Fate of the metabolically healthy obese – Is this term a misnomer? A study from the Clinical Practice Research Datalink

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Longitudinal analysis of transition.

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Abstract

Introduction

The metabolically healthy obese (MHO) phenotype may express typical characteristics on long-term follow-up. Little is known about the initiation of this phenotypes and its future stability.

Aim

The Clinical Practice Research Datalink (CPRD) is a large-scale primary care database. The aim of this study was to assess the stability of, and evaluate the factors associated with a transition into an unhealthy outcome in, a metabolically healthy obese population in the UK.

Methods

The CPRD was interrogated for a diagnosis of 'obesity' and cross-referenced with a body mass index BMI≥35kg/m^2; participants were further classified as metabolically healthy (MH) using a clinical diagnostic code or a relative therapeutic code. A hazard cox regression univariate and multivariate analysis evaluated the time to transition for independent variables.

Results

There were 231,399 patients with a recorded BMI of 35Kg/m^2 or greater. Incomplete records were eliminated and follow-up limited to 300 months, the cohort was reduced to 180,560 patients. The prevalence of MHO within the obese population from the CPRD was 128,191/180,560(71%). Metabolically healthy obese individuals who were of male gender [Hazard Ratio 1.23(1.21-1.25),p=<0.01], older age group [HR 3.93(3.82-4.04),p=<0.01], BMI of 50-60Kg/m^2 at baseline [HR 1.32(1.26-1.38),p=0.01], smokers [HR 1.07(1.05-1.09),p=<0.01] and regionally from North West England [HR 1.15(1.09-1.21), p=<0.01] were more prone to an unhealthy transition (to develop comorbidities). Overall, of those metabolically healthy at baseline, 71,485/128,191(55.8%) remained healthy on follow-up, with a mean follow-up of 113.5(SD 78.6) months or 9.4(SD 6.6) years.

Conclusion

From this unique large dataset, there is a greater prevalence of MH obese individuals in the UK population than in published literature elsewhere. Female gender, younger age group, and lower initial weight and BMI were found to be significant predictors of sustained metabolic health in this cohort. However, there remains a steady progressive transition from a healthy baseline over the years.

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Introduction

The term obesity can be defined as a state of being excessively overweight. Obesity is a global epidemic that affects more than 600 million adults. In 2014, more than 1.9 billion people were reported to be overweight by the World Health Organization WHO (1). A phenotype of patients who do not present metabolic abnormalities among the obese population, are the metabolically healthy obese (MHO) (2). The natural course of the MHO condition is unidentified and no agreement exists on the definite MHO definition (3). This group of individuals is believed to be associated with a subordinate risk of developing obesity-related complications and are referred to as Metabolically Healthy Obese (MHO) (4).

Some research on the clinical outcomes of MHO have produced different results (5). A few studies have shown that MHO individuals have a lower risk of cardiovascular disease (CVD) than unhealthy counterparts but different research has reported no differences between MHO individuals and normal-weight ones in terms of cardiovascular risks (6,7). Further studies have reported that MHO can significantly increase the risk of developing diabetes (8). Clinical results in MHO may be influenced by differences in fitness, (the percentage of fat, bone, water, and muscle in the human body), and inflammatory profiles. MHO individuals have been reported to have better fitness than metabolically at-risk obese individuals (9). They have also been found to have more favourable inflammatory profiles than individuals with metabolically abnormal individuals (10). Several definitions have been put forward to explain the presence of Metabolic Syndrome in adults by five different sources (4,11–13).

To identify the magnitude of this cohort of patients in the UK, the authors set out to use the UK CPRD, a computerised database established in 1987 containing longitudinal medical records from primary care that have been anonymised. The CPRD contains prospectively collected computerised data that is submitted by practitioners in live-patient time after a experimental period of data entry training. Starting in 1991, most practices participating in the CPRD have been providing data as well as attribute and completeness validation necessary for various research projects. About 1,500 general practitioners, with a population coverage of more than 3 million, provide their computerised clinical primary data anonymously to the CPRD as well as the Office of National Statistics (ONS). Of all the European databases, the CPRD in the UK is considered amongst the

largest and has been the most widely used for pharmaco-epidemiological research (14). The ability to offer prospective follow-up data for research is driven by the fact that nearly all residents in the United Kingdom are registered with a National Health Service (NHS) general practitioner. The availability of long-term follow-up data since 1987 inspired this study to investigate what happens to metabolic healthy individuals within a large UK community database.

The CPRD is constantly assembling anonymised data from millions of individuals, currently denoting almost 10% of the UK population, with other consistent research standard data (15). Studies that have investigated the validity of diagnosis on the CPRD have postulated that a high accuracy of diagnosis exists within the recordings in the CPRD, as well as reporting to have found strong measures of positive predictive value (PPV), sensitivity and specificity (16,17). This was particularly demonstrated in cardiovascular disease (15), dementia (18), cancers (19,20) and other morbidity diagnostic codes generally (17,21–23).

Aim

The Clinical Practice Research Datalink (CPRD) is a large-scale clinical general practice care database tool for community clinical follow-up. The aim of this analysis was to assess the stability of, and evaluate the factors associated with a transition into an unhealthy outcome in, a metabolically healthy obese population in the UK. The authors also sought to determine the prevalence of metabolic health within this obese population from long-term follow-up within the primary care setup.

Methods

Clinical Practice Research Datalink

Data for this study was extracted from CPRD records to the end of August 2016. Severe obesity diagnosis was made with a documented recorded body mass index BMI greater than or equal to 35 Kg/m^2 on at least 2 occasions, (to eliminate bias from a smaller BMI cohort towards metabolic health), and the reference date was the first recorded BMI date. The medcodes (medical diagnostic codes entered by general practitioners on the CPRD) use a code list to extract a subset of the data, adding a row with a category for each record. Similarly, (or prodcodes) (therapeutic medications codes entered by general practitioners on the CPRD) are numeric vectors representing relative therapies. The authors used Read terms to establish the relevant medcodes of comorbidities and other associated characteristics examined.

Metabolic Health definition

Various definitions are available for defining metabolic syndrome and health in obesity. Participants were further classified as metabolically healthy according to a strict modified definition to accommodate criteria accessible from the CPRD. The authors defined metabolic healthy obesity (MHO) as those patients with no comorbidity and not on any relevant therapy for the metabolic syndrome-associated morbidities of established diabetes, hypertension, hyperlipidaemia, cardiovascular disease, or cerebrovascular disease, liver or renal disease and obstructive sleep apnea. This definition was used to define metabolic health at baseline and follow-up to determine the prevalence of MHO. The database was compiled to include patient demographics, regional distribution and also Index of Multiple Deprivation (IMD). IMD is a score of the socio-economic background of a neighbourhood taking into account: income, employment, health deprivation and disability, educational attainment, barriers to housing and services, crime, and living environment (24).

Data restriction

The initial cohort extracted limited to a BMI $\geq$ 35Kg/m^2 was 231,399 patients; primarily this was restricted to between 18-60 years of age, excluding 48,141 patients of which 44,265 patients were aged 60 years and above. The cut-off age of 60 years was chosen to reduce age bias and assess follow-up for a time period of at least 5 years. Similarly, a further 6,574 patients with erroneous extremes of weight and BMI measurements were excluded.

Data restrictions:

- BMI 231,399
- Age restricted (18-60 years) 187,134
- Weight restricted (60-220 Kg) 187,028
- Follow-up restricted (300 months) 180,560
- Deceased 8,534 (4.7%)

Timeline definitions

The first BMI$\geq$35Kg/m^2 reading was considered the baseline reference date. Comorbidities were considered at baseline similar to previous studies (23), the authors define time of diagnosis within 3 years prior and up to 6 months after initial reference baseline diagnosis. As in previous studies, this was to avoid left censoring, accounting for patients already diagnosed and on therapy and not repeatedly coded longitudinally as a new onset diagnosis or therapy at baseline. End of follow-up was defined as the last episode entered for a diagnosis, therapy, relevant associated clinical episode or transfer out of practice reasons (including death). Similarly, time

to unhealthy outcome indicates the time to either acquire a comorbidity code or be started on a regular relevant therapy prodcodes.

Time to final outcome, unhealthy outcome or final follow-up was limited to patients followed up after 1987 (i.e. the start of CPRD database collection nationwide).

Statistical Analysis

Data was prepared and analysed using the Statistical Package for Social Sciences (SPSS) [IBM Statistics version 24 SPSS Inc., (New York), USA]. Normally- distributed continuous outcomes were presented as means (standard deviations [SD], while non-normal variables were presented with medians and interquartile ranges [IQR]), and categorical outcomes were presented as relative frequencies (%). Significance of differences among BMI with metabolically healthy or unhealthy phenotypes were tested. A Chi-squared test was used to compare categorical variables. Student's t-test and one-way analysis of variance (ANOVA) were applied to compare between 2 groups, or more than 2 groups in case of normally distributed quantitative variables. To evaluate the factors associated with a metabolically healthy status, survival analysis was performed using unhealthiness due to metabolic comorbidities as the status and with independent variables such as gender, age categories, BMI categories, geographical region, smoking status, and bariatric surgery as well as index of multiple deprivation.

Associations and longitudinal analysis

Univariate and then multivariate analysis were undertaken to determine associations and predictors of transition into an unhealthy status. A Kaplan-Meier and Cox regression hazard analysis was implemented to assess factors associated with time to final outcomes allowing for censored cases lost to follow-up.

Ethics

Scientific approval was acquired from the Regulatory Agency's Independent Scientific Advisory Committee (ISAC), and ethical agreement was sought through the Health Research Authority IRAS Project ID: 203143. ISAC approval registration number 16_140R2.

Results

Patients extraction

The Clinical Practice Research Datalink contained 123,760,872 records for 414,522 patients that had a clinical medcode diagnosis of obesity. There were 231,399/414,522 (55.8%) actual measured BMI ≥35 Kg/m^2 recorded, and therefore initially included in our study population. After age, BMI, and weight restriction for erroneous values our cohort contained 180,560 patients. There were 155,113 patients with up to 10 years follow-up and prevalence of MHO was 64,732 (41.7%). This displays the strength of long-term follow-up on CPRD. Time to final outcome ranged between 1 and 1,088.7 months; erroneous date entry is recognised within the CPRD database and to eliminate time bias this was limited to 300 months (25 years). The final number of patients in this study included amounted to 180,560 patients.

Baseline patient characteristics:

The mean age in the study was 40.3 (SD 11.5) years and the majority of patients were in the age group 40-50 years (27.4%). There were 57,990 (32.1%) males in the cohort while 122,570 (67.9%) were females. Weight was recorded in 180,560 patients, with a mean of 108.6 (SD 17.2Kg). Recorded BMI was available for 180,560 patients with a mean of 38.8 (SD 4.5 Kg/m^2). Most of the patients were in the BMI category 35-40 Kg/m^2 (70.4%) and the BMI category with least patients was >60 Kg/m^2 (0.4%).

MHO prevalence

A comorbidity was defined as a diagnosis code and associated relevant therapy code. Hence, the authors defined metabolic health as a strict absence both of coded diagnosis of co-morbidity and of therapeutic codes for relevant medication. Therefore, the prevalence of MHO within the obese population from the CPRD was 128,191/180,560 (71.0%).

Follow-up

All obese patients were followed up until a final outcome within database to a restricted range of up to 300 months (25 years). Data was also verified for comorbidities in the entirety of their database presence; this reflected that 80.8% of patients were never diagnosed or started on treatment prior to the 3 years to first body mass index date. Overall, of those patients who were metabolically healthy at baseline, 71,485/128,191 (55.8%) remained healthy on follow-up, (Chi-square 16.0, p=<0.01) with a mean follow-up of 68.2 (SD 62.6) months. Meanwhile, of the 56,706 (44.2%) metabolically healthy at baseline recorded as comorbid on follow up: 23.8% ($p<0.01$) had one comorbidity, 11.7% ($p<0.01$) had 2 comorbidities and 20.2% ($p<0.05$) 3 comorbidities or more

on Chi square cross tabulation.

The authors constructed a life table for survival to metabolic un-healthiness and found a decreasing annual rate, from an initial 26% in the first year to a gradual decrease over the years to 7% annual cumulative incidence of developing an unhealthy state over a 10-year follow-up period, and a nearly similar rate when performed over a 30-year period (table 1). Median time to transition was calculated for different age (figure 1) and BMI categories (figure 2). Further characteristics of metabolically healthy obese versus those individuals who transition to unhealthy are displayed in (table 2).

A univariate Kaplan-Meier analysis, as displayed in (table 3), was performed for BMI categories (figure 2) to unhealthy transition and was longest in the 35-40Kg/m^2 BMI group (median 114.2 months, p = <0.01), while shortest in the BMI >60Kg/m^2 (median 96.3 months, p = <0.01). Difference in gender transition was significantly reduced in males (87.9 months) compared to females (123.1 months). Smoking was associated with a reduction in disease-free period (104.8 months compared to 116.3 months, p = <0.01) in non-smokers. Regional distribution was found to vary; the longest was demonstrated in Yorkshire and the Humber, averaging 86.2 months (p = <0.01), with the shortest being in the North West of England (59.6 months, p = <0.01). Regional metabolically healthy distribution was demonstrated in (supplementary figure 1).

There were various independent factors all found to affect progressing to comorbidity significantly on univariate Cox regression hazard analysis, being: male gender (HR=1.43 CI 1.41-1.45, p = <0.01); higher age group, mostly 50-60 years (HR=4.16 CI 4.07-4.24, p=<0.01); BMI of 50-60Kg/m^2 at baseline (HR=1.28 CI 1.13-1.36, p=<0.01); and a higher index of multiple deprivation (HR=1.14 CI 1.11-1.17, p = <0.01) on univariate analysis (Kaplan-Meier analysis). Bariatric surgery (HR=0.92 CI 0.89-0.96, p = <0.01) was a significant independent protective factor from progression to unhealthy state. Being on a lipase inhibitor also had a protective factor (HR=0.89 CI 0.86-0.91, p = <0.01) against transition into an unhealthy state.

A multivariate analysis Cox hazard regression model was performed using the significant univariate factors which also confirmed significant variables affecting transition to unhealthy outcome on follow-up as demonstrated in (table 4).

Mortality

Overall, there was an 8,534/180,560 (4.7%) all-cause mortality rate documented within the CPRD for our cohort. A Kaplan-Meier survival curve was constructed (supplementary figure 2). When compared, the all-cause

mortality for the metabolically healthy obese was 4,795/128,191 (3.7%) versus 3,739/52,369 (7.1%) in the non-metabolically healthy obese. The overall mean time from baseline diagnosis to mortality was 64.47 (SD 33.71) months.

Discussion

Long-term outcomes of being metabolically healthy obese remain controversial. Dispute surrounds how the MHO state should be considered and its relevant practical implications for managing this in the obese population. It is unclear whether patients with MHO are simply in a temporary state that will later convert to metabolically unhealthy obesity, or whether they are actually in some way genetically able to function without still developing the sequelae that are generally observed in obese patients. This is an important distinction for clinicians, as it may have implications for early intervention, how aggressively weight loss is followed up, and how long-term risks of excess weight are specifically outlined for these individuals. Some studies have demonstrated that MHO individuals are at diminished prospect of developing cardiovascular disease compared with the unhealthy obese individuals (24), and not at increased risk when compared to metabolically healthy normal weight individuals (6,12). In an 11-year follow-up study, Meigs et al. established that MHO was associated with a 3- to 4-fold risk to develop Type 2 Diabetes Mellitus (T2DM) or cardiovascular disease events, accounting for 2-3% of these events in the population (12). The strongest predictor of both MHO and MUO was previously reported as baseline BMI (25). This was also demonstrated in our study on univariate and multivariate analysis, reflecting the higher BMI category predicted a quicker transition to comorbidity and metabolic syndrome. The overall risk of transition to metabolic comorbidities on medium to long-term follow-up was increased in our study and there was found to be a steady decrease in metabolically healthy prevalence annually (table 1).

An American longitudinal study similarly reported two-thirds of healthy obese individuals, during 10 years of follow-up, established metabolic syndrome(26). From 10 years within the Pizarra study, 42% of their subjects with MHO developed the metabolic syndrome within 10 years in the Pizarra Study and highlighted a decreasing prevalence of MHO in 11 years of subsequent surveillance (27). Another cohort reported 42% of their subjects with MHO developed the metabolic syndrome within 10 years (28). The authors of this study report an initial prevalence of 71%, of which 55.8% of remained healthy on long-term follow-up. All obese patients were followed up until a final outcome within database to a restricted range of up to 300 months (25 years) which

remains the longest follow-up period in UK published literature from a long-term primary care follow-up. A recent published study from the larger European Prospective Investigation into Cancer and Nutrition concluded that those in the metabolically healthy group were at greater risk of coronary heart disease (29). Lassale et al. reported a 12-year follow-up to a European population study, however the authors could not monitor the evolution of the subjects' metabolic health along time. This study also reports the steady metabolic progression on a cohort followed up through long-term community monitoring. It was quite apparent that there was a steady decline in metabolic health annually; this was demonstrated at a steady rate ranging between 5-9% annually. This does suggest, despite the limitations of this large clinical database perhaps, that metabolic health in the presence of obesity is impermanent To the author's knowledge, this has not been reported in the literature on such a large obese population in the UK.

This data is from a unique large UK clinical community database, interrogating longitudinal outcomes of the metabolically healthy obese by use of the established criteria. The results are original to the UK and the CPRD extends over a period from 1987-2016, which provides a large coverage representative of the UK population as reported previously by Campbell et al. (30).

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These results suggest that there is a reasonably steady transition into an unhealthy state as years go by; nevertheless, maintaining a healthy state can possibly be prolonged by regular weight and BMI measurements, weight control advice, early obesity intervention, and rigorous follow-up. This is supported by the longer median duration to transition in the lower BMI group (35-40Kg/m^2). The data demonstrates that the presence of metabolic risk identifies BMI and age sub-phenotypes, amongst other predictors, to progression to an unhealthy state. These predictors were: male gender, a higher baseline BMI category and age category, a higher index of multiple deprivation, and smoking. Population-based data on the prevalence within various BMI sub-phenotypes are few, and different definitions for metabolic risk allow only indirect comparisons.

Limitations

The CPRD, despite benefiting from the analysis of a large population is still subject to limitations. Any analysis from a database relies upon correct and timely coding of all clinical parameters. This may not be possible to confirm on an individual patient basis. Nevertheless, the analysis was not subject to selection bias as all included patients are derived from a databank that was previously validated as expressive of the national population (28).

Physically inputted data into the patient record may sometimes be incomplete (eg. dates, diagnoses, tests performed, length of stay). However, the variability in completeness of data is possible; restriction to those with complete data may result in biased analyses (31,32). The authors were aware that the CPRD data files contain millions of rows on a statistical package for data handling, requiring extensive data management and an in-depth appreciation of how such large databases are archived and processed for purpose of research.

The CPRD is a vast international statistical and epidemiological mean of research and has witnessed large number of publications in peer-reviewed journals across a broad range of health outcomes. However, academics must be cautious of the complexity of routinely collected electronic health records, including ways to manage variable completeness, misclassification, and development of disease definitions for research.

Conclusion

Our study proves that metabolic health status is a relatively stable condition with a steady annual decline. Around half of these entities will progressively transition into unhealthy status on long-term follow-up. This large population analysis of obese patients concludes that the UK population is prevalently metabolically healthy. Being female, aged 30-40 years at baseline, of a lower BMI category, lower index of multiple deprivation, a non-smoker, free of any other associated comorbidities at baseline, and being on lipase inhibitors decreases the relative risk of transitioning into an unhealthy state.

'Supplementary information is available at IJO's website'

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Figures

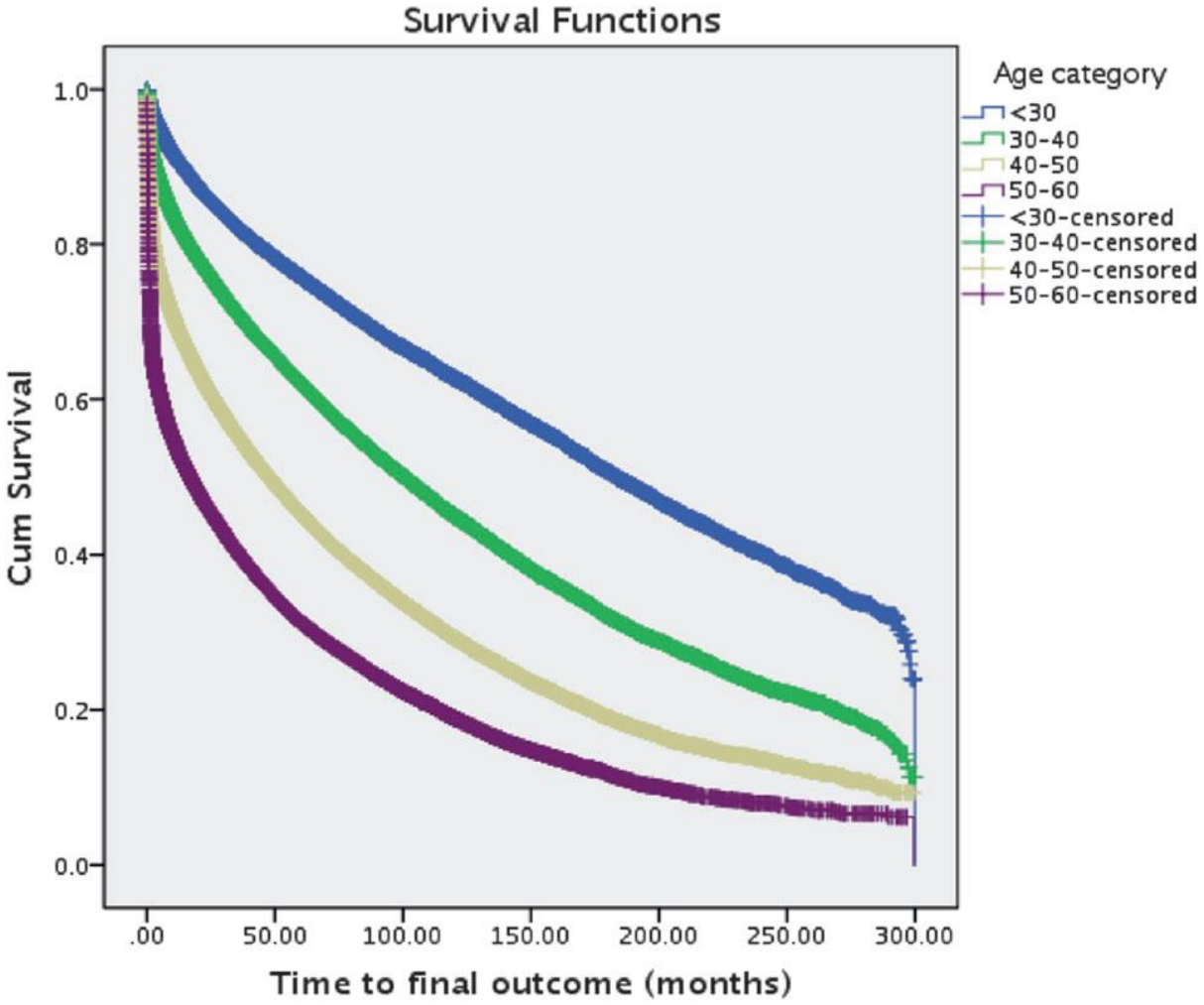


Figure 1. Kaplan-Meier Time to healthy survival without comorbidities for the categorised age category (Time to survival without comorbidity used throughout the manuscript indicates the time longitudinally to either acquire a comorbidity code or be started on a relevant therapy prodcodes)

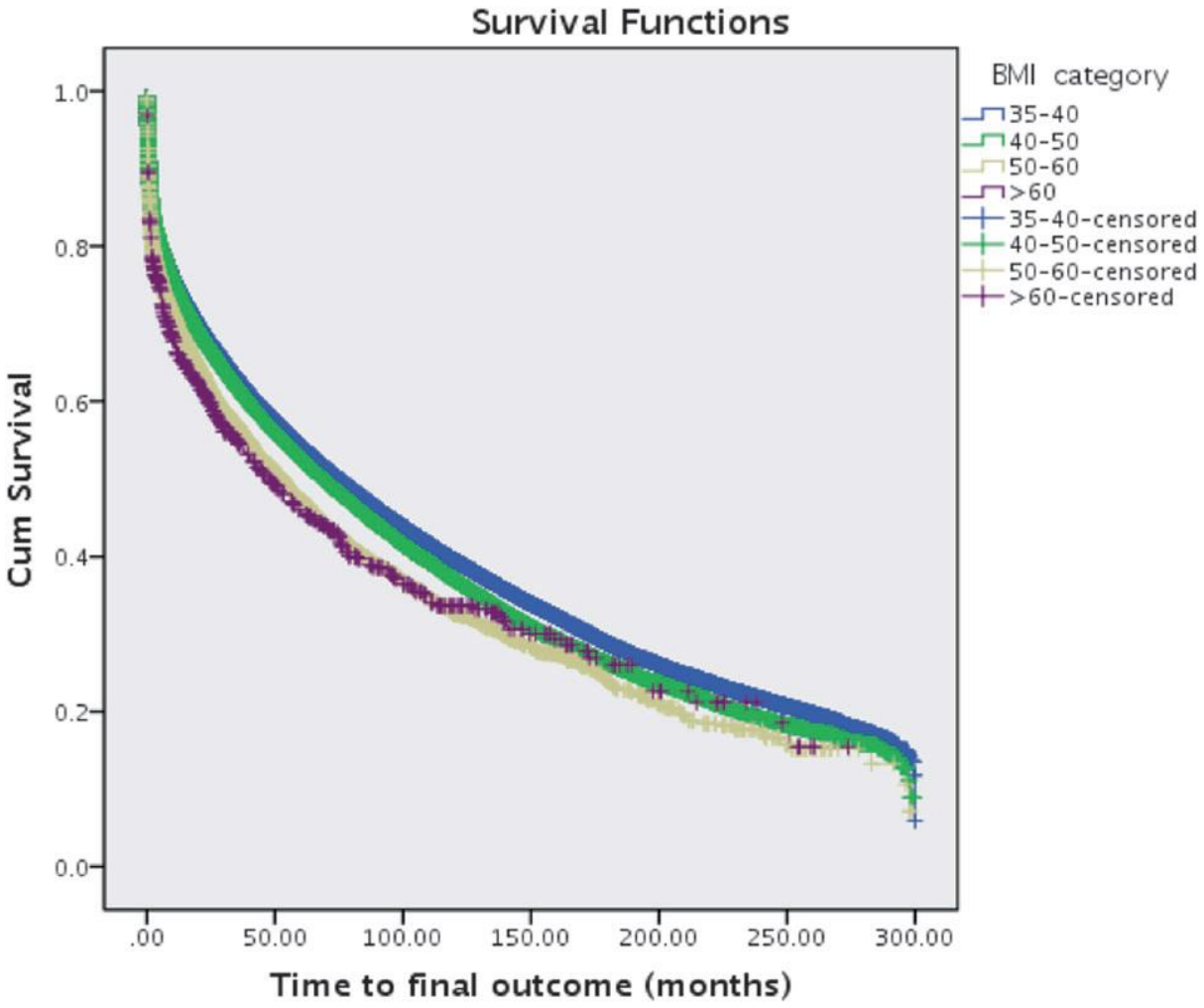
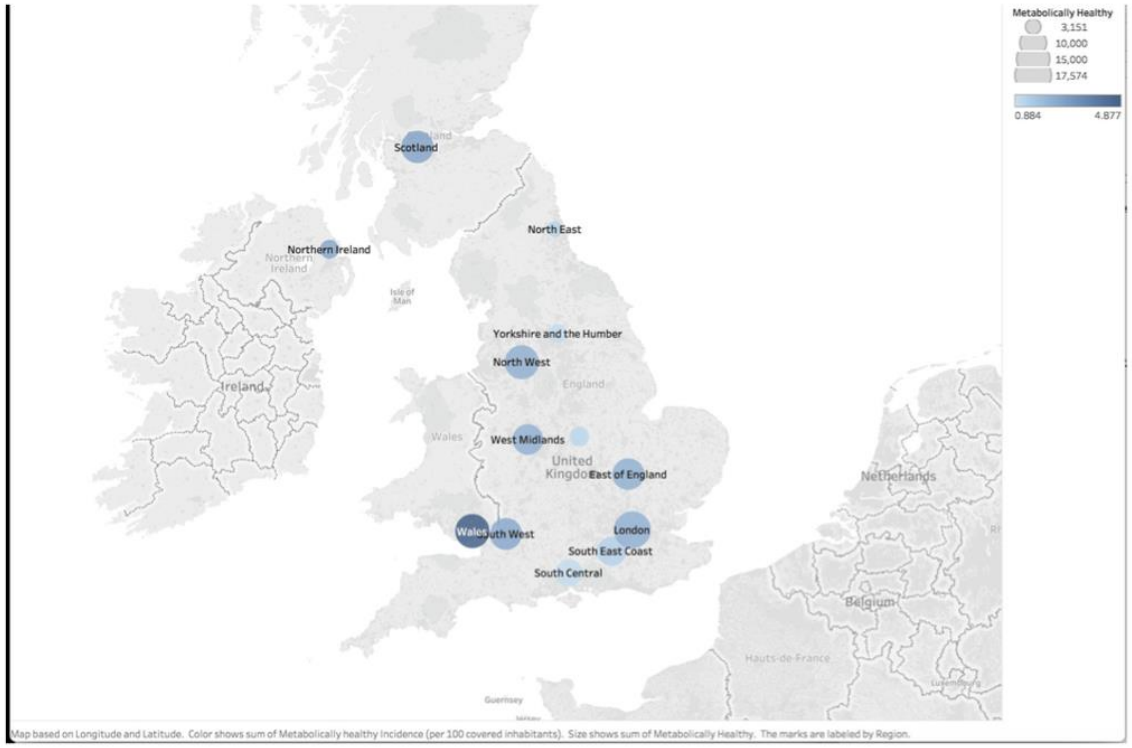


Figure 2. Kaplan-Meier Time to healthy survival without comorbidities for BMI category (Time to survival without comorbidity used throughout the manuscript indicates the time longitudinally to either acquire a comorbidity code or be started on a relevant therapy prodcodes)

Supplementary Figure 1. Map region distribution of prevalence of metabolically healthy obesity within UK



Supplementary Figure 2. Kaplan Meir survival curve to death (months) within the Metabolically Healthy Obese after initial diagnosis