	
no relapse	156	109	265
relapse	48	46	94
	204	155	359

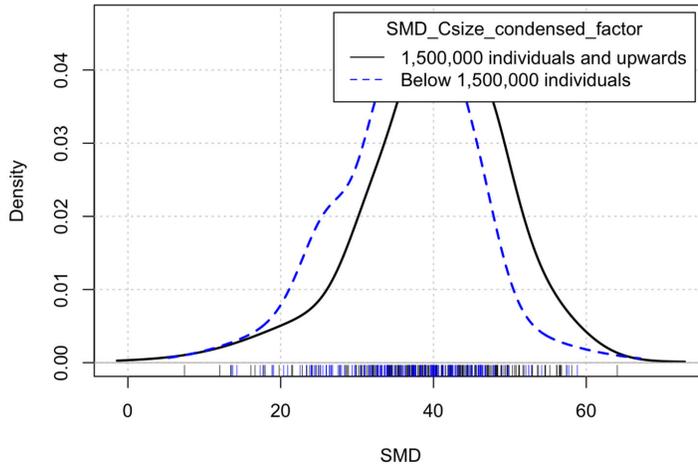


Notes: Slightly larger proportion of lower community size in those with relapse.

Csize_condensed and SMD



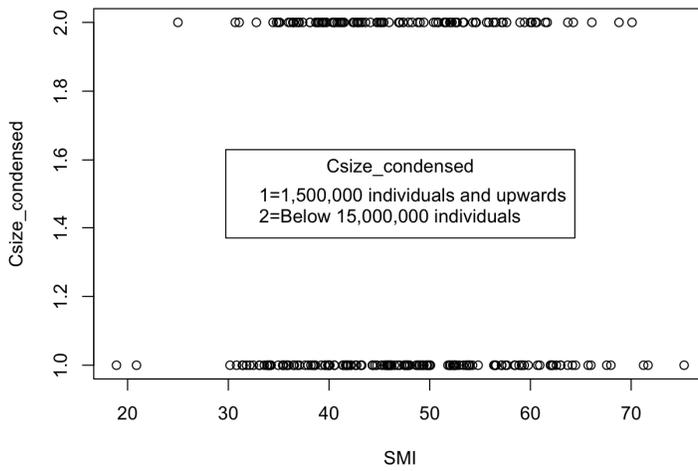
Relationship between SMD and Csize_condensed

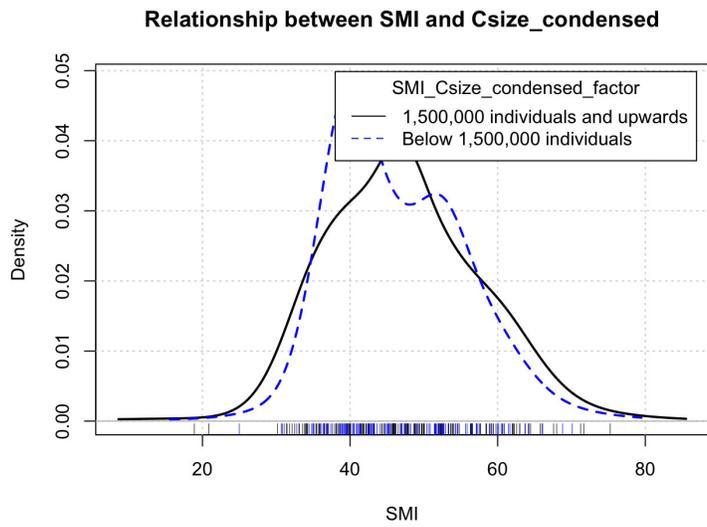
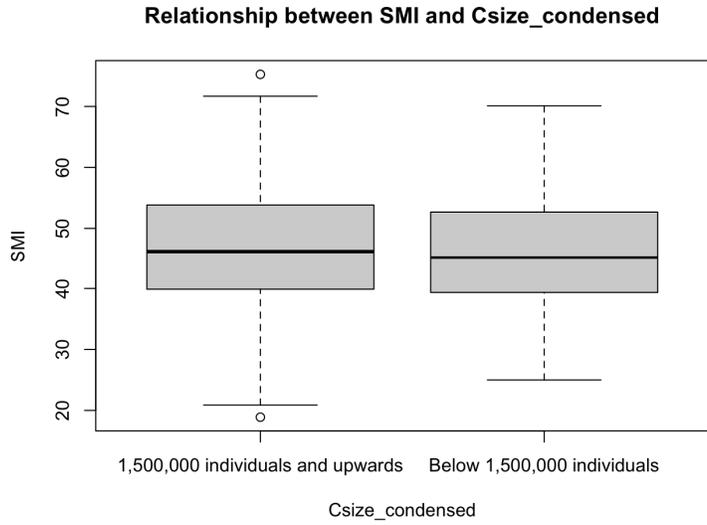


Notes: Those from lower communities do appear to have a lower SMD, as compared to those from Vancouver. Still overlap but there does seem to be some sort of association here.

Csize_condensed and SMI

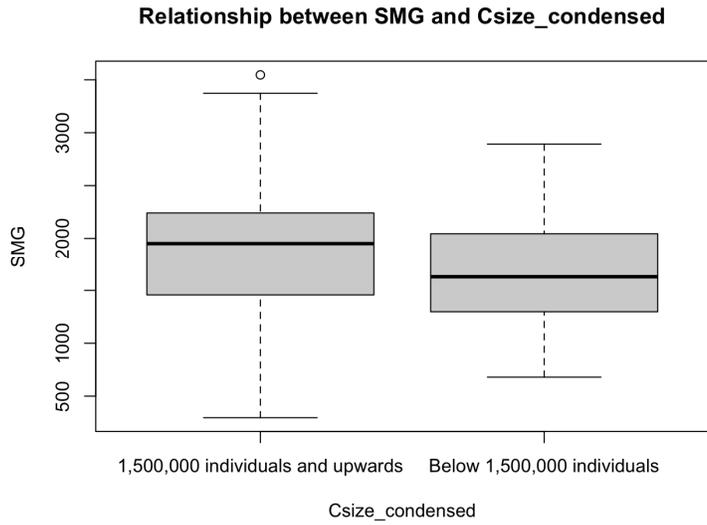
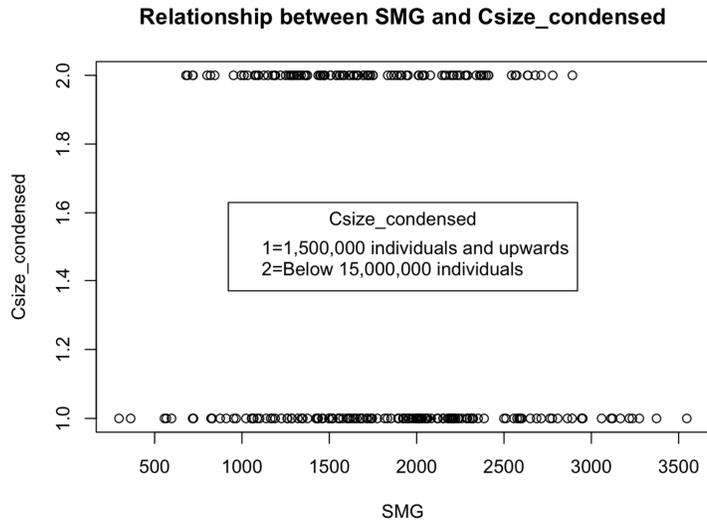
Relationship between SMI and Csize_condensed

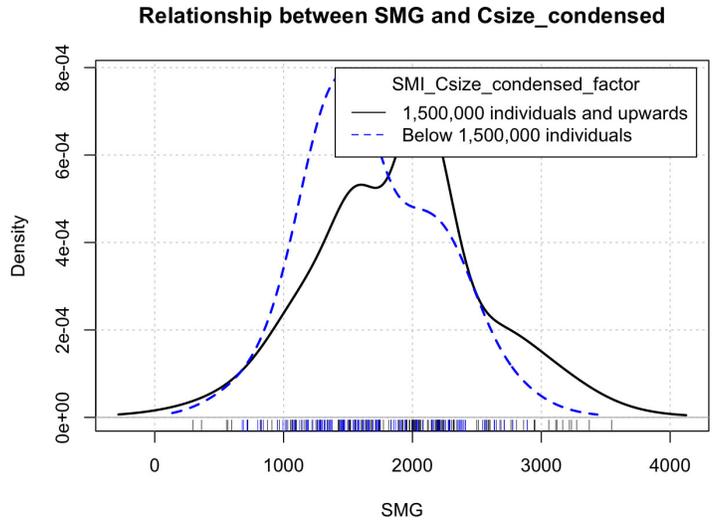




Notes: No evidence of this relationship once condensed variable included.

Csize_condensed and SMG

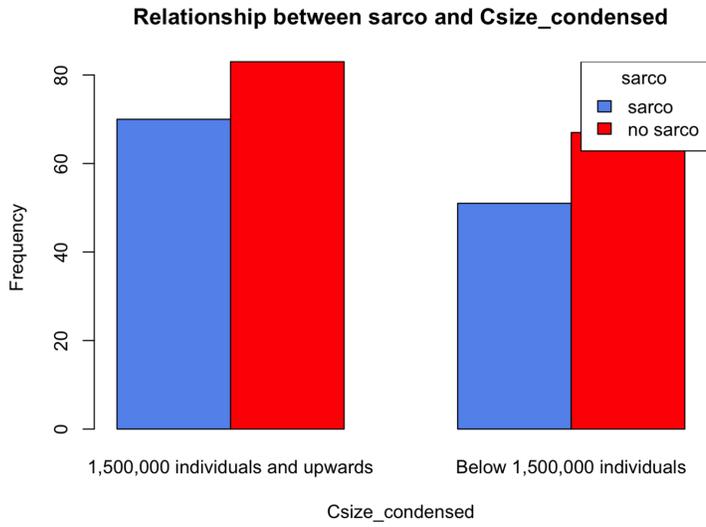


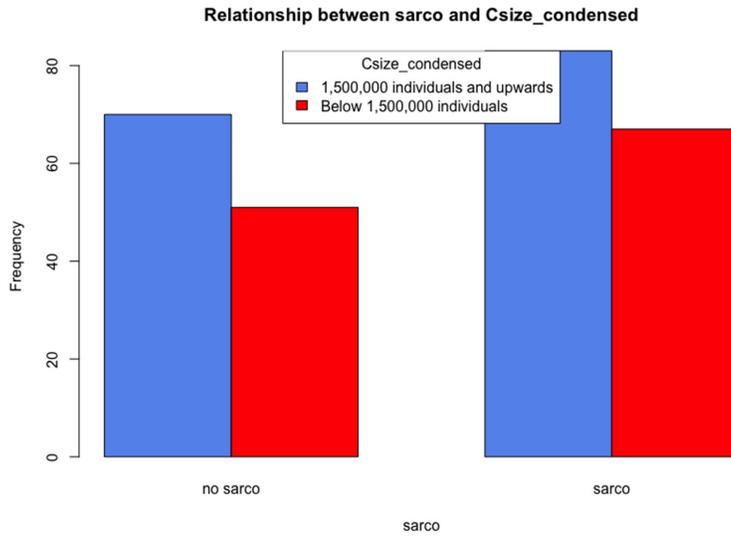


Notes: Much overlap, but potential that those from smaller communities have a lower SMG overall.

Csize_condensed and sarco bar graph

	1,500,000 individuals and upwards	Below 1,500,000 individuals	
no sarco	70	51	121
sarco	83	67	150
	153	118	271



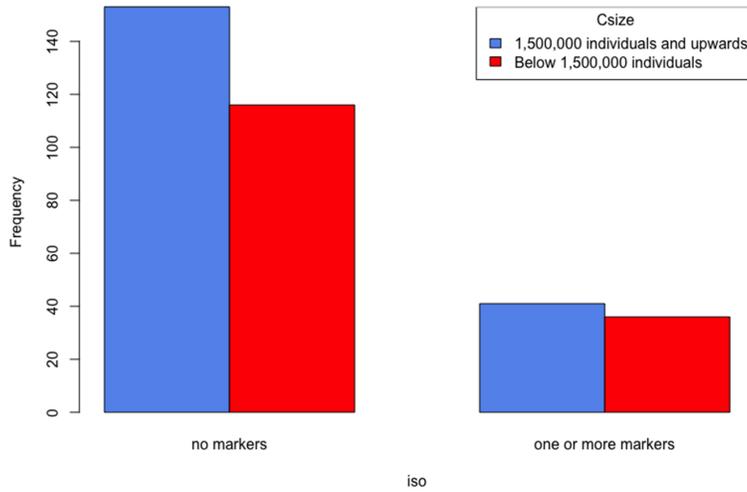


Notes: No evidence of relationship. More without sarco in both groups and very equal proportions of sarco:no sarco in both groups. More from Vancouver in both groups of sarcopenia and no sarcopenia.

Csize condensed and iso

	No markers	1 or more markers	
1,500,000 individuals and upwards	153	41	194
Below 1,500,000 individuals	116	36	152
	269	77	346

Relationship between iso and Csize_condensed

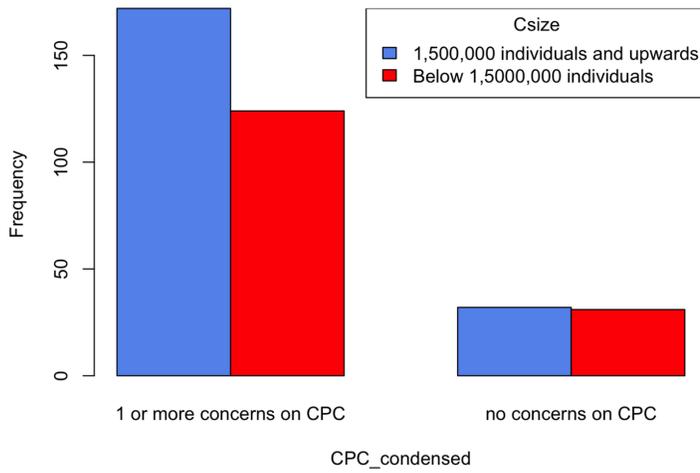


Notes: No strong evidence of a relationship.

Csize condensed and CPC condensed bar graph

	1 or more concerns on CPC	no concerns on CPC	
1,500,000 individuals and upwards	172	32	204
Below 1,500,000 individuals	124	31	155
	296	63	359

Relationship between CPC_condensed and Csize

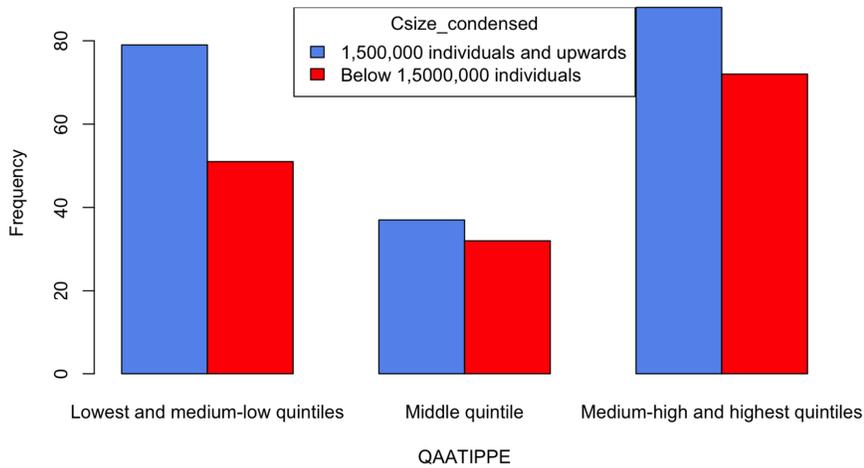


Notes: No strong evidence of a relationship.

Csize_condensed and QAATIPPE bar graph

	Lowest and medium-low quintiles	Middle quintile	Medium-high and highest quintiles	
1,500,000 individuals and upwards	79	37	88	204
Below 1,500,000 individuals	51	32	72	155
	130	69	160	359

Relationship between QAATIPPE and Csize_condensed

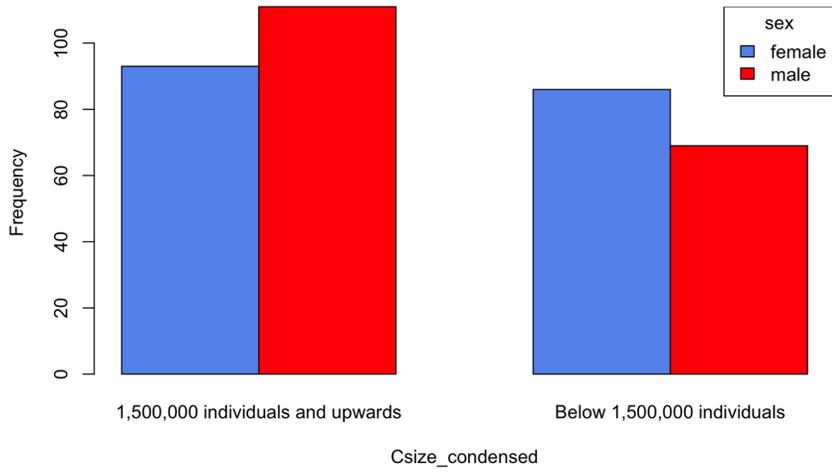


Notes: No strong evidence of a relationship. In all groups there is the same trend, with slightly more being from a larger city/Vancouver.

Csize_condensed and sex bar graph

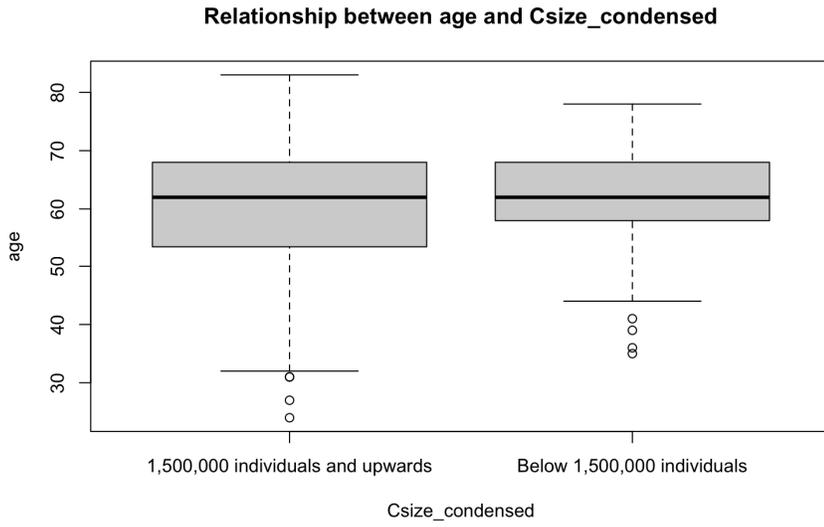
	1,500,000 individuals and upwards	Below 1,500,000 individuals	
Female	93	86	179
Male	111	69	180
	204	155	359

Relationship between Csize_condensed and sex

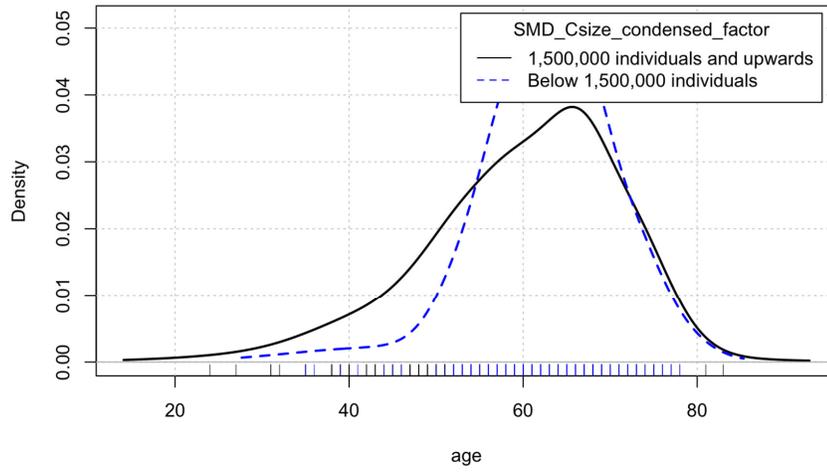


Notes: Potential relationship. In Vancouver, more males. In smaller places, more females.

Csize_condensed and age



Relationship between age and Csize_condensed



Notes: No strong evidence of a relationship.

Appendix D Backwards selection process to create final primary and exploratory multivariate logistic regression models

Primary multivariable logistic regression models for skeletal muscle index (SMI):

Variable	β	p-value
Step 1		
SMI	-0.02	0.29
Age at diagnosis	0.003	0.82
Sex (v. female)	0.48	0.21
Step 2		
SMI	-0.02	0.30
Sex	0.43	0.21
Step 3		
SMI	0.005	0.78

Abbreviations: SMI, skeletal muscle index; v, versus.

Note: Bolded lines highlight the variable removed.

Primary multivariable logistic regression models for skeletal muscle density (SMD):

Variable	β	p-value
Step 1		
SMD	-0.03*	0.02
Age at diagnosis	-0.01	0.40
Sex (v. female)	0.07	0.78
Step 2		
SMD	-0.03*	0.02
Age at diagnosis	-0.01	0.42
Step 3		
SMD	-0.03*	0.03

Abbreviations: SMD, skeletal muscle density; v, versus.

Legend: * $p \leq 0.05$.

Note: Bolded lines highlight the variable removed.

Primary multivariable logistic regression models for skeletal muscle gauge (SMG):

Variable	β	p-value
Step 1		
SMG†	-0.07*	0.01
Age at diagnosis††	-0.02	0.23
Sex (v. female)	0.68*	0.04
Step 2		
SMG	-0.06	0.02
Sex††	0.57	0.07
Step 3		
SMG	-0.04	0.12

Abbreviations: SMG, skeletal muscle gauge; v, versus.

Legend: * $p \leq 0.05$; † One unit represented $100 \text{ cm}^2 \times \text{HU}/\text{m}^2$; †† The model was influenced by age at diagnosis and sex (seen through removal of these variables). Therefore, the Step 1

Note: Bolded lines highlight the variable removed.

Primary multivariable logistic regression models for sarcopenia:

Variable	β	p-value
Step 1		
Sarcopenia (v. no sarcopenia)	0.59*	0.03
Age at diagnosis	0.004	0.79
Sex (v. female)	0.20	0.48
Step 2		
Sarcopenia (v. no sarcopenia)	0.58*	0.03
Sex (v. female)	0.19	0.49
Step 3		
Sarcopenia (v. no sarcopenia)	0.59*	0.03

Abbreviations: v, versus.

Legend: * $p \leq 0.05$.

Note: Bolded lines highlight the variable removed.

Exploratory multivariable logistic regression models for SMI:

Variable		β	p-value
Step 1			
SMI		-0.03	0.19
Age at diagnosis		-0.01	0.43
Sex (v. female)		0.62	0.11
Community size (v. 1,500,000 and above)		0.49	0.10
Neighbourhood income after tax†	Middle income quintile after tax (v. medium-low and lowest quintile)	0.38	0.34
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.02	0.96
Social isolation (v. no isolation)		0.69*	0.04
Step 2			
SMI		-0.03	0.21
Sex (v. female)		0.60	0.13
Community size		0.45	0.12
Neighbourhood income after tax	Middle income quintile after tax (v. medium-low and lowest quintile)	0.37	0.35
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.03	0.92
Social isolation (v. no isolation)		0.68*	0.04
Step 3			
SMI		-0.02	0.30
Sex (v. female)		0.54	0.16
Community size (v. 1,500,000 and above)		0.48	0.10
Social isolation (v. no isolation)		0.68*	0.03
Step 4			
SMI		-0.02	0.37
Sex (v. female)		0.44	0.45
Social isolation		0.69*	0.03
Step 5			
SMI		-0.002	0.87
Social isolation		0.70*	0.03

Abbreviations: SMI, skeletal muscle index; v, versus.

Legend: * $p \leq 0.05$; † Neighbourhood income after tax was a single variable. Therefore, it was removed based on the lowest p-value of the two comparisons.

Exploratory multivariable logistic regression models for SMD:

Variable		β	p-value
Step 1			
SMD		-0.03*	0.02
Age at diagnosis		-0.02	0.25
Sex (v. female)		0.08	0.75
Community size (v. 1,500,000 and above)		0.19	0.45
Neighbourhood income after tax†	Middle income quintile after tax (v. medium-low and lowest quintile)	0.13	0.70
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.07	0.81
Social isolation (v. no isolation)		0.71*	0.01
Step 2			
SMD		-0.03*	0.02
Age at diagnosis		-0.02	0.26
Community size (v.1,500,000 and above)		0.18	0.46
Neighbourhood income after tax	Middle income quintile after tax (v. medium-low and lowest quintile)	0.13	0.71
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.08	0.78
Social isolation (v. no isolation)		0.71*	0.02
Step 3			
SMD		-0.03*	0.03
Age at diagnosis		-0.02	0.24
Community size (v. 1,500,000 and above)		-0.19	0.46
Social isolation (v. no isolation)		0.73*	0.01
Step 4			
SMD		-0.03*	0.02
Age at diagnosis		-0.02	0.27
Social isolation (v. no isolation)		0.73*	0.01
Step 5			
SMD		-0.03*	0.03
Social isolation (v. no isolation)		0.72*	0.01

Abbreviations: SMD, skeletal muscle density; v, versus.

Legend: * $p \leq 0.05$; † Neighbourhood income after tax was a single variable. Therefore, it was removed based on the lowest p-value of the two comparisons.

Note: Bolded lines highlight the variable removed.

Exploratory multivariable logistic regression models for SMG:

Variable		β	p-value
Step 1			
SMG†		-0.07*	0.02
Age at diagnosis		-0.03	0.10
Sex (v. female)		0.79*	0.03
Community size (v. 1,500,000 and above)		0.43	0.15
Neighbourhood income after tax††	Middle income quintile after tax (v. medium-low and lowest quintile)	0.42	0.29
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	0.06	0.86
Social isolation (v. no isolation)		0.77*	0.02
Step 2			
SMG†		-0.07*	0.02
Age at diagnosis		-0.03	0.11
Sex (ref: female)		0.75*	0.03
Community size (v. 1,500,000 and above)		0.46	0.12
Social isolation (v. no isolation)		0.73*	0.02
Step 3			
SMG†		-0.07*	0.02
Age at diagnosis‡		-0.03	0.14
Sex (v. female)		0.70*	0.04
Social isolation (v. no isolation)		0.74*	0.02
Step 4			
SMG†		-0.05*	0.05
Sex (v. female)‡		0.57	0.08
Social isolation (v. no isolation)		0.72*	0.02
Step 5			
SMG†		-0.02	0.21
Social isolation (v. no isolation)		0.71*	0.02

Abbreviations: SMG, skeletal muscle gauge; v, versus.

Legend: * $p \leq 0.05$; † One unit represented $100 \text{ cm}^2 \times \text{HU}/\text{m}^2$; †† Neighbourhood income after tax was a single variable. Therefore, it was removed based on the lowest p-value of the two comparisons; ‡ The model was influenced by age at diagnosis and sex (seen through removal of these variables). Therefore, the Step Three model was reported.

Note: Bolded lines highlight the variable removed.

Exploratory multivariable logistic regression models for sarcopenia:

Variable		β	p-value
Step 1			
Sarcopenia (v. no sarcopenia)		0.72*	0.02
Age at diagnosis		-0.01	0.37
Sex (v. female)		0.28	0.34
Community size (v. 1,500,000 and above)		0.50	0.09
Neighbourhood income after tax†	Middle income quintile after tax (v. medium-low and lowest quintile)	0.44	0.28
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.01	0.98
Social isolation (v. no isolation)		0.69*	0.04
Step 2			
Sarcopenia (v. no sarcopenia)		0.69*	0.02
Sex (v. female)		0.27	0.35
Community size (v.: 1,500,000 and above)		0.47	0.11
Neighbourhood income after tax	Middle income quintile after tax (v. medium-low and lowest quintile)	0.42	0.29
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.03	0.93
Social isolation (v. no isolation)		0.68	0.04
Step 3			
Sarcopenia (v. no sarcopenia)		0.69*	0.02
Community size (v. 1,500,000 and above)		0.44	0.13
Neighbourhood income after tax	Middle income quintile after tax (v. medium-low and lowest quintile)	0.40	0.32
	Medium-high and highest income quintile after tax (v. medium-low and lowest quintile)	-0.07	0.84
Social isolation (v. no isolation)		0.66*	0.04
Step 4			
Sarcopenia (v. no sarcopenia)		0.63*	0.03
Community size (v. 1,500,000 and above)		0.47	0.11
Social isolation (v. no isolation)		0.67*	0.03
Step 5			
Sarcopenia (v. no sarcopenia)		0.60*	0.04
Social isolation (v. no isolation)		0.68*	0.03

Abbreviations: v, versus.

Legend: * $p \leq 0.05$; † Neighbourhood income after tax was a single variable. Therefore, it was removed based on the lowest p-value of the two comparisons.

Note: Bolded lines highlight the variable removed.

Appendix E Model diagnostics

The four assumptions and corresponding statistical tests for logistic regression models are as follows:

1. Independence of observations: The independence assumption can be checked by investigating the study design. Additionally, the Durbin Watson (DW) statistic can be used to test for autocorrelation in successive residuals and should be approximately equal to two. A value less than one or greater than three indicates potential autocorrelation.
2. Multicollinearity among independent variables: The variance inflation factor (VIF) should be less than 2.5. A VIF of greater than five indicates a serious collinearity problem.
3. Influential observations: Cook's distance (Cook's D) can test for the influence of a continuous data point in logistic regression analysis. A Cook's distance of greater than 0.5 indicates that the observation should be further examined. A Cook's distance of greater than one indicated a high influence observation.
4. Linearity between continuous independent variables and the logit of dependent variable: This assumption can be checked graphically by plotting the continuous variable on the X-axis and the logit function on the Y-axis.

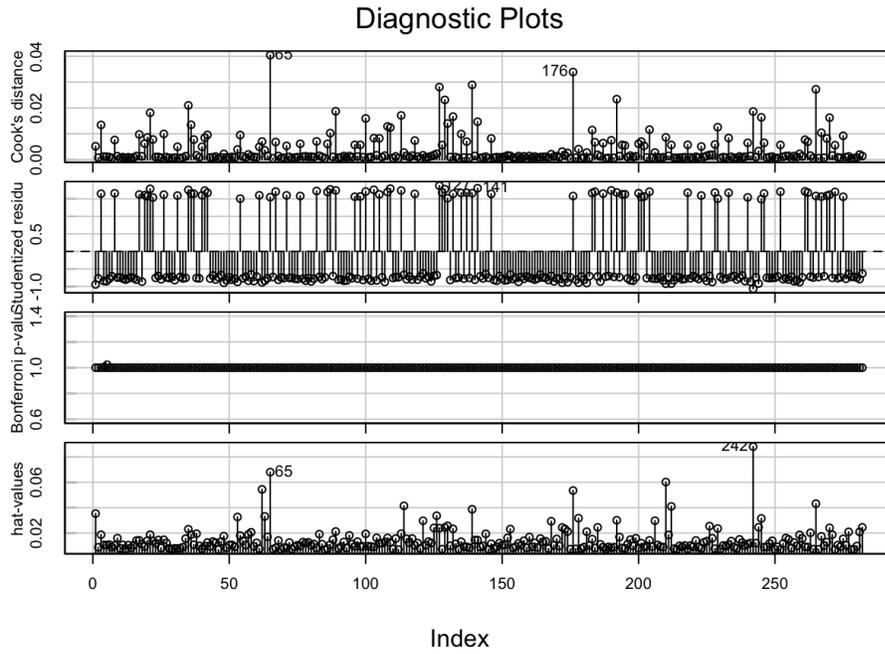
Primary multivariable logistic regression models for skeletal muscle index (SMI):

Step 1:

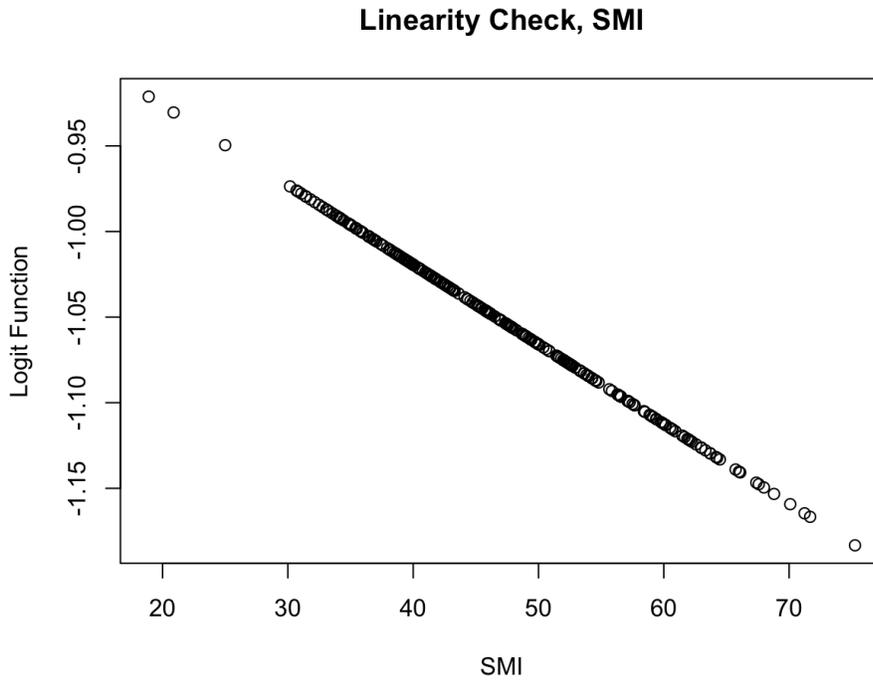
1. Independence: DW statistic= 1.9
2. Multicollinearity:

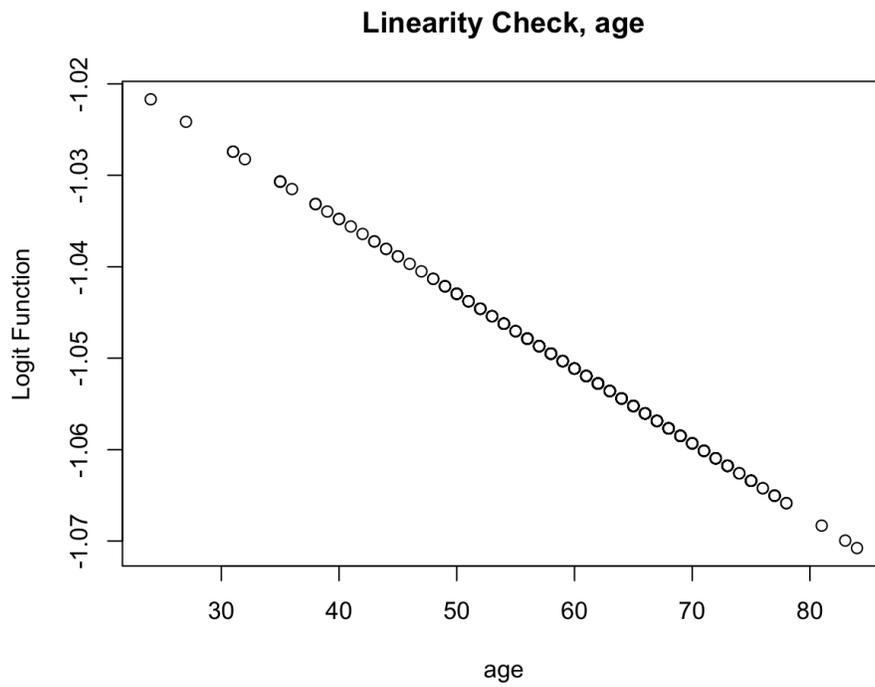
Variable	VIF
SMI	1.7
Age at diagnosis	1.0
Sex	1.7

3. Influential observations:



4. Linearity:





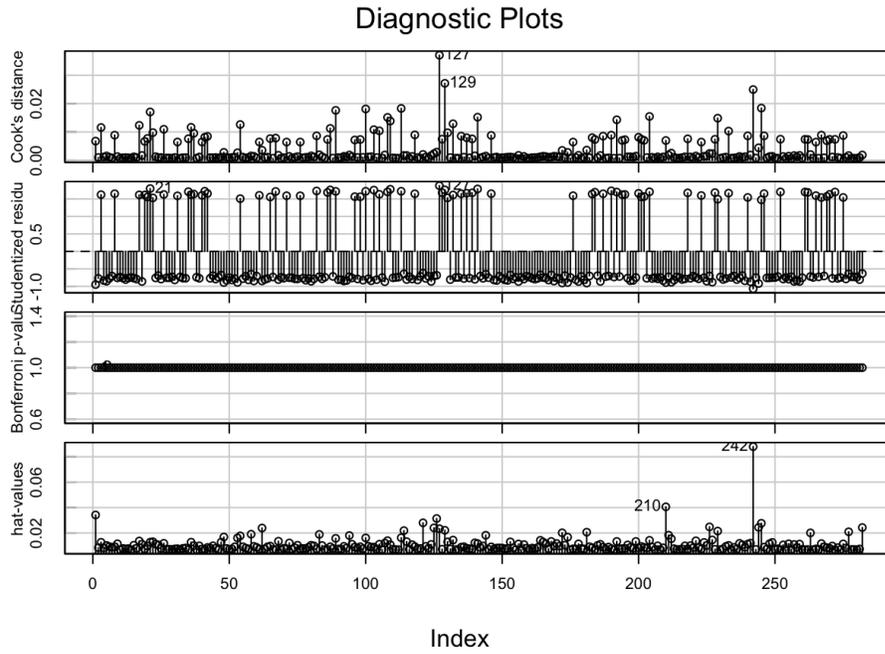
Step 2:

1. Independence: DW statistic= 1.9

2. Multicollinearity:

Variable	VIF
SMI	1.7
Sex	1.7

3. Influential observations:



4. Linearity: Same as above.

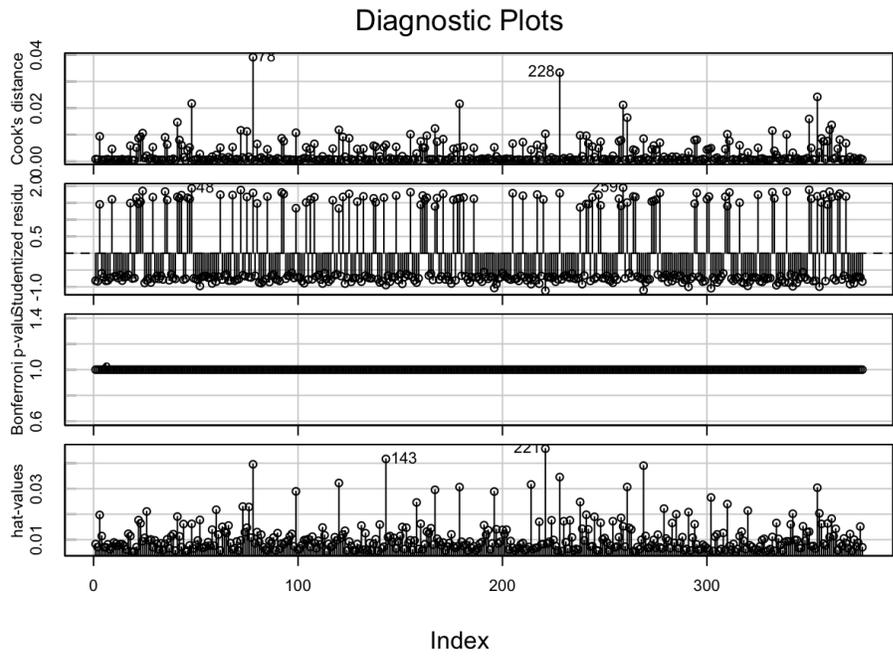
Primary multivariable logistic regression models for skeletal muscle density (SMD):

Step 1:

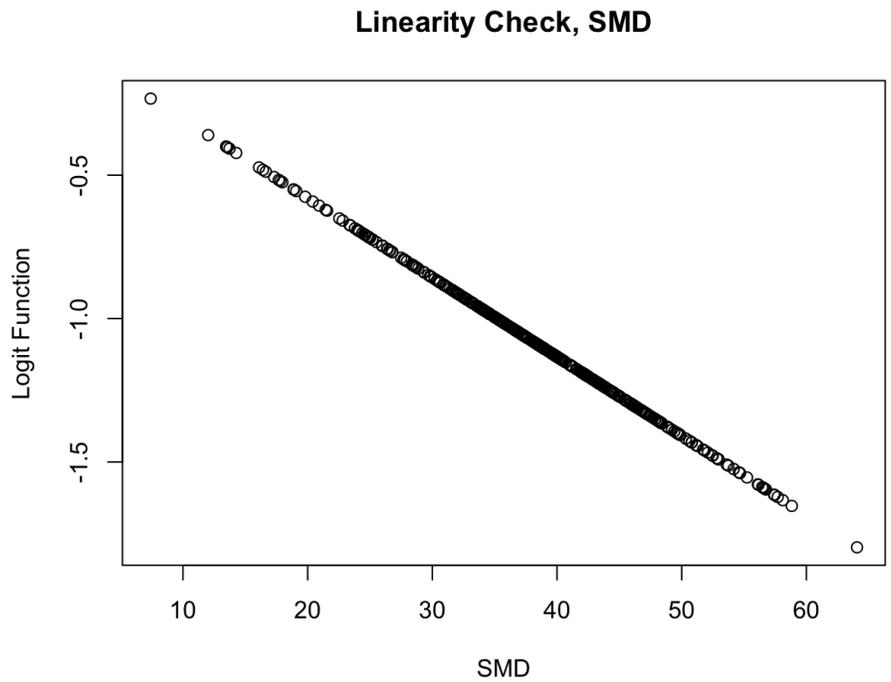
1. Independence: DW statistic= 1.8
2. Multicollinearity:

Variable	VIF
SMD	1.2
Age at diagnosis	1.2
Sex	1.1

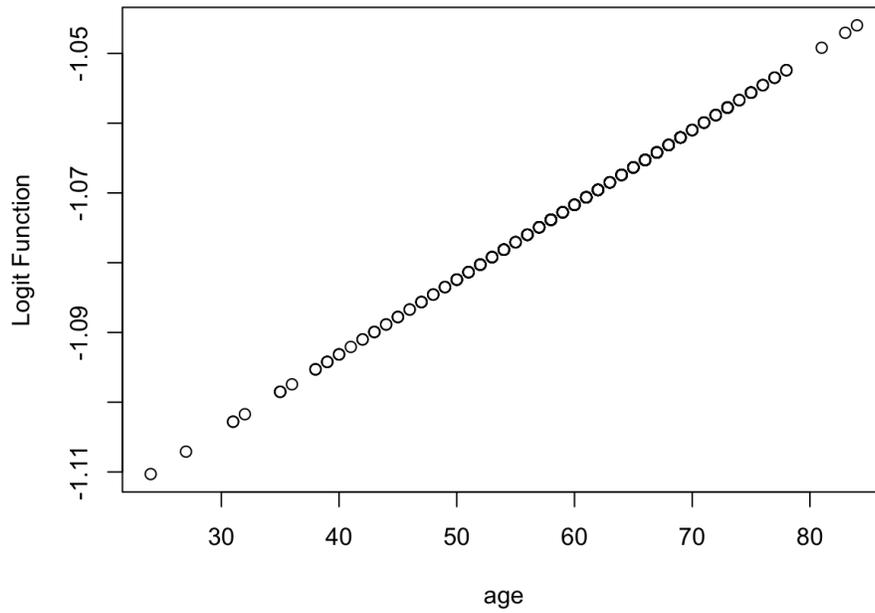
3. Influential observations:



4. Linearity:



Linearity Check, age

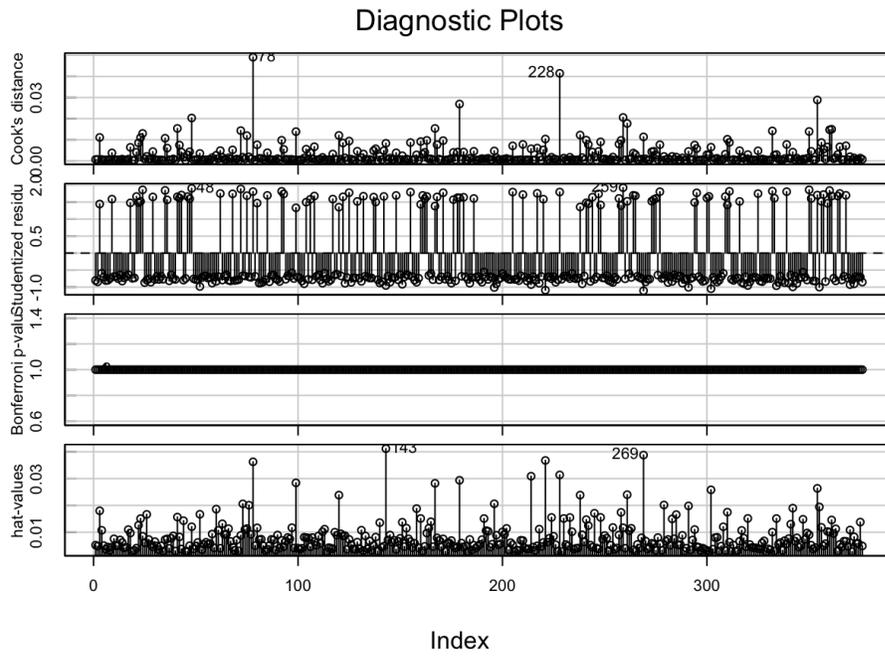


Step 2:

1. Independence: DW statistic= 1.8
2. Multicollinearity:

Variable	VIF
SMD	1.2
Age at diagnosis	1.2

3. Influential observations:

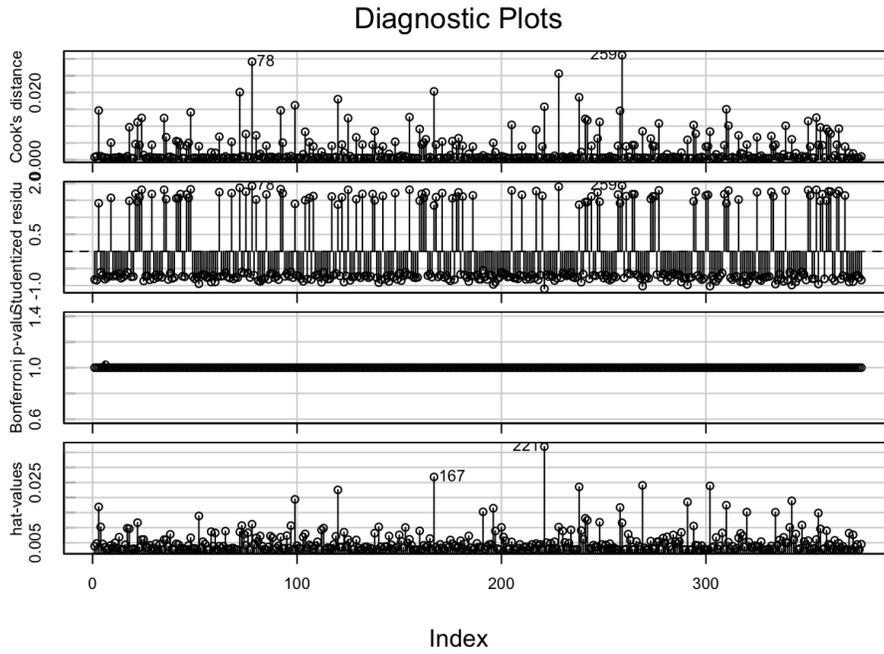


4. Linearity: Same as above.

Step 3:

1. Independence: DW statistic= 1.8
2. Multicollinearity: Not applicable.

3. Influential observations:



4. Linearity: Same as above.

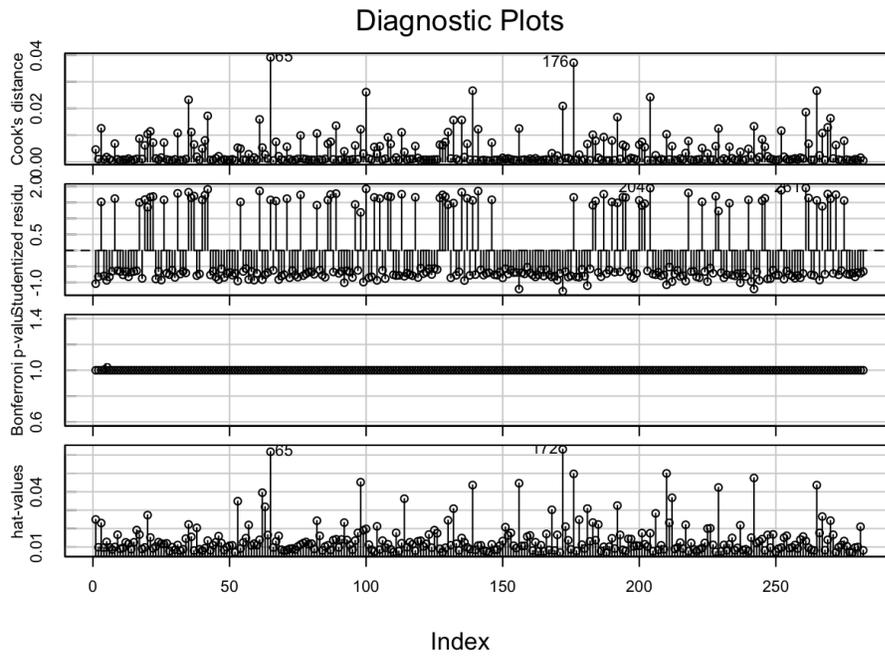
Primary multivariable logistic regression model for skeletal muscle gauge (SMG):

Step 1:

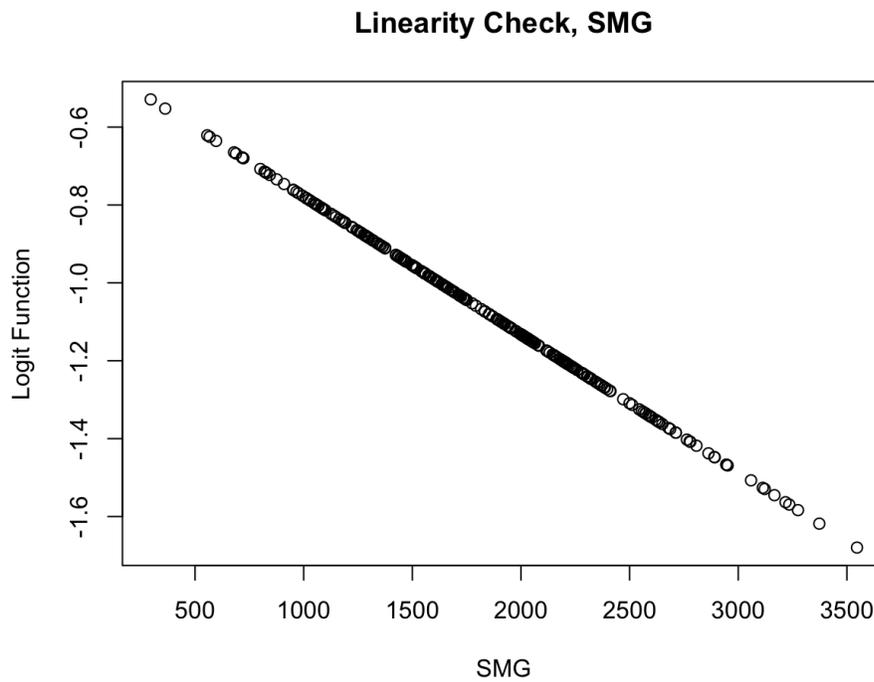
1. Independence: DW statistic= 1.9
2. Multicollinearity:

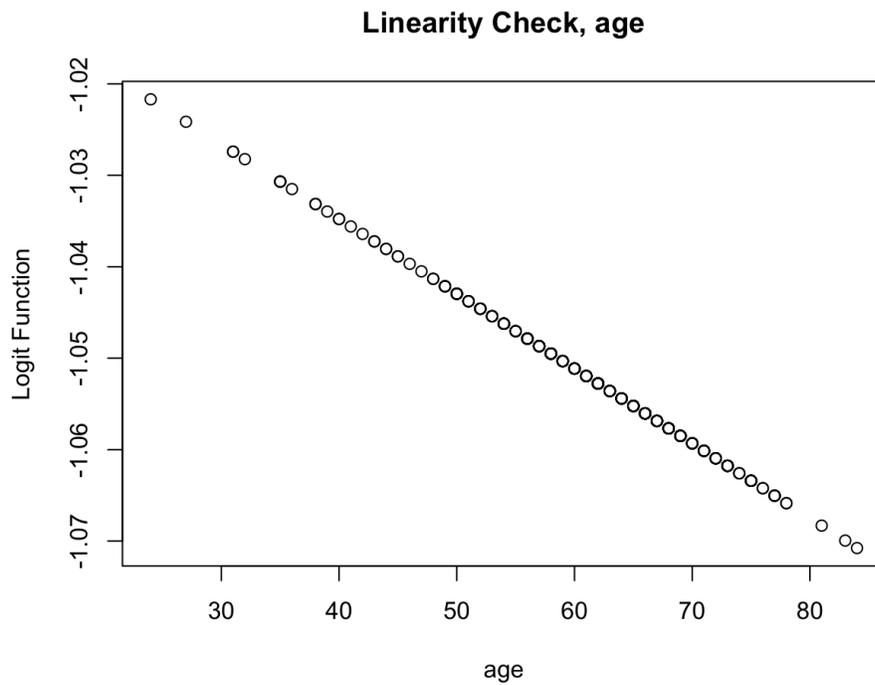
Variable	VIF
SMG	1.6
Age at diagnosis	1.2
Sex	1.5

3. Influential observations:



4. Linearity:





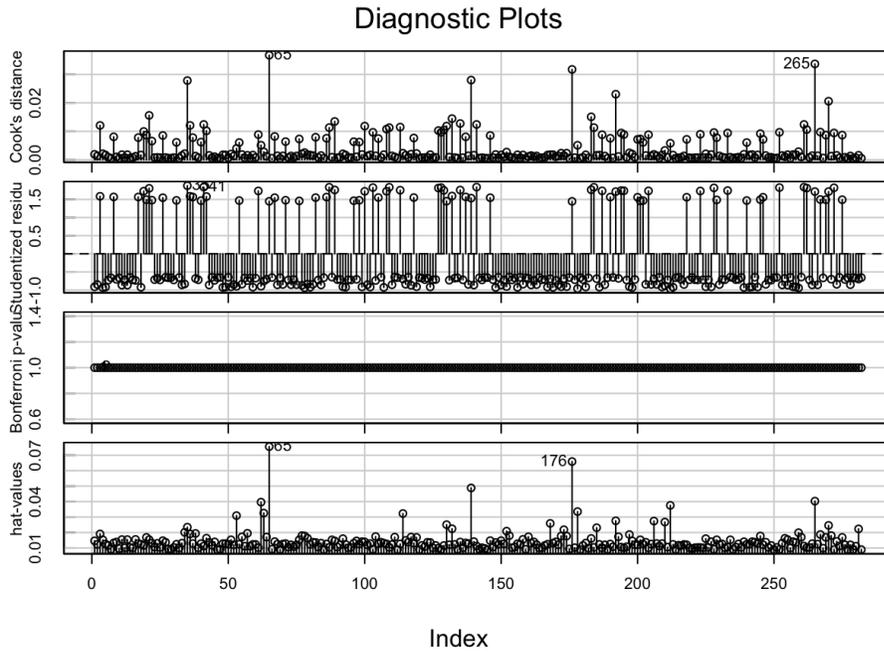
Primary multivariable logistic regression model for sarcopenia:

Step 1:

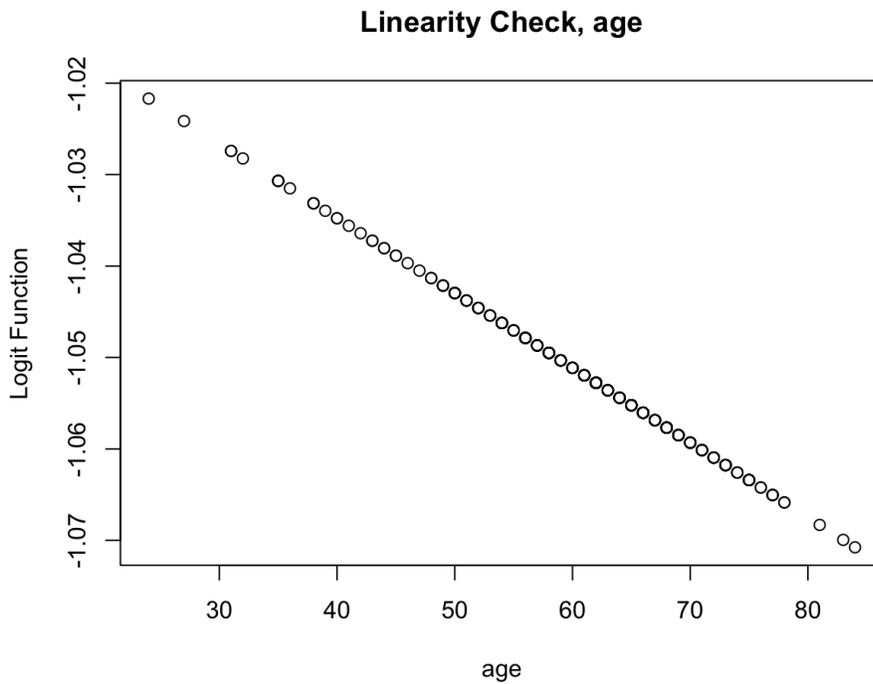
1. Independence: DW statistic= 1.9
2. Multicollinearity:

Variable	VIF
Sarcopenia	1.0
Age at diagnosis	1.0
Sex	1.0

3. Influential observations:



4. Linearity:



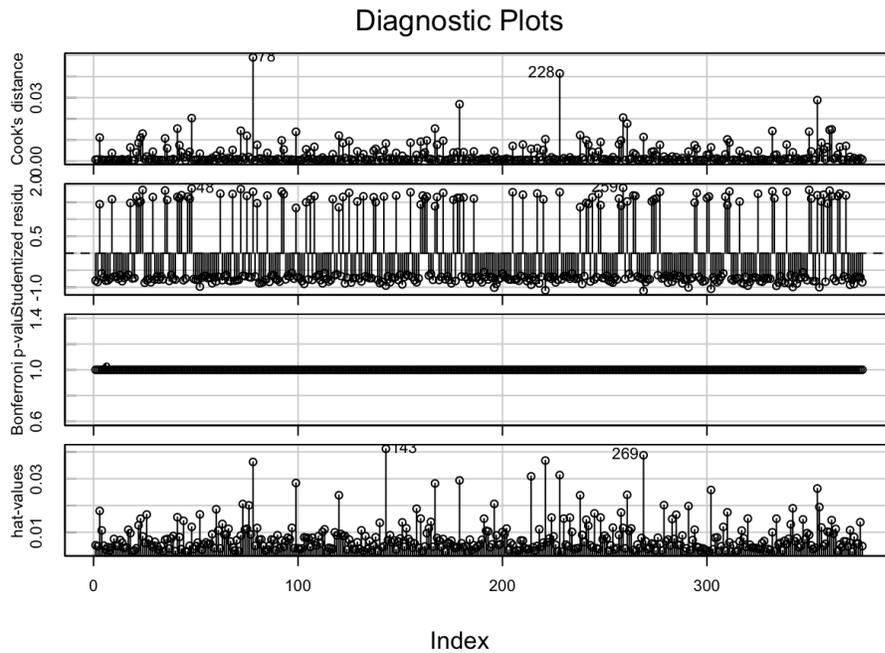
Model with Step 2:

1. Independence: DW statistic= 1.9

2. Multicollinearity:

Variable	VIF
SMG	1.0
Sex	1.0

3. Influential observations:

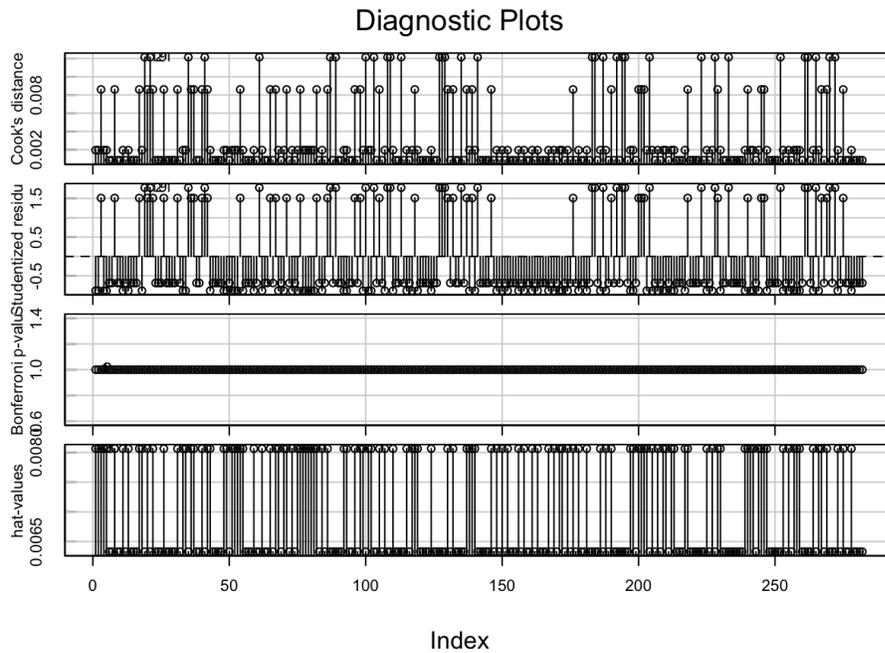


4. Linearity: Not applicable (i.e., not continuous variables left in model).

Step 3:

1. Independence: DW statistic= 1.9
2. Multicollinearity: Not applicable (i.e., univariable model).

3. Influential observations:



4. Linearity: Same as above.

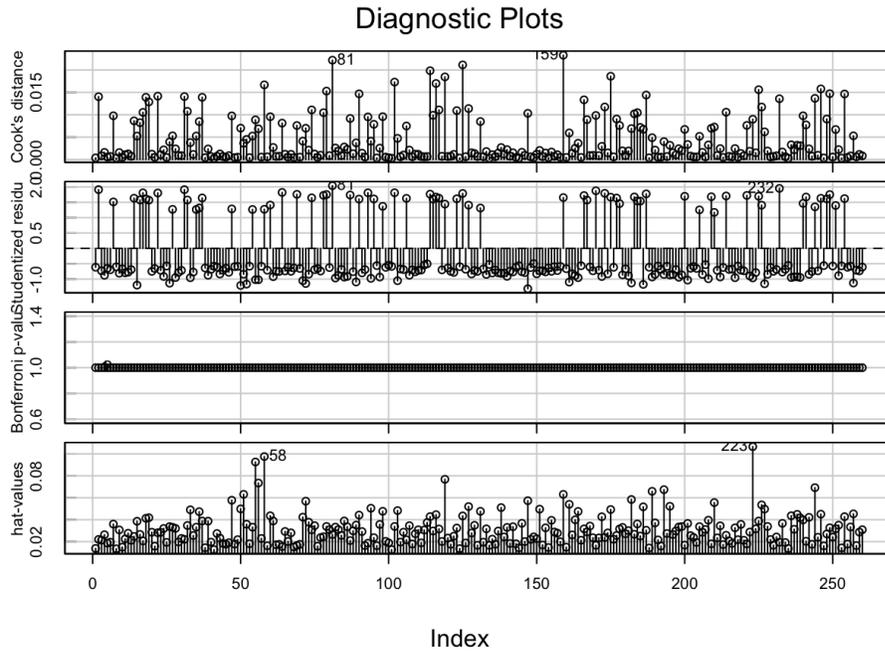
Exploratory multivariable logistic regression model for SMI:

Step 1:

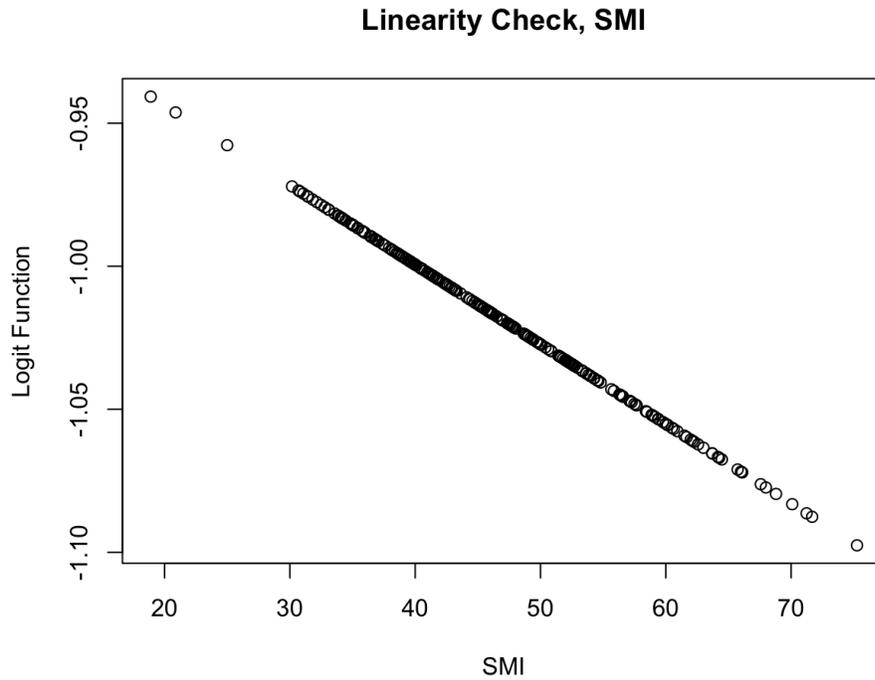
1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
SMI	1.9
Age at diagnosis	1.0
Sex	1.9
Community size	1.1
Neighbourhood income after tax	1.2
Social isolation	1.1

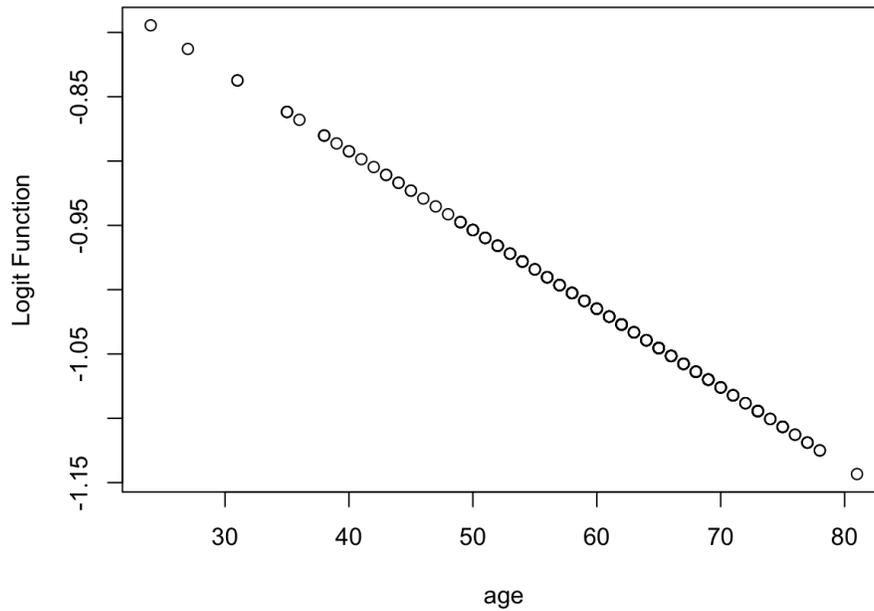
3. Influential observations:



4. Linearity:



Linearity Check, age

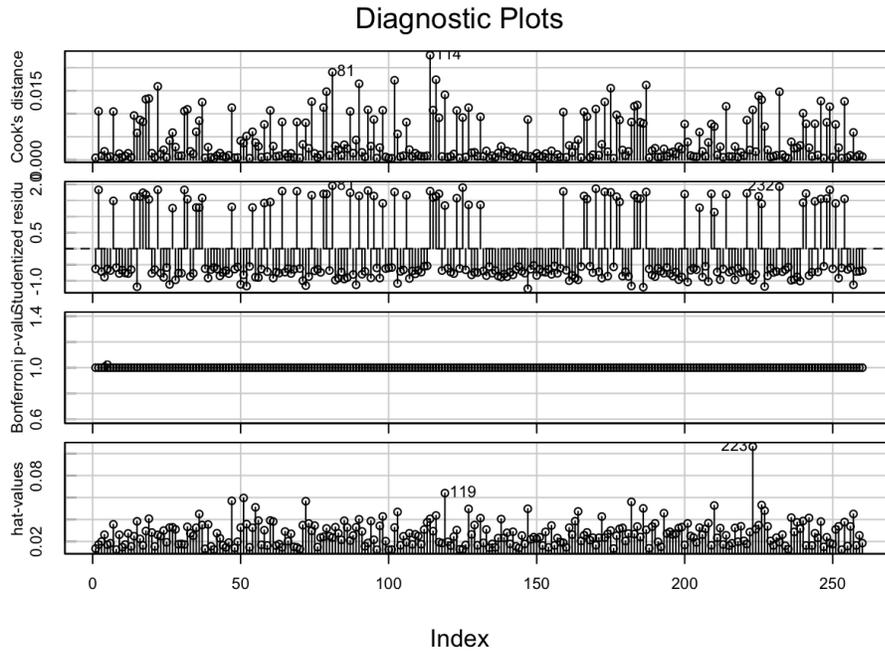


Step 2:

1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
SMI	1.8
Sex	1.8
Community size	1.0
Neighbourhood income after tax	1.2
Social isolation	1.1

3. Influential observations:



4. Linearity: Same as above.

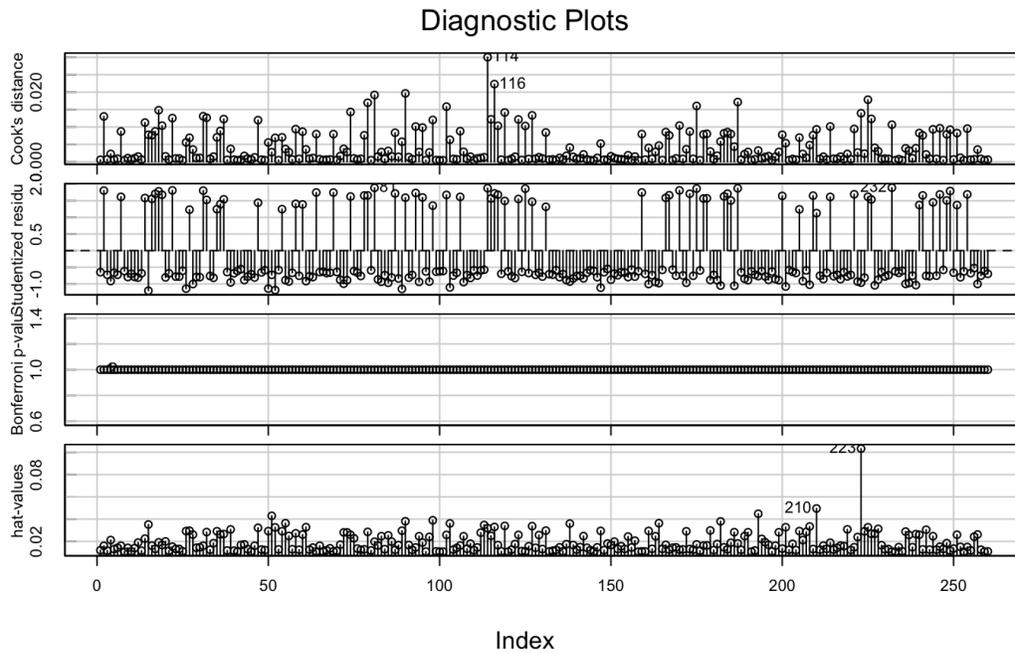
Step 3:

1. Independence: DW statistic= 2.0

2. Multicollinearity:

Variable	VIF
SMI	1.8
Sex	1.8
Community size	1.0
Social isolation	1.0

3. Influential observations:



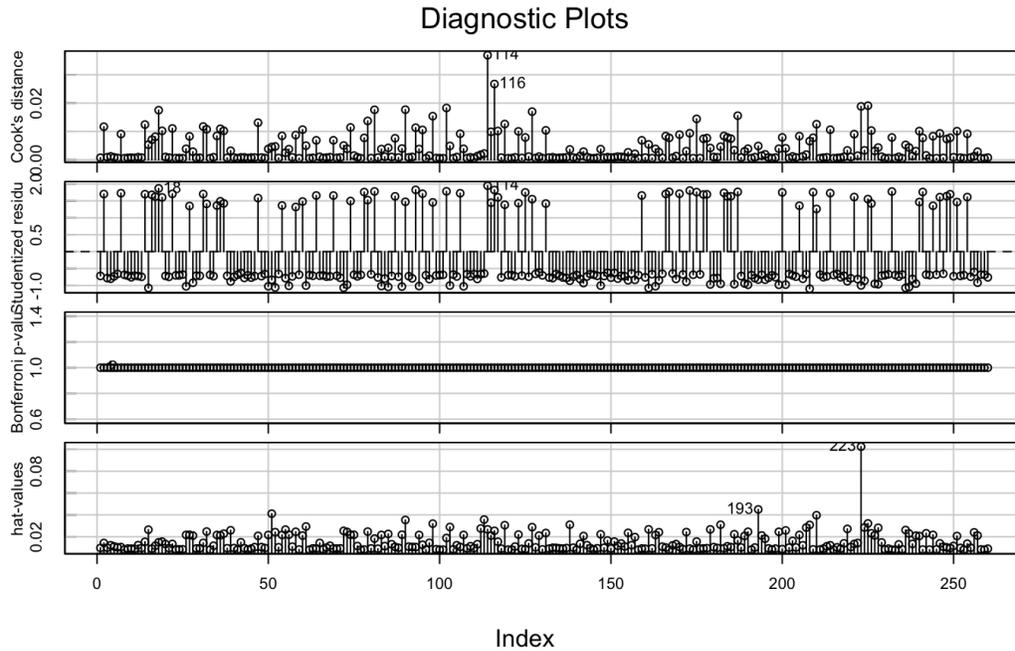
4. Linearity: Same as above.

Step 4:

1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
SMI	1.8
Sex	1.8
Social isolation	1.0

3. Influential observations:



4. Linearity: Same as above.

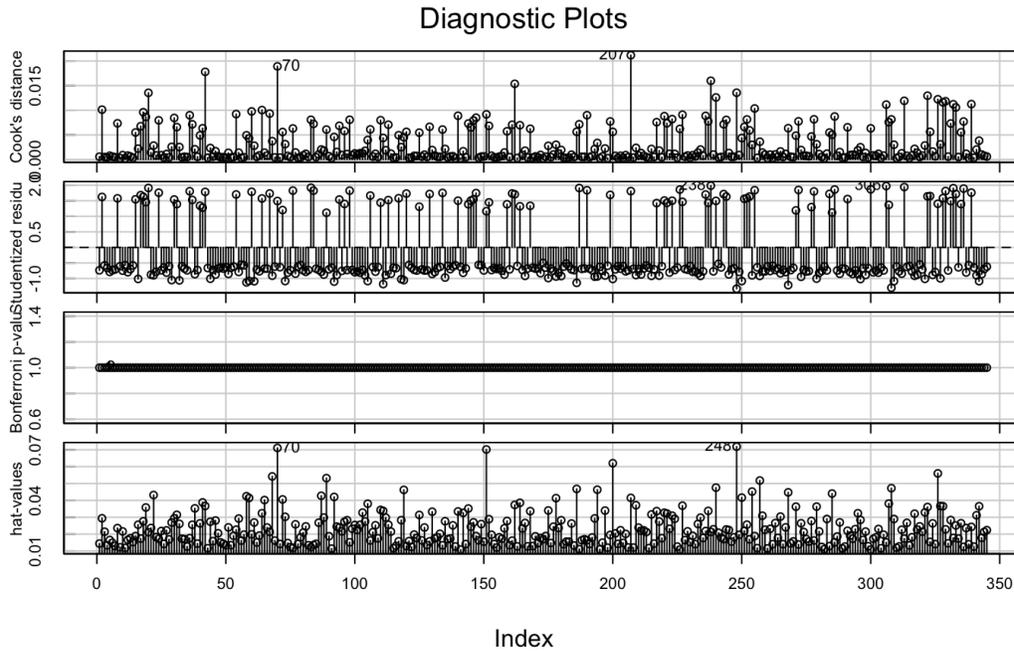
Exploratory multivariable logistic regression model for SMD:

Step 1:

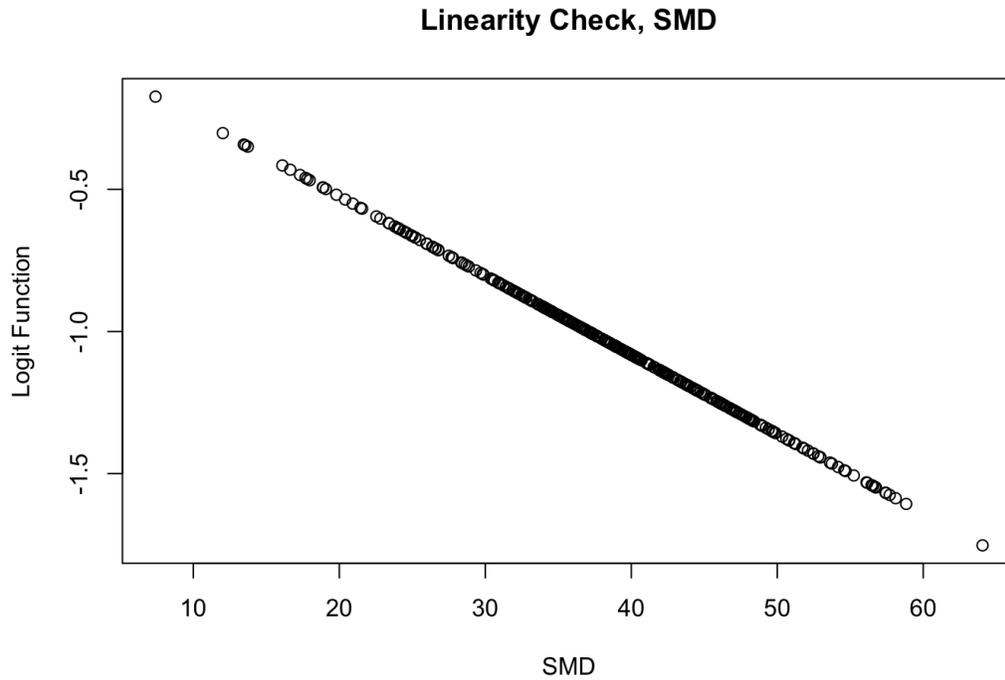
1. Independence: DW statistic= 1.8
2. Multicollinearity:

Variable	VIF
SMD	1.3
Age at diagnosis	1.2
Sex	1.1
Community size	1.1
Neighbourhood income after tax	1.0
Social isolation	1.1

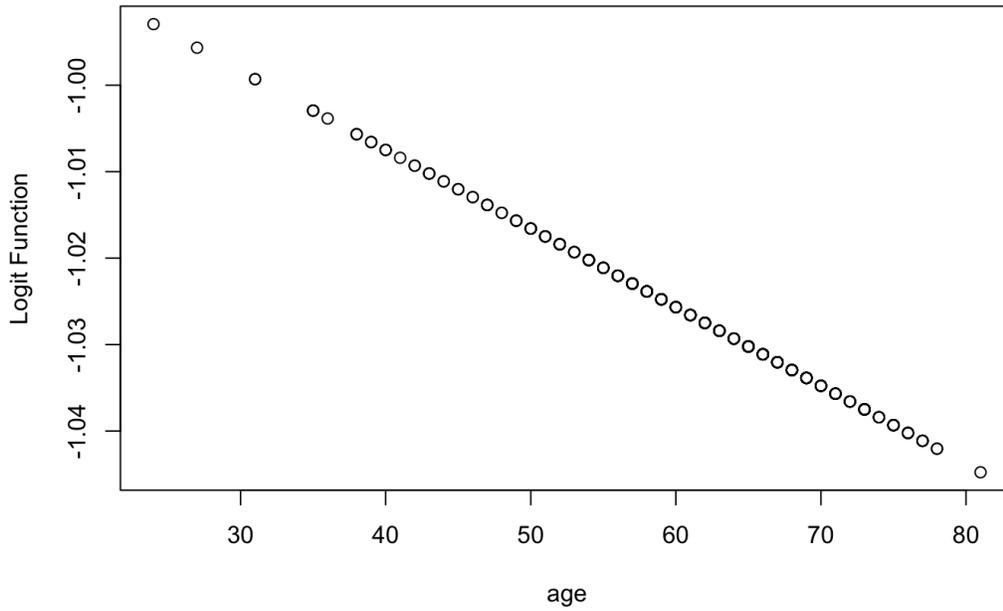
3. Influential observations:



4. Linearity:



Linearity Check, age

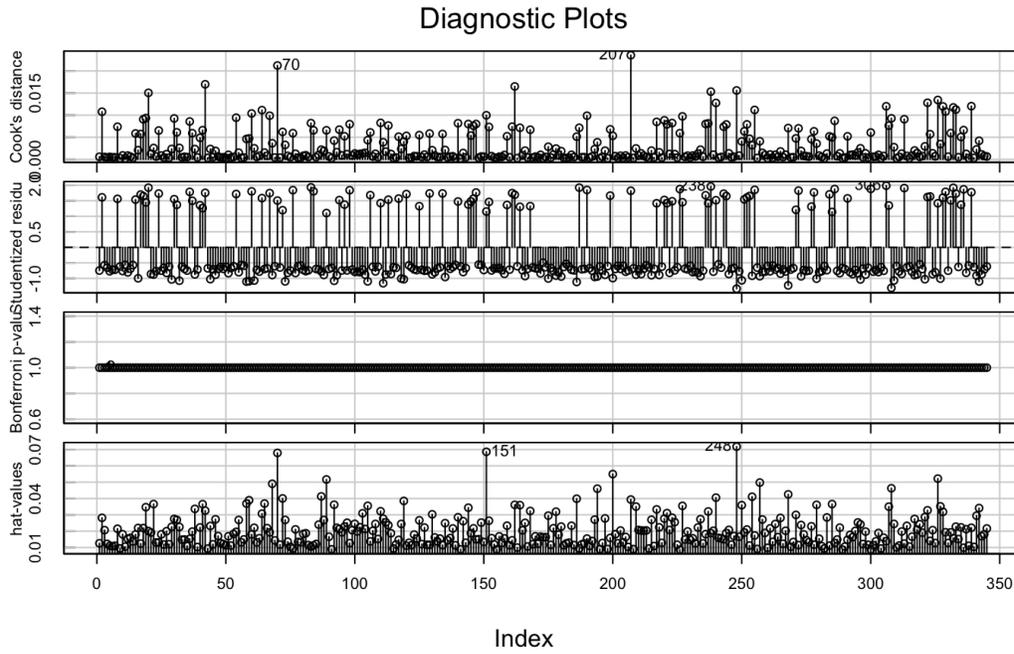


Step 2:

1. Independence: DW statistic= 1.8
2. Multicollinearity:

Variable	VIF
SMD	1.2
Age at diagnosis	1.2
Community size	1.0
Neighbourhood income after tax	1.1
Social isolation	1.1

3. Influential observations:



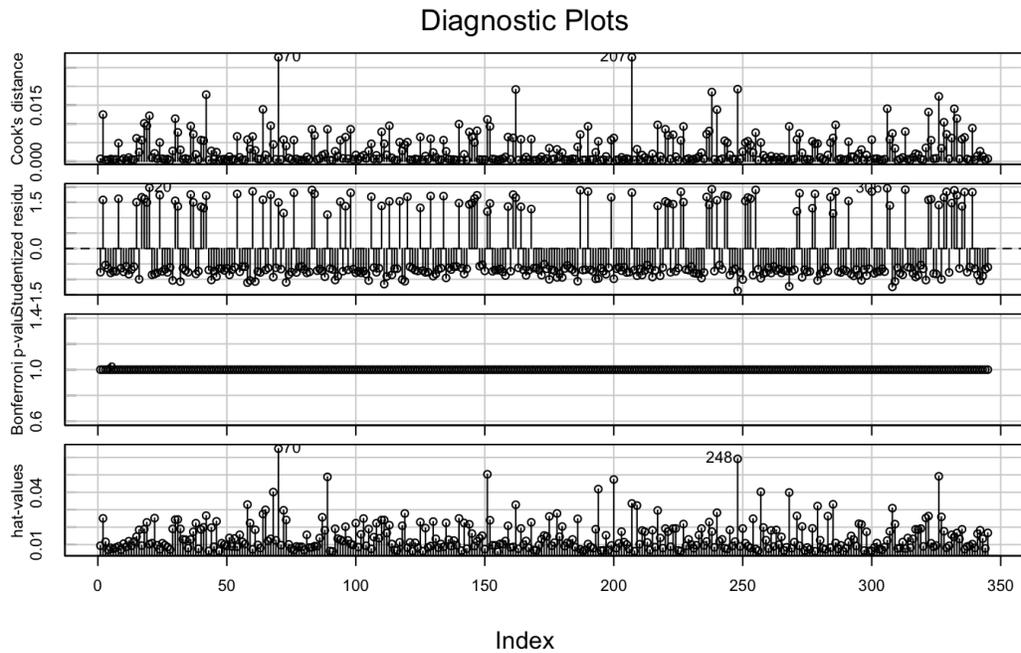
4. Linearity: Same as above.

Step 3:

1. Independence: DW statistic= 1.8
2. Multicollinearity:

Variable	VIF
SMD	1.2
Age at diagnosis	1.2
Community size	1.0
Social isolation	1.0

3. Influential observations:



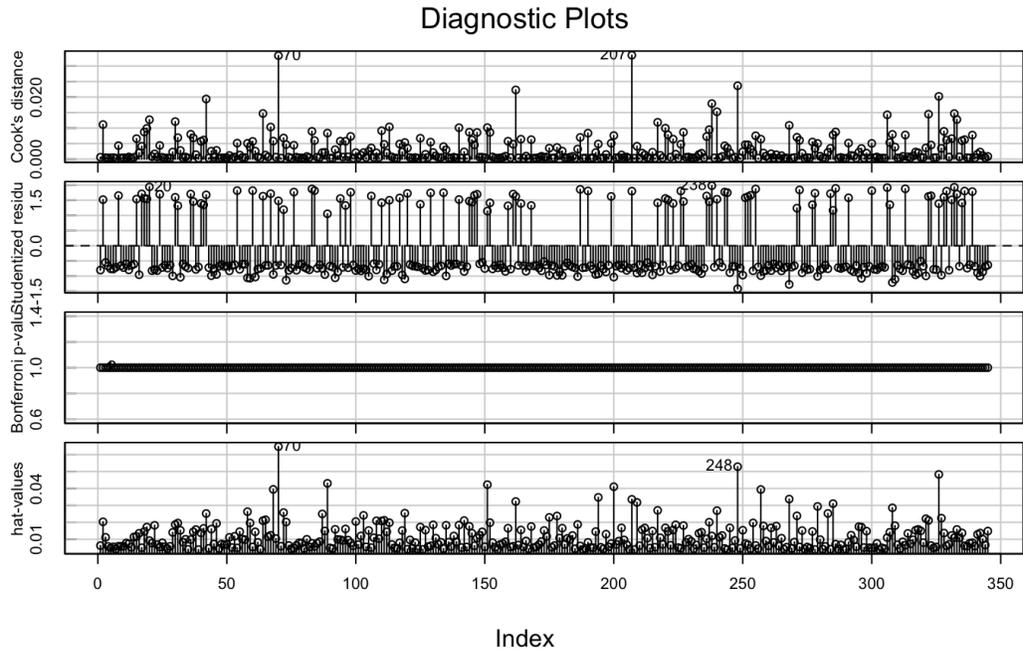
4. Linearity: Same as above.

Step 4:

1. Independence: DW statistic= 1.8
2. Multicollinearity:

Variable	VIF
SMD	1.2
Age at diagnosis	1.2
Social isolation	1.0

3. Influential observations:



4. Linearity: Same as above.

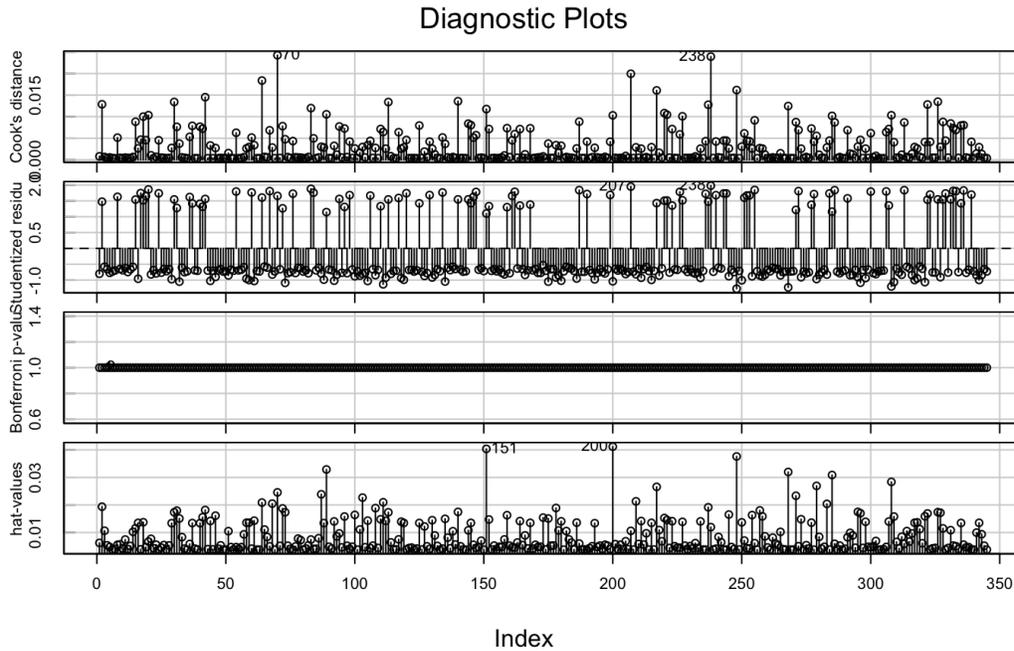
Step 5:

1. Independence: DW statistic= 1.8

2. Multicollinearity:

Variable	VIF
SMD	1.0
Social isolation	1.0

3. Influential observations:



4. Linearity: Same as above.

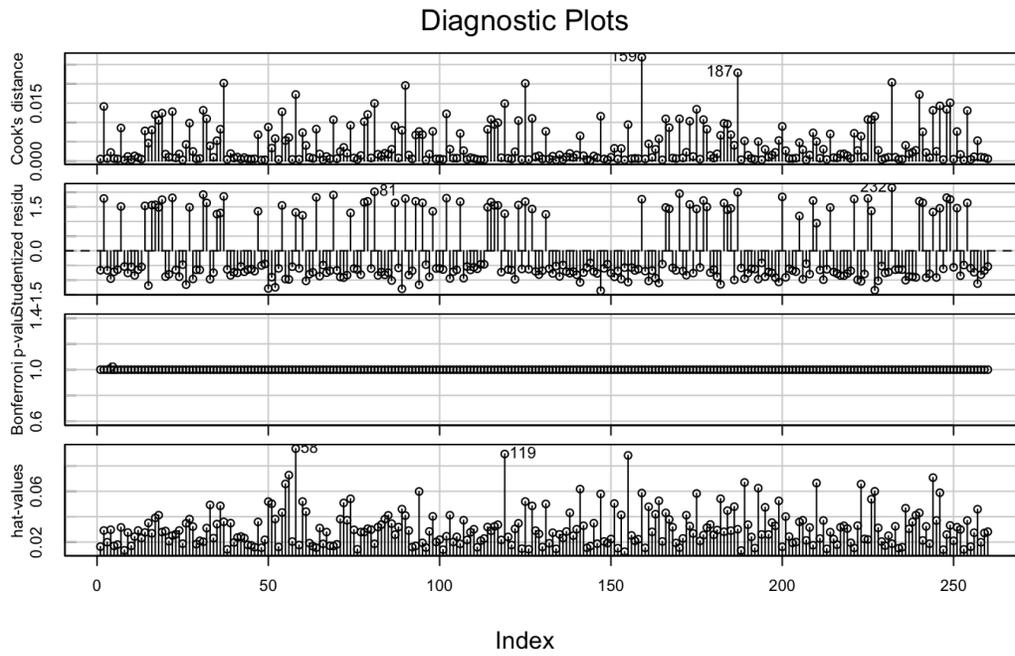
Exploratory multivariable logistic regression model for SMG:

Step 1:

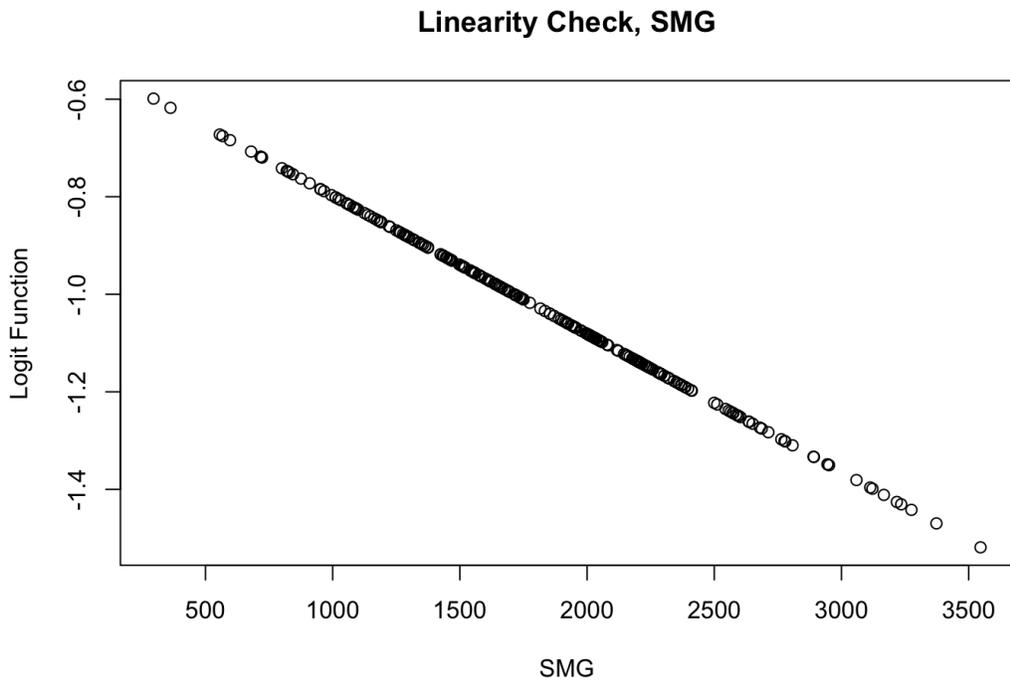
1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
SMG	1.7
Age at diagnosis	1.3
Sex	1.5
Community size	1.0
Neighbourhood income after tax	1.2
Social isolation	1.1

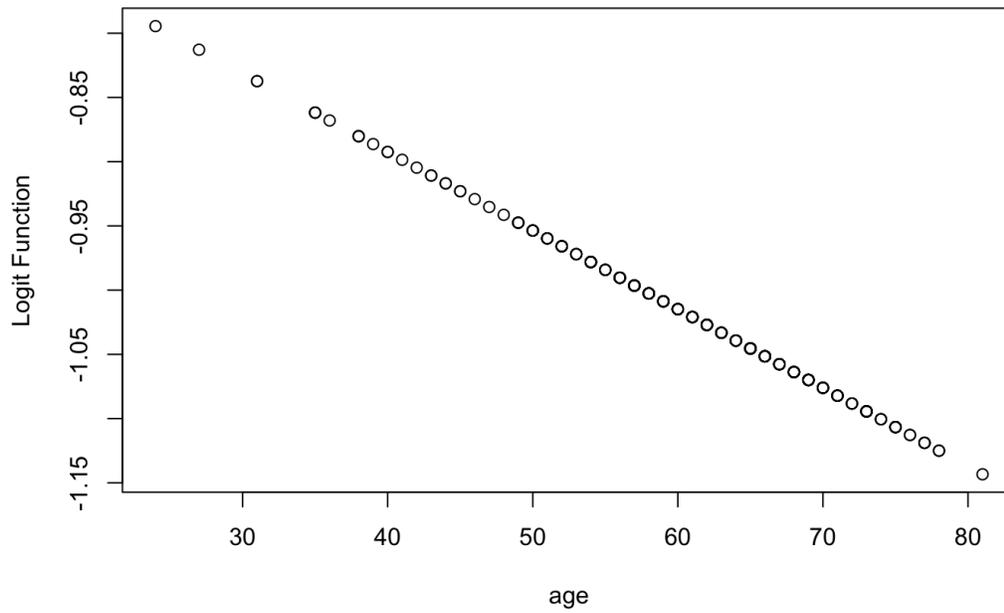
3. Influential observations:



4. Linearity:



Linearity Check, age

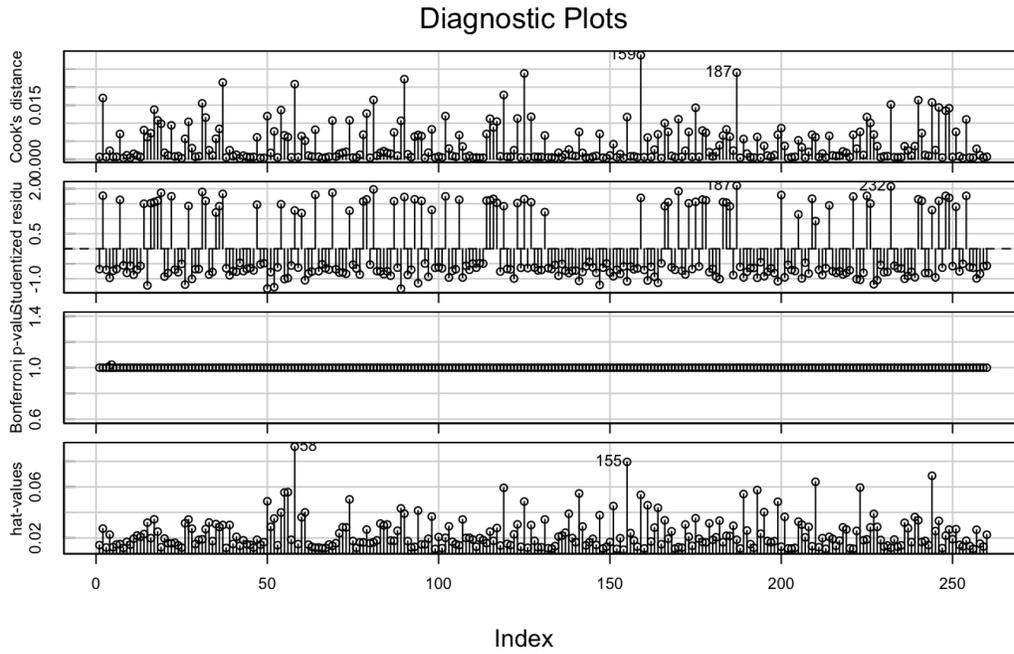


Step 2:

1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
SMG	1.7
Age at diagnosis	1.2
Sex	1.5
Community size	1.0
Social isolation	1.0

3. Influential observations:



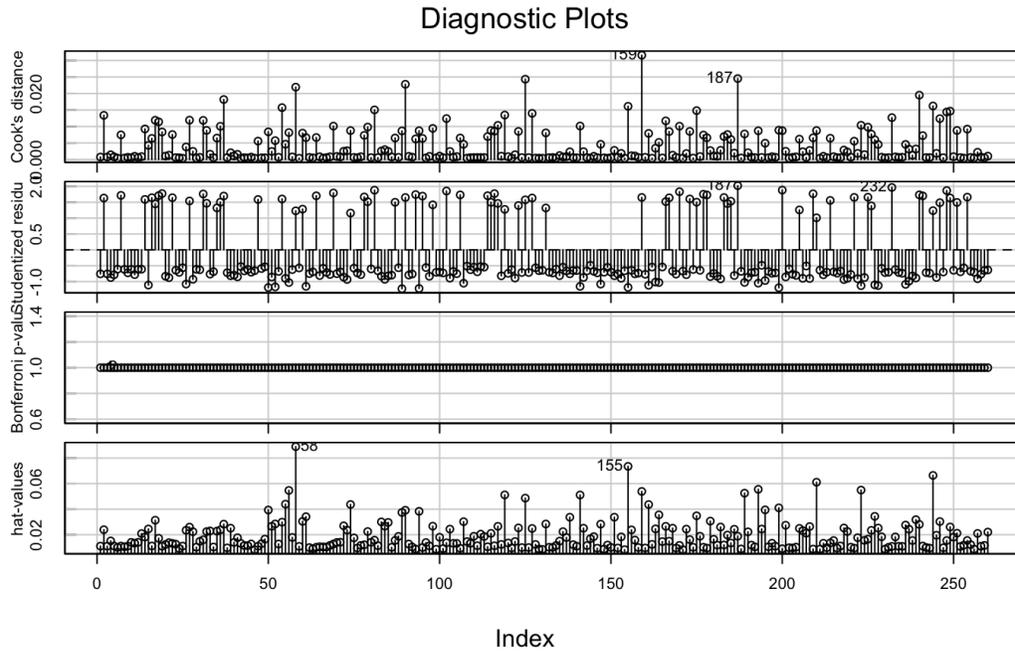
4. Linearity: Same as above.

Step 3:

1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
SMG	1.7
Age	1.2
Sex	1.5
Social isolation	1.0

3. Influential observations:



4. Linearity: Same as above.

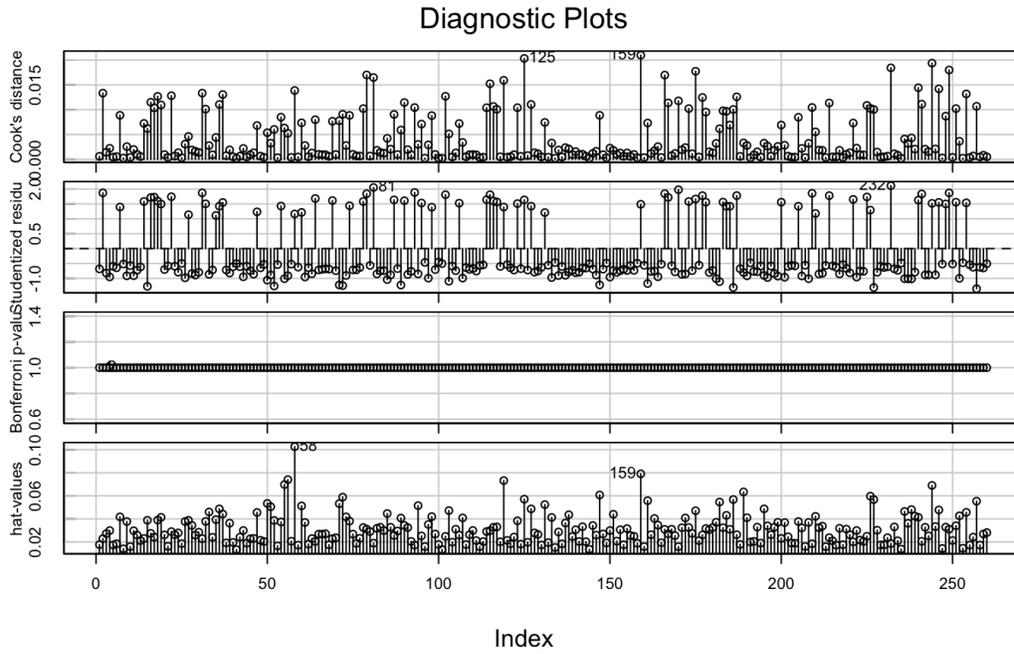
Exploratory multivariable logistic regression model for sarcopenia:

Step 1:

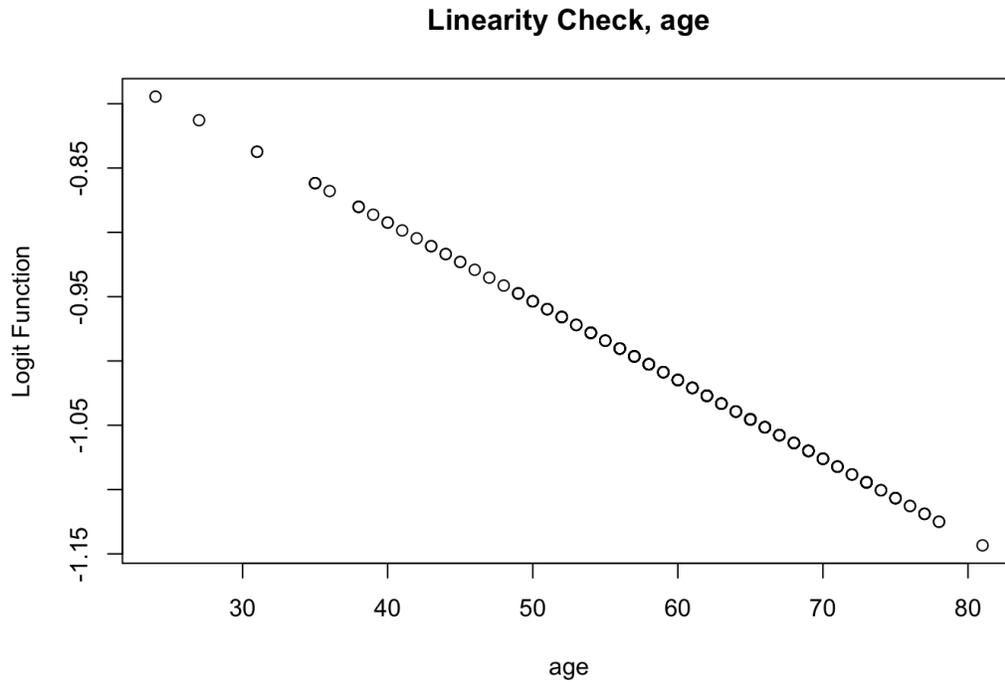
1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
Sarcopenia	1.1
Age at diagnosis	1.0
Sex	1.0
Community size	1.1
Neighbourhood income after tax	1.2
Social isolation	1.1

3. Influential observations:



4. Linearity:



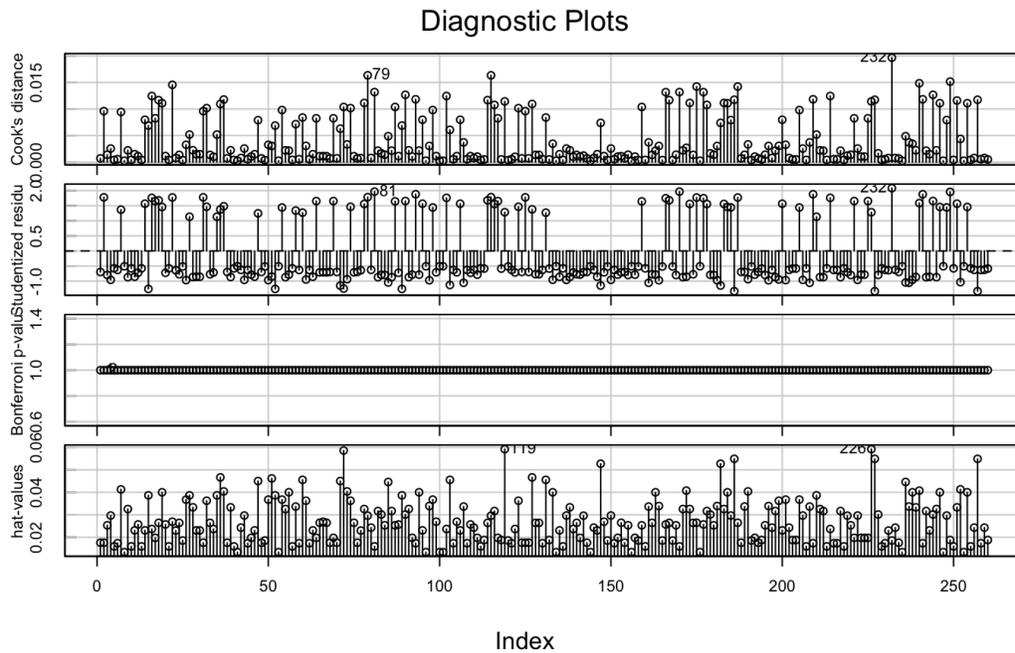
Step 2:

1. Independence: DW statistic= 2.0

2. Multicollinearity:

Variable	VIF
Sarcopenia	1.0
Sex	1.0
Community size	1.0
Neighbourhood income after tax	1.2
Social isolation	1.1

3. Influential observations:



4. Linearity: Not applicable.

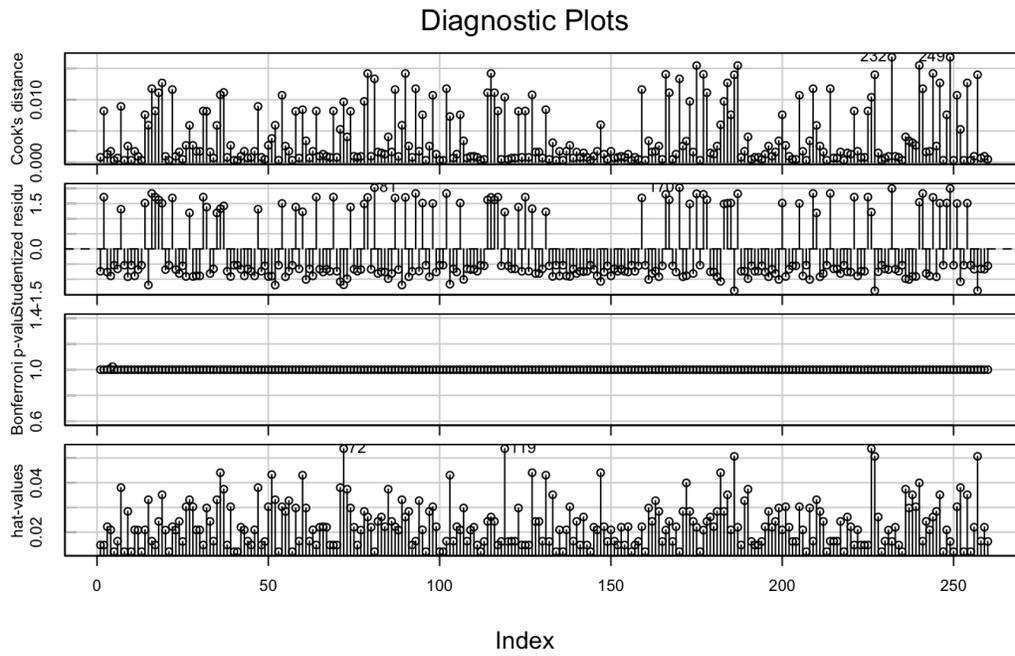
Step 3:

1. Independence: DW statistic= 2.0

2. Multicollinearity:

Variable	VIF
Sarcopenia	1.0
Community size	1.0
Neighbourhood income after tax	1.2
Social isolation	1.1

3. Influential observations:



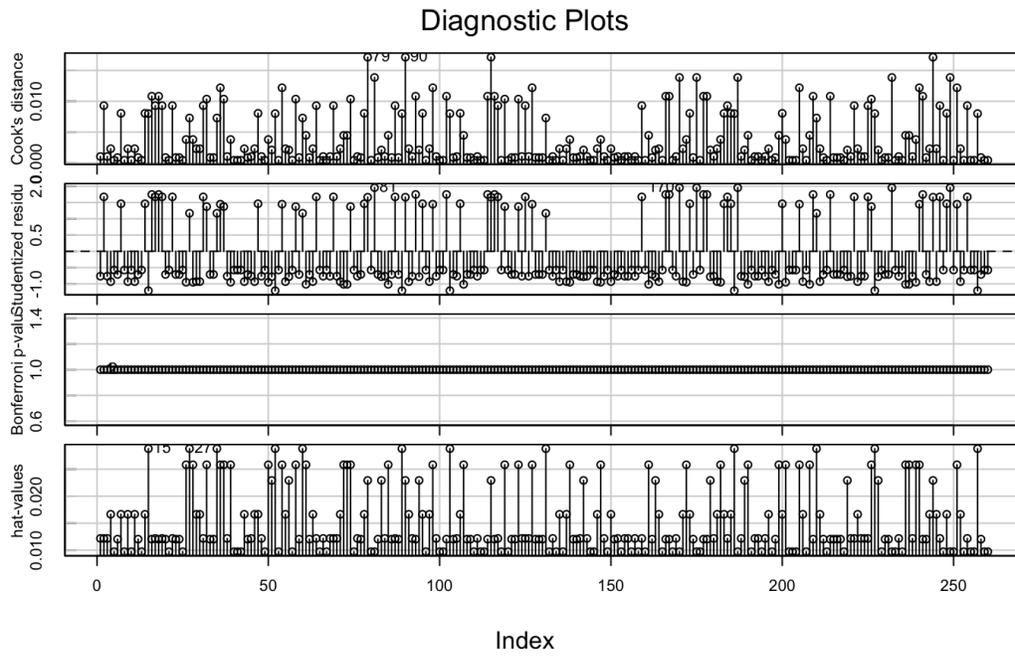
4. Linearity: Not applicable.

Step 4:

1. Independence: DW statistic= 2.0
2. Multicollinearity:

Variable	VIF
Sarcopenia	1.0
Community size	1.0
Social isolation	1.0

3. Influential observations:



4. Linearity: Not applicable.

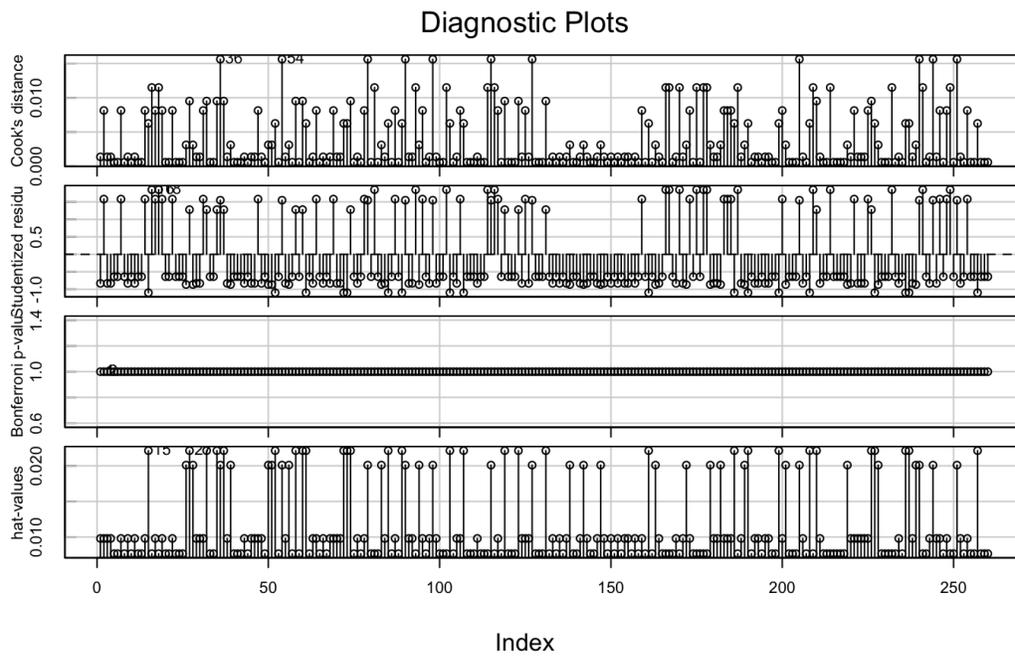
Step 5:

1. Independence: DW statistic= 2.0

2. Multicollinearity:

Variable	VIF
Sarcopenia	1.0
Social isolation	1.0

3. Influential observations:



4. Linearity: Not applicable.