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he Relationship of Body Mass Index to Percutaneous Coronary Intervention Outcomes: Does the Obesity Paradox Exist in Contemporary Percutaneous Coronary Intervention Cohorts? Insights From the British Cardiovascular Intervention Society Registry.

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The relationship of body mass index to percutaneous coronary intervention outcomes: Does the obesity paradox exist in contemporary PCI cohorts? Insights from the British Cardiovascular Intervention Society registry.

Running Title: Relationship of BMI to PCI outcome

Authors: Eric W Holroyd[1] MD*, Alex Sirker[2] MB BChir*, Chun Shing Kwok[1,3] MBBS MSc BSc*, Evangelos Kontopantelis[4] PhD, Peter F Ludman[5] MD, Mark A. De Belder[6] MD, Robert Butler[1] MD, James Cotton[7] PhD, Azfar Zaman[8] PhD, Mamas A. Mamas[1,3] DPhil On behalf of the British Cardiovascular Interventional Society and National Institute of Cardiovascular Outcomes Research.

1. Academic Department of Cardiology, Royal Stoke Hospital, University Hospital of North Midlands, Stoke-on-Trent, UK.
2. Department of Cardiology, University College London Hospitals and St. Bartholomew's Hospital, London, UK.
3. Keele Cardiovascular Research Group, Institute of Applied Clinical Science, Keele University, Stoke-on-Trent, UK.
4. Institute of Population Health, University of Manchester, Manchester, UK.
5. Queen Elizabeth Hospital, University Hospital of Birmingham, Birmingham, UK.
6. The James Cook University Hospital, Middlesbrough, UK.
7. Department of Cardiology, The Heart and Lung Centre, The Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK.
8. Freeman Hospital and Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK.

* Joint first authors having contributed equally to manuscript

Corresponding Author:
Professor Mamas A. Mamas
Keele Cardiovascular Research Group
Institute of Applied Clinical Science
Keele University, Stoke-on-Trent,
United Kingdom, ST4 7QB
Email: mamasmamas1@yahoo.co.uk

Tel: +44 1782671652
Fax: +44 1782674467
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Abstract

Objectives: To examine the relationship between BMI and clinical outcomes following percutaneous coronary intervention (PCI) in contemporary UK practice and to determine the relevance of different clinical presentations requiring PCI on this relationship.

Background: Prior studies have identified more favourable outcomes following PCI in obese patients, the so-called 'obesity paradox'. This effect has been variously attributed to differences in comorbidities, procedural techniques or other aspects of clinical care, compared to non-obese patient groups. Another potential explanation is a genuine protective effect some how conferred by obesity. However, the finding of an obesity paradox with PCI has not been consistent across published series.

Methods: To re-examine this issue, we undertook multivariable analysis using data from the comprehensive UK national PCI registry, spanning a recent 9-year period.

Results: At 30 days post-PCI, significantly lower mortality was seen in patients with elevated BMI. However, after multivariable adjustment for confounding factors, this relationship was no longer significant for obese patients but remained so in overweight patients. At 1 year post-PCI, and up to 5 years post-PCI, elevated BMI (either overweight or obese) was an independent predictor of greater survival compared to normal weight. Major periprocedural bleeding was less common in overweight and obese patients.

Conclusions: A paradox regarding the independent association of elevated BMI to reduced short and long term mortality after PCI is still evident in contemporary UK practice. This is seen in both stable and more acute clinical settings. Factors underlying this phenomenon remain uncertain and controversial.

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Introduction

Obesity is a growing ~~international~~worldwide health concern. In the United States, recent data indicate that more than one third of adults, and around one in five children or adolescents, are obese.[1,2] The estimated cost of obesity in the US was $147 billion in 2008, based on Center of Disease Control and Prevention data.[3] Obesity predicts coronary artery disease and premature death,[4,5] and it is estimated that obese non-smokers lose up to 7 years of life expectancy compared to normal weight non-smokers.[6]

Notwithstanding these statistics, multiple studies have demonstrated an apparently protective effect from obesity, compared to a 'normal' BMI, when considering in-hospital and even longer-term clinical endpoints.[7] This so-called 'obesity paradox' has been noted in various settings but was first described in the context of PCI outcomes by Ellis *et al,*[8] who noted a decreased risk of in-hospital mortality associated with a BMI of 26-34 compared to levels greater or lower than this. Subsequent work by Gruberg and colleagues,[9] looking at over 9000 consecutive PCIs between 1994 and 1999 in their centre, grouped patients as normal BMI (18.5-25), overweight (25-30) or obese (>30) - they observed that obese patients were, on average, younger and had a higher incidence of cardiac risk factors, including hypertension, diabetes, high cholesterol and smoking. There was no difference in PCI acute procedural success between BMI groups in their study. However, obese patients had fewer complications and lower in-hospital and 1-year mortality, ~~-~~and BMI ~~was~~ was an independent predictor of favourable clinical outcomes. Several other published studies have supported this association,[10,11,12,13] including a meta-analysis combining outcomes at 1-5 years from 5 separate studies.[Oreopoulos 2008] However, there have been some conflicting results from other work[14,15,16] which did not identify this survival paradox.

The largest single study in this field retrospectively analysed 50,149 STEMI patients from the US National Cardiovascular Data Registry (NCDR).[17] It demonstrated a 'U-shaped'

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curve relationship between obesity and outcome in unadjusted analyses, with an 'obesity paradox' benefit for overweight and obese patients but a detrimental outcome in the extreme, class III obese (BMI>40). However, when confounding variables were taken into account, the obesity paradox (obese vs. normal BMI) for in-hospital mortality was eliminated, although there remained an increased propensity for major bleeding in both normal weight patients and class III obese BMI, compared to class 1 obese (BMI 30-35).[Das 2011] Elsewhere, there are very limited data on whether the relationship of PCI outcome to obesity is similar across the different indications for PCI (i.e. STEMI, NSTEMI and stable angina)[18] and here again, discordant findings have resulted in uncertainty.

We ~~have therefore~~ analysed contemporary UK PCI ~~practice~~data from an unselected ~~and comprehensive~~ national cohort, derived from the British Cardiovascular Interventional Society (BCIS) database, between 2005 and 2013.~~-~~ Our aim was to ~~to determine whether an~~explore the 'obesity paradox'~~ was evident~~following PCI~~, in the shorter or longer term, for major clinical outcomes after PCI~~. We also ~~investigated whether there were~~analysed differences in the relationship of obesity to outcomes based on the clinical indication for PCI.

Methods

We analyzed PCI data collected by the British Cardiovascular Intervention Society (BCIS). The data was collected via the Central Cardiac Audit Database (CCAD) which is managed by the National Institute of Cardiovascular Outcomes Research (NICOR). This dataset records PCI procedures performed in all UK hospitals. In 2012, the database contained 99.4% of all PCI procedures performed in the National Health Service (NHS) hospitals in England and Wales (web reference www.bcis.org.uk).

The BCIS-NICOR database records clinical, procedural and outcome information with a total of 113 variables. Mortality information was collected by the Medical Research Information Service (MRIS) using patients' unique National Health Service (NHS) numbers and linkage via these to UK Government mortality records in England and Wales.[19,20,21] For participants from Scotland or Northern Ireland, such mortality tracking was not possible so these patients were excluded from mortality analysis here.

We analyzed all patients who underwent PCI in England and Wales between 1 January 2005 to 31 December 2013 with values for body mass index (BMI) and mortality outcomes ~~followed them up for~~at 30-days and 1 year~~ post-PCI mortality outcomes~~. Patients were classified according to BMI groups: BMI <18.5 kg/m^2, BMI 18.5-24.9 kg/m^2, BMI 25.0-30.0 kg/m^2 and BMI >30 kg/m^2. The main outcomes were 30-day mortality, 1-year mortality, major adverse cardiovascular events (MACE) and major bleeding. MACE was defined as the composite of in-hospital re-infarction, re-PCI, emergency CABG and in hospital mortality.

Statistical analysis

Statistical analysis was performed using Stata v13.1 (College Station, Texas, USA). To account for missing data among included patients, we used the *mi impute* procedure to perform multiple imputation using chained equations and generate 10 datasets. Across the two groups, we used one-way analysis of variance and chi-square tests to compare continuous and categorical variables, respectively. Multiple imputation logistic regressions (*mi estimate: logistic*) were used to calculate crude and adjusted odds of 30-day mortality according to BMI group. Data was adjusted for age, gender, year, race, smoking, family history of coronary artery disease, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous myocardial infarction (MI), previous stroke, valvular heart disease, renal disease, previous PCI, previous coronary artery bypass surgery (CABG), left ventricular ejection fraction (LVEF), receipt of ventilation, receipt of circulatory support, cardiogenic shock, left main intervention, use of drug eluting stents, radial access, glycoprotein IIb/IIIa inhibitor use and diagnosis. We also performed the analysis stratifying by the diagnosis (stable angina, NSTEMI or STEMI). As a sensitivity analysis, and to better control for the baseline differences across the groups, we used an inverse probability treatment weighting approach: firstly, we calculated propensity scores for all binary BMI combinations we investigated: BMI 25-30 kg/m^2 vs BMI 18.5-24.9 kg/m^2, BMI >30 kg/m^{2}vs BMI 18.5-24.9 kg/m^2 and BMI <18.5 kg/m^2 vs BMI 18.5-24.9 kg/m^2. The inverse of the propensity scores were used as probability weights in multiple imputation logistic regressions where only the respective treatment was included as a predictor. We conducted a sensitivity analysis considering risk of adverse outcomes for different grades of patients who had BMI >30 (BMI 30.0-34.9 kg/m^2, BMI 35.0-39.9 kg/m^2 and BMI ≥40 kg/m^2).

Results

A flow diagram showing ~~the~~ participant inclusion is given in **Figure 1**. The extent of available and missing data is shown in **Supplementary Table 1**.

The proportion of patients undergoing PCI who ~~are~~were obese from 2005 to 2013.

The percentage of participants with a BMI >30kg/m^2 rose modestly from 30% in 2005 to 32% in 2013 (**Figure 2**).

Baseline clinical characteristics, periprocedural factors and unadjusted outcomes.

Between 2005 to 2013, there ~~are~~were 345,192 records in the BCIS database with data for BMI for patients who underwent PCI procedures ~~in England and Wales~~. **Table 1** presents ~~their~~ baseline characteristics, divided by BMI into four groups as defined by the ~~w~~WHO~~orld health organisation~~: lean BMI <18.5kg/m^2, normal BMI 18.5-24.9 kg/m^2, overweight BMI 25-30 kg/m^2 and obese BMI >30 kg/m^2. We compared characteristics in each group. Obese patients were, as a group, significantly younger ($p<0.001$) compared to other groups. Obese patients, when compared to normal BMI patients, were more often smokers (66% c.f. 63%, $p<0.001$) and had features of the metabolic syndrome associated with obesity, namely hypertension (62% c.f. 49%, $p<0.001$), hypercholesterolaemia (61% c.f. 53%, $p<0.001$) and diabetes (29% c.f. 13%, $p<0.001$). Left ventricular ejection fraction was more likely to be good in obese patients prior to starting the procedure (76% had good LV function c.f. 72% of normal BMI patients). Radial access was more commonly used in obese patients (48% c.f. 44% in normal BMI, $p<0.001$) but there was no significant difference in the proportion receiving drug eluting stents. In lean BMI patients, a higher proportion of PCI's were performed for STEMI compared to PCIs in obese patients (24% c.f. 12%, $p<0.001$).

Conversely, a greater proportion of PCIs in obese patients were performed for stable angina compared to lean BMI patients (52% c.f. 30%, p<0.001).

Lean patients (BMI <18.5 kg/m^2) were significantly older, less likely to be male (46% c.f. 71%), tended to have a poorer starting left ventricular function (67% had good LV c.f. 72%), less radial access use (41% c.f. 44%) and less frequent treatment with drug eluting stents (66% c.f. 69%) compared to normal BMI patients.

Unadjusted crude mortality suggested the presence of an obesity paradox with better survival in obese patients, and this relationship was more evident at longer follow up timeframes. Crude 30-day mortality was 1% in the obese, compared to 2% in patients with normal BMI and 4% in the lean (p<0.001). At one year, mortality in the obese was 3%, compared to 6% in patients with normal BMI and 14% in the lean (p<0.001). At 5 years, crude mortality is 19% in the obese, 28% in normal BMI and 53% in the lean (p<0.001).

Statistical analysis of adverse outcome according to BMI group.

Statistical multivariable analysis of outcome data at between 30 days and 5 years post-PCI is presented in **Table 2.** At 30 days, the unadjusted odds ratio in the obese group was 0.49, compared to 1 in normal BMI and 1.68 in lean patients (p<0.001). After adjusting for the factors above, the odds of 30-day mortality remained significantly decreased in both the BMI 25-30 (OR 0.86; 95% CI 0.80-0.93, P=0.001) and BMI>30 (OR 0.90; 95% CI 0.82-0.98, P=0.016) groups but did not reach statistical significance in the BMI <18.5 group (OR 1.23; 95% CI 0.98-1.54, P=0.077). Similar observations were recorded at 1–year with independent decreases in the odds of mortality in the BMI 25-30 (OR 0.70; 95% CI 0.67-0.73, P<0.001) and BMI >30 (OR 0.73; 95% CI 0.69-0.77, P<0.001) groups, and independent increases in odds of mortality for the BMI <18.5 group (OR 1.85; 95% CI 1.63-2.10, P<0.001). Similar trends were recorded at 3 years and 5 years.

In-hospital major adverse cardiac events (MACE) were more likely in the crude, unadjusted data with rising BMI (odds ratio of 0.68 c.f. 1 in normal BMI and 1.24 in lean patients). After adjustments for differences in baseline covariates, the effect of BMI on MACE events was no longer significant. The odds for in-hospital bleeding complications were significantly less in obese patients following multivariate analysis compared to normal BMI and lean patients (0.87 c.f. 1 c.f. 1.24, $p<0.001$).

Adjusted odds of adverse outcome in obese patients depending on clinical syndrome.

We then ~~split~~divided the recorded PCI data ~~into~~based on clinical presentation~~syndrome~~, i.e. stable angina, non-ST elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI), to ~~determine if there was~~ examine the differential effect of BMI according to ~~the~~PCI indication ~~for the PCI~~ (**Table 3**). Multivariable regression analysis yielded similar results to the overall PCI data. 30-day mortality was lower with higher BMI in stable angina, NSTEMI and STEMI but this effect was no longer significant after statistical adjustment in the STEMI group. At 1 year, 3 years and 5 years, the odds of mortality in patients with obesity was significantly less than in patients with normal BMI in PCIs for stable angina, NSTEMI and STEMI. Similarly, in ~~L~~lean patients (BMI<18.5) the odds for mortality were significantly increased at ~~the~~ 1, 3 and 5 years ~~timepoints~~. There were significantly fewer in hospital bleeds in obese patients compared to normal and lean patients in all three clinical syndromes, an effect that remained significant even after statistical adjustment.

Inverse probability weighting by propensity scores analysis of adverse outcomes and BMI.

Inverse probability weighting (by propensity scores) analysis of adverse outcomes directly comparing different BMI groups is shown in **Table 4**. Using this method of analysis, both overweight and obese groups are seen to have a significantly lower odds of mortality than the normal BMI group at all studied time points (30 days out to 5 years), whilst the lean group had an increased odds of mortality at 1 year, 3 years and 5 years.

Sensitivity analysis considering patients with BMI ≥30 kg/m^2 compared to those with normal BMI

Supplementary Table 2 shows the risk of adverse outcomes among participants with BMI ≥30 kg/m^2 by BMI group. Unadjusted estimates suggest that participants in all elevated BMI groups have lower odds mortality, MACE and bleeding compared to normal BMI controls. However, after adjustment it appears that participants with BMI ≥40 kg/m^2 have no significant difference in the odds of in-hospital MACE, in-hospital major bleeding or 5-year mortality,

Discussion

~~To our knowledge, this is the by far~~ Our data shows significant differences in short, medium and long-term mortality independently associated with baseline BMI group –greater survival being seen in patients classified as overweight (BMI 25-30) or obese (BMI>30), as opposed to having normal BMI (BMI 18.5-24.9) at the time of PCI. ~~largest study to date examining the relationship between BMI and PCI outcomes, and also the first to analyse outcomes with respect to clinical indication for the PCI. We identified significant differences in short, medium and long-term mortality independently associated with baseline BMI group –greater survival being seen in those patients classified as overweight (BMI 25-30) or obese (BMI>30), as opposed to having normal BMI (BMI 18.5-24.9) at the time of PCI.~~ In patients with BMI<18.5, worse clinical outcomes were observed both in the short and longer term.

This significant effect persisted (albeit with reduced magnitude) even after adjustment for multiple potential confounding~~s~~ factors, as described. Furthermore, there was overall consistency between the findings from our main analysis, using multivariable logistic regression, and the alternate methodology using inverse probability weighting by propensity scores. The very large patient numbers involved also allowed us to undertake a meaningful subgroup analysis based on clinical presentation - here too a consistent pattern of findings was seen with better outcomes observed in overweight patients and worse outcomes recorded in those with a BMI<18.5, even after adjustment for differences in baseline covariates.

Our study findings are consistent with ~~the~~ results from two recent systematic reviews and meta-analyses of the published literature for outcomes based on BMI after coronary revascularisation.[22,23] Those studies involved 91,582 patients (in whom detailed medication use data were available) and 242,377 patients respectively, and hence each was significantly smaller than our cohort, in whom 30 day post-PCI mortality data were available in over 350,000 patients. The findings also are consistent with those of a recent meta-analysis of over 1.3 million patients that re-examined the link between mortality and BMI in coronary artery disease patients (not restricted solely to a PCI or revascularisation setting).[24] This too found short and long term mortality advantages for overweight or obese groups compared to normal BMI patients.

~~Having demonstrated the persistence of this~~ The confirmation of a BMI paradox (for overweight and obese patients) in ~~our~~this large contemporary PCI population~~,~~ raises questions~~ as to its origin and implications naturally arise. With regard to its origin, the first concern must relate to~~ about potential unrecognized confounders, for which adjustment has not been made in our analysis. This is a feature common to all registry-based studies. For our BCIS cohort ~~here~~, 3 specific aspects are recognized as limitations. First~~ly~~, there is only limited recording of other (non-cardiac) comorbidities, which are ~~of course~~ pertinent to

mortality at all-time points post-PCI.[2526] Second~~ly~~, we do not have access to accurate recording of guideline-recommended medical therapy use for these patients. Differences in their use would ~~of course~~ potentially impact on clinical outcomes and recent published work confirms that this may explain some, although seemingly not all, of the observed obesity paradox.[Tan] Third~~ly~~, overall frailty (as distinct from known documented 'comorbidity') is another facet of clinical assessment recognized as being difficult to capture accurately on datasets, including ours.

With regard to this last point, weight loss may, ~~of course,~~ be a manifestation of (identified or unidentified) pre-existing ill health due to numerous conditions~~, including~~such as heart failure~~,~~ or malignancy ~~etc.~~which ~~I~~in its most marked form, ~~this~~ may present as cachexia. Inclusion of such patients in the 'low BMI' group will ~~doubtless~~ contribute to a higher rate of adverse clinical outcomes ~~in this group,~~ compared to those with greater BMI.[Anker] By extension, some of those in the 'normal weight' group may likewise have experienced prior weight loss due to comorbidity. However, the very large patient numbers involved in our study should ameliorate the impact from such an influence, since 'hitherto healthy' normal weight patients are likely to account for the majority of patients in this BMI grouping.

A separate, more relevant ~~issue~~ however, ~~likely to be more pertinent here~~, is the acknowledged limitation of BMI as a measure of obesity. Important additive prognostic information comes from knowledge of fat distribution, with a recognized detriment~~i~~al impact from 'central obesity[27]. Relevant data, such as waist circumference, are not available in the BCIS dataset. Hence, it is not possible to identify those who would fall into the category of 'normal weight central obesity' in order to refine our group classification system beyond BMI alone. Whether this would change our key findings is currently unknown.

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Is it possible to look at an analysis that excludes (for example) BMI<15 so that the likelihood of excluding those with cachexia is increased?
Just a thought…rather than an action point

In considering other explanations for our key study findings on mortality, we note that retrospectively recorded in-hospital major bleeding complications were lower in overweight and obese patients, and with bleeding independently associated with worse short and longer term mortality outcomes (Kwok open Heart 2014, Kwok Circ Intv 2014). ~~We recognize that there may be a degree of under recording of bleeding on the BCIS database (in comparison to very robust linkage to mortality data) making firm conclusions harder to draw here.~~ A reduction in bleeding is likely driven to some extent by higher rates of radial access in patients with greater BMI. However other potential mechanisms for bleeding differences between BMI groups include appropriate dosing of peri-PCI anticoagulant therapy and differences in sheath-to-artery ratios.[Akin review]

Finally, when trying to interpret our findings, consideration should be given to evidence of potentially protective effects from adipose tissue itself in various post-operative and post-procedural settings. Adipose tissue is important in the production of various hormones and cytokines including tissue necrosis factor, adiponectin and leptin.[28] Whether these factors or others may be involved in the protective mechanisms against PCI-related complications is unclear.[29] Some experimental models indicate a protective effect of obesity against ischaemia-reperfusion injury: for example, a hyperphagia-induced obese rat model has been shown to have smaller infarcts and improved functional recovery following reperfusion, with increased signalling shown in the reperfusion injury salvage kinase pathway (RISK).[30] Obesity-inducing diets in rats (sucrose-supplemented or a high fat diet) have also been shown to be cardioprotective.[31] Harvested hearts were less susceptible to ischaemia-reperfusion injury and had smaller infarct sizes, an effect not due to RISK signalling. Whilst a role for such pathways in influencing clinical outcomes is plausible in acute presentations (particularly ST elevation myocardial infarction)~~,~~ their relevance to PCI in ~~more~~ stable settings is questionable. ~~seems much less likely.~~Nevertheless, our confirmation of earlier

studies demonstrating a "BMI paradox" should provide support for mechanistic studies to explore this observation.

Conclusions

In this largest study to date examining the relationship between BMI and PCI outcomes, ~~A~~an obesity paradox is still evident in contemporary PCI. ~~from UK national data and t~~This ~~is~~paradox is encountered with PCI in both stable coronary disease and in more acute clinical situations. Factors underlying this phenomenon remain uncertain and controversial and this study provides support for further exploration.

Acknowledgments

Funding

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Table 1: Descriptive statistics

Variable	BMI <18.5kg/m^2 (n=3,007)	BMI 18.5-24.9 kg/m^2 (n=87,279)	BMI 25-30 kg/m^2 (n=146,517)	BMI >30 kg/m^2 (n=108,190)	p-value
Age	69.6 (±12.7)	67.1 (±12.0)	64.8 (±11.3)	62.4 (±10.9)	<0.001
Male gender	1,368/2,996 (46%)	61,398/86,873 (71%)	114,697/145,786 (79%)	77,805/107,677 (72%)	<0.001
Country					<0.001
England	2845 (95%)	82,431 (94%)	137,586 (94%)	100,983 (93%)	
Wales	163 (5%)	4,889 (6%)	9,005 (6%)	7,250 (7%)	
Year					<0.001
2005	155 (5%)	5,217 (6%)	9,399 (6%)	6,374 (6%)	
2006	214 (7%)	7,724 (9%)	12,359 (8%)	8641 (8%)	
2007	243 (8%)	8,936 (10%)	14,615 (10%)	10,553 (10%)	
2008	321 (11%)	9,605 (11%)	16,615 (11%)	12,361 (11%)	
2009	379 (13%)	10,318 (12%)	17,588 (12%)	12,910 (12%)	
2010	388 (13%)	10,854 (12%)	18,779 (13%)	13,902 (13%)	
2011	447 (15%)	11,114 (13%)	18,459 (13%)	13,904 (13%)	
2012	389 (13%)	11,142 (13%)	18,867 (13%)	14,075 (13%)	
2013	472 (16%)	12,410 (14%)	19,910 (14%)	15,513 (14%)	
Race					<0.001
Caucasian	2,015 (86%)	58,708 (85%)	99,096 (86%)	73,923 (88%)	
Black	18 (1%)	516 (1%)	817 (1%)	640 (1%)	
Asian/Oriental	157 (7%)	5,323 (8%)	7,507 (7%)	4,220 (5%)	
Other	153 (7%)	4,346 (6%)	7,492 (7%)	5,416 (6%)	
Smoker (current/ex)	1,839/2,741 (67%)	50,039/79,364 (63%)	86,814/135,039 (64%)	66,519/100,039 (66%)	<0.001
Family history of CAD	1,012/2,644 (38%)	35,229/77,784 (45%)	65,314/131,334 (50%)	51,725/97,069 (53%)	<0.001
Hypertension	1,364/2,898 (47%)	41,509/84,480 (49%)	76,475/142,171 (54%)	64,889/105,166 (62%)	<0.001
Hypercholesterolaemia	1,360/2,898 (47%)	44,900/84,480 (53%)	81,500/142,171	64,019/105,166	<0.001

			(57%)	(61%)	
Diabetes	284/2,867 (10%)	10,666/84,134 (13%)	23,980/141,347 (17%)	30,022/104,274 (29%)	<0.001
Peripheral vascular disease	214/2,898 (7%)	4,434/84,480 (5%)	6,151/142,171 (5%)	5,071/105,166 (5%)	<0.001
Previous MI	851/2,874 (30%)	23,609/83,192 (28%)	41,224/139,505 (30%)	32,135/103,004 (31%)	<0.001
Previous stroke	137/2,898 (5%)	3,499/84,480 (4%)	5,296/142,171 (4%)	4,095/105,166 (4%)	<0.001
Valvular heart disease	81/2,898 (3%)	1,262 /84,480 (1%)	1,689/142,171 (1%)	1,130/105,166 (1%)	<0.001
Renal disease	97/2,984 (3%)	2,310/86,634 (3%)	3,222/145,421 (2%)	2,686/107,407 (3%)	<0.001
Previous PCI	515/2,925 (18%)	17,927/85,288 (21%)	33,700/143,319 (24%)	26,896/105,874 (25%)	<0.001
Previous CABG	162/2,929 (6%)	6,706/85,349 (8%)	13,374/143,089 (9%)	9,943/105,726 (9%)	<0.001
LV ejection fraction Good Moderate Poor	 954 (67%) 346 (24%) 123 (9%)	 30,713 (72%) 9,473 (22%) 2,642 (6%)	 54,742 (76%) 14,139 (20%) 3,295 (5%)	 41,160 (76%) 10,665 (20%) 2,349 (4%)	<0.001
Receipt of ventilation	28/2,766 (1%)	1,005/80,035 (1%)	1,418/133,418 (1%)	822/98,309 (1%)	<0.001
Receipt of circulatory support	79/2,837 (3%)	1,946/82,603 (2%)	2,182/137,987 (2%)	1,255/101,765 (1%)	<0.001
Cardiogenic shock	74/2,872 (3%)	1,791/83,017 (2%)	2,035/138,543 (1%)	1,148/102,193 (1%)	<0.001
Left main	127/2,895 (4%)	3,176/84,464 (4%)	4,647/141,314 (3%)	3,346/104,367 (3%)	<0.001
Use of drug eluting stents	56,140/84,621 (66%)	97,649/141,722 (69%)	71,530/104,477 (68%)	1,660/2,909 (57%)	<0.001
Radial access	1,208/2,942 (41%)	38,007/85,438 (44%)	65,562/143,257 (46%)	51,228/105,646 (48%)	<0.001
Glycoprotein IIb/IIIa inhibitor	597/2,823 (21%)	19,756/82,240 (24%)	33,021/137,244 (24%)	22,698/101,206 (22%)	<0.001
Diagnosis Stable angina NSTEMI STEMI	 842 (30%) 1,330 (47%) 678 (24%)	 33,295 (40%) 33,683 (41%) 15,528 (19%)	 66,808 (48%) 51,575 (37%) 20,172 (15%)	 53,610 (52%) 37,029 (36%) 12,145 (12%)	<0.001

30 day mortality	103/2,945 (4%)	1,817/85,595 (2%)	1,858/143,741 (1%)	1,125/106,294 (1%)	<0.001
1 year mortality	373/2,754 (14%)	5,044/80,420 (6%)	4,792/135,485 (4%)	3,137/99,673 (3%)	<0.001
3 years mortality	669/2,130 (31%)	9,035/60,473 (15%)	9,628/100,536 (10%)	6,652/73,138 (9%)	<0.001
5 years mortality	833/1,577 (53%)	11,818/42,476 (28%)	13,311/67,957 (20%)	9,317/48,705 (19%)	<0.001
MACE	84/2,938 (3%)	1,993/85,057 (2%)	2,611/142,797 (2%)	1,696/105,602 (2%)	<0.001
Bleed	91/2,938 (3%)	1,895/85,065 (2%)	2,730/142,802 (2%)	1,878/105,607 (2%)	<0.001

Table 2: Crude and adjusted odds of adverse outcome according to BMI group using imputed data

Outcome/adjustment	BMI <18.5 kg/m^2	BMI 18.5-24.9 kg/m^2	BMI 25-30 kg/m^2	BMI >30 kg/m^2
Unadjusted 30 day mortality (n=345,152) Odds ratio (95% CI) p-value	1.68 (1.38-2.06)* <0.001	1.00 (ref)	0.61 (0.57-0.65)* <0.001	0.49 (0.46-0.53)* <0.001
Adjusted 30 day mortality (n=345,152) Odds ratio (95% CI) p-value	1.23 (0.98-1.54) 0.077	1.00 (ref)	0.86 (0.80-0.93)* 0.001	0.90 (0.82-0.98) 0.016
Unadjusted 1 year mortality (n=318,332) Odds ratio (95% CI) p-value	2.34 (2.09-2.62)* <0.001	1.00 (ref)	0.55 (0.53-0.67)* <0.001	0.49 (0.46-0.51)* <0.001
Adjusted 1 year mortality (n=318,332) Odds ratio (95% CI) p-value	1.85 (1.63-2.10)* <0.001	1.00 (ref)	0.70 (0.67-0.73)* <0.001	0.73 (0.69-0.77)* <0.001
Unadjusted 3 year mortality (n=230,639) Odds ratio (95% CI) p-value	2.58 (2.32-2.86)* <0.001	1.00 (ref)	0.61 (0.59-0.64)* <0.001	0.58 (0.56-0.61)* <0.001
Adjusted 3 year mortality (n=230,639) Odds ratio (95% CI) p-value	2.18 (1.93-2.45)* <0.001	1.00 (ref)	0.75 (0.72-0.78)* <0.001	0.82 (0.78-0.85)* <0.001
Unadjusted 5 year mortality (n=145,958) Odds ratio (95% CI) p-value	2.70 (2.39-3.05)* <0.001	1.00 (ref)	0.66 (0.64-0.69)* <0.001	0.65 (0.63-0.68)* <0.001
Adjusted 5 year mortality				

(n=145,958) Odds ratio (95% CI) p-value	 2.48 (2.16-2.85)* <0.001	 1.00 (ref)	 0.78 (0.75-0.81)* <0.001	 0.88 (0.84-0.92)* <0.001
Unadjusted MACE (n=345,152) Odds ratio (95% CI) p-value	 1.24 (1.00-1.55) 0.054	 1.00 (ref)	 0.78 (0.73-0.83)* <0.001	 0.68 (0.64-0.72)* <0.001
Adjusted MACE (n=345,152) Odds ratio (95% CI) p-value	 1.02 (0.81-1.29) 0.85	 1.00 (ref)	 0.96 (0.90-1.02) 0.21	 0.95 (0.89-1.02) 0.17
Unadjusted bleed (n=345,152) Odds ratio (95% CI) p-value	 1.40 (1.13-1.73)* 0.002	 1.00 (ref)	 0.86 (0.81-0.91)* <0.001	 0.79 (0.74-0.85)* <0.001
Adjusted bleed (n=163,473) Odds ratio (95% CI) p-value	 1.24 (1.00-1.54) 0.049	 1.00 (ref)	 0.92 (0.86-0.97)* 0.005	 0.87 (0.81-0.93)* <0.001

Adjusted for age, gender, year, race, smoker, family history of CAD, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous MI, previous stroke, valvular heart disease, renal disease, previous PCI, previous CABG, lvef, receipt of ventilation, receipt of circulatory support, cardiogenic shock, left main, use of drug eluting stents, radial access, glycoprotein IIb/IIIa inhibitor use and diagnosis.

*=significant

Table 3: Adjusted odds of adverse outcome according to BMI group using imputed data according to diagnosis

Outcome	Stable angina Odds ratio (95% CI)	UA / NSTEMI Odds ratio (95% CI)	STEMI Odds ratio (95% CI)
30 day mortality			
n	163,473	130,468	50,854
BMI <18.5 kg/m^2	1.06 (0.39-2.91)	1.10 (0.76-1.59)	1.32 (0.97-1.81)
BMI 18.5-24.9 kg/m^2	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25-30 kg/m^2	0.76 (0.60-0.96)*	0.81 (0.72-0.91)*	0.94 (0.84-1.05)
BMI >30 kg/m^2	0.90 (0.70-1.16)	0.84 (0.74-0.97)*	0.95 (0.82-1.09)
1 year mortality			
n	152,330	120,057	45,619
BMI <18.5 kg/m^2	1.74 (1.27-2.39)*	1.99 (1.66-2.37)	1.69 (1.35-2.11)*
BMI 18.5-24.9 kg/m^2	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25-30 kg/m^2	0.66 (0.60-0.72)*	0.67 (0.63-0.71)*	0.79 (0.73-0.86)*
BMI >30 kg/m^2	0.71 (0.64-0.78)*	0.71 (0.66-0.77)*	0.78 (0.70-0.87)*
3 year mortality			
n	117,525	86,905	25,945
BMI <18.5 kg/m^2	2.34 (1.87-2.92)*	2.12 (1.79-2.52)*	2.07 (1.60-2.67)*
BMI 18.5-24.9 kg/m^2	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25-30 kg/m^2	0.74 (0.70-0.79)*	0.75 (0.71-0.80)*	0.76 (0.69-0.83)*
BMI >30 kg/m^2	0.81 (0.76-0.87)*	0.82 (0.77-0.87)*	0.80 (0.71-0.90)*
5 year mortality			
n	80,485	54,598	10,693
BMI <18.5 kg/m^2	2.46 (1.95-3.10)*	2.60 (2.13-3.18)*	2.12 (1.46-3.09)*
BMI 18.5-24.9 kg/m^2	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25-30 kg/m^2	0.78 (0.74-0.83)*	0.77 (0.72-0.82)*	0.82 (0.72-0.93)*
BMI >30 kg/m^2	0.88 (0.83-0.94)*	0.87 (0.81-0.93)*	0.87 (0.74-1.01)
MACE			
n	163,473	130,468	50,854
BMI <18.5 kg/m^2	0.94 (0.51-1.73)	1.14 (0.79-1.65)	0.92 (0.64-1.33)
BMI 18.5-24.9 kg/m^2	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25-30 kg/m^2	0.84 (0.75-0.95)*	0.97 (0.86-1.08)	1.08 (0.96-1.20)
BMI >30 kg/m^2	0.82 (0.72-0.93)*	0.94 (0.79-1.65)	1.12 (0.98-1.28)
Bleed			
n	163,473	130,468	50,854
BMI <18.5 kg/m^2	1.37 (0.89-2.12)	1.32 (0.95-1.84)	1.01 (0.65-1.57)
BMI 18.5-24.9 kg/m^2	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25-30 kg/m^2	0.90 (0.82-1.00)*	0.90 (0.81-0.99)*	0.99 (0.86-1.14)
BMI >30 kg/m^2	0.86 (0.77-0.95)*	0.86 (0.77-0.96)*	0.89 (0.75-1.05)

Adjusted for age, gender, year, race, smoker, family history of CAD, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous MI, previous stroke, valvular heart disease, renal disease, previous PCI, previous CABG, lvef, receipt of ventilation, receipt of circulatory support, cardiogenic shock, left main, use of drug eluting stents, radial access, glycoprotein IIb/IIIa inhibitor use and diagnosis.

*=significant

Table 4: Inverse probability weighting by propensity scores analysis of adverse outcomes and BMI group using imputed data

Outcome	BMI <18.5 kg/m^{2}vs BMI 18.5-24.9 kg/m^2	BMI 25-30 kg/m^{2}vs BMI 18.5-24.9 kg/m^2	BMI >30 kg/m^{2}vs BMI 18.5-24.9 kg/m^2
30 day mortality Odds ratio (95% CI) p-value	 1.63 (0.97-2.75) 0.065	 0.63 (0.55-0.73)* <0.001	 0.47 (0.39-0.56)* <0.001
1 year mortality Odds ratio (95% CI) p-value	 2.76 (2.11-3.61)* <0.001	 0.56 (0.52-0.61)* <0.001	 0.48 (0.43-0.53)* <0.001
3 year mortality Odds ratio (95% CI) p-value	 2.78 (2.17-3.55)* <0.001	 0.60 (0.56-0.64)* <0.001	 0.57 (0.52-0.62)* <0.001
5 year mortality Odds ratio (95% CI) p-value	 2.23 (1.66-2.98)* <0.001	 0.65 (0.61-0.70)* <0.001	 0.64 (0.58-0.69)* <0.001
MACE Odds ratio (95% CI) p-value	 1.07 (0.63-1.82) 0.80	 0.76 (0.68-0.85)* <0.001	 0.63 (0.55-0.72)* <0.001
Bleed Odds ratio (95% CI) p-value	 1.20 (0.75-1.94) 0.45	 0.83 (0.75-0.91)* <0.001	 0.75 (0.67-0.85)* <0.001

Adjusted for age, gender, year, race, smoker, family history of CAD, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous MI, previous stroke, valvular heart disease, renal disease, previous PCI, previous CABG, lvef, receipt of ventilation, receipt of circulatory support, cardiogenic shock, left main, use of drug eluting stents, radial access, glycoprotein IIb/IIIa inhibitor use and diagnosis.

*=significant

Figure 1: Flow diagram of participant inclusion

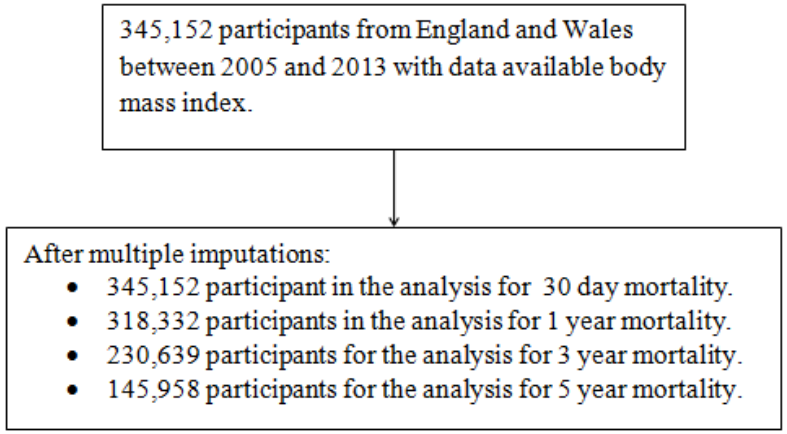
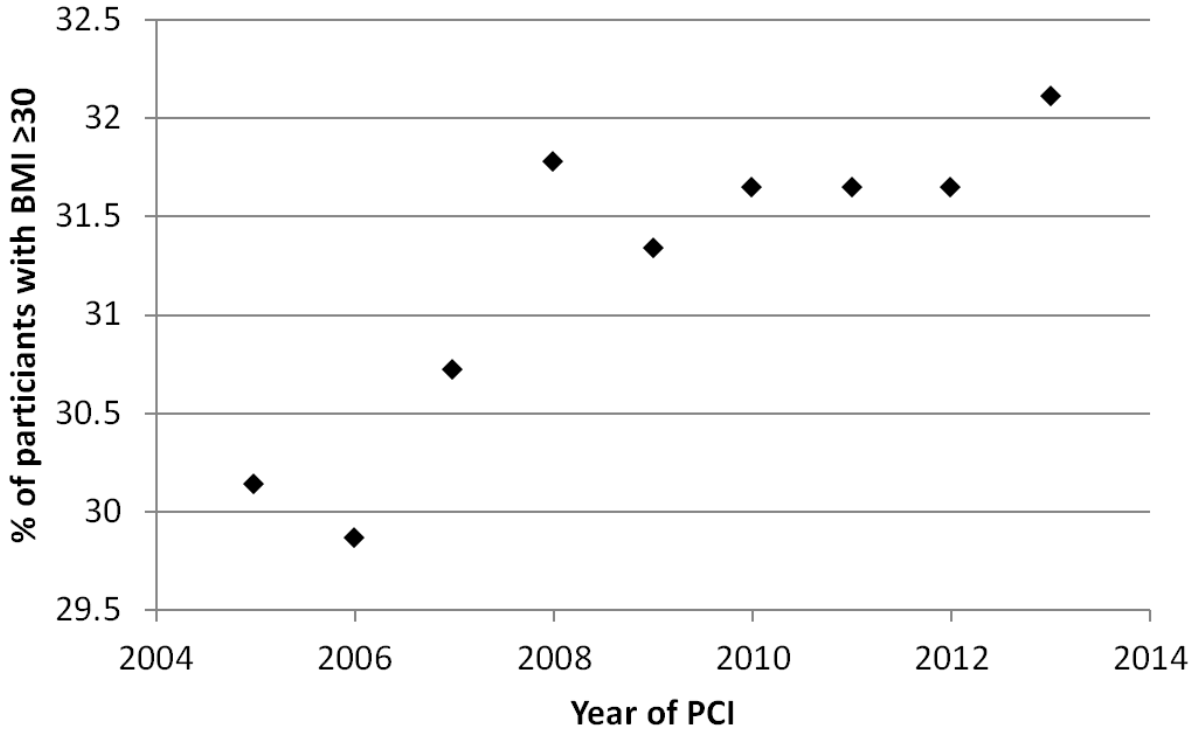


Figure 2: Percentage of participants with BMI >30 kg/m^2



Supplementary Table 1: Missing Data Table

Variable	Included	Missing
Age	344,993 (99.95%)	159 (0.05%)
Sex	343,332 (99.5%)	1,820 (0.5%)
Country	345,152 (100%)	0 (0%)
Year	345,152 (100%)	0 (0%)
Race	270,347 (78%)	74,805 (22%)
Smoker (current/ex)	317,183 (92%)	27,969 (8%)
Family history of CAD	308,831 (89%)	36,321 (11%)
Hypertension	334,715 (97%)	10,437 (3%)
Hypercholesterolaemia	334,715 (97%)	10,437 (3%)
Diabetes	332,622 (96%)	12,530 (4%)
Peripheral vascular disease	334,715 (97%)	10,437 (3%)
Previous MI	328,575 (95%)	16,577 (5%)
Previous stroke	334,715 (97%)	10,437 (3%)
Valvular heart disease	334,715 (97%)	10,437 (3%)
Renal disease	342,446 (99.2%)	2,706 (0.8%)
Previous PCI	337,406 (98%)	7,746 (2%)
Previous CABG	337,093 (98%)	8,059 (2%)
LV ejection fraction	170,601 (49%)	174,551 (51%)
Receipt of ventilation	314,528 (91%)	30,624 (9%)
Receipt of circulatory support	325,192 (94%)	19,960 (6%)
Cardiogenic shock	326,625 (95%)	18,527 (5%)
Left main	333,040 (96%)	12,112 (4%)
Use of drug eluting stents	333,729 (97%)	11,423 (3%)
Access site	337,283 (98%)	7,869 (2%)
Glycoprotein IIb/IIIa inhibitor	323,513 (94%)	21,639 (6%)
Diagnosis	326,695 (95%)	18,457 (5%)
MACE	336,394 (97%)	8,758 (3%)
Bleed	336,412 (97%)	8,740 (3%)

Supplementary Table 2: Risk of adverse outcomes among participants with BMI ≥30 kg/m^2 by BMI group

Outcome	BMI 18.5-24.9 kg/m^2	BMI 30.0-34.9 kg/m^2	BMI 35.0-39.9 kg/m^2	BMI ≥40 kg/m^2
30 day mortality (n=195,577)				
Unadjusted OR (95% CI)	1.00 (ref)	0.46 (0.43-0.50)*	0.51 (0.45-0.59)*	0.69 (0.58-0.82)*
p-value		<0.001	<0.001	<0.001
Adjusted value OR (95% CI)	1.00 (ref)	0.82 (0.74-0.90)*	0.99 (0.85-1.15)	1.42 (1.16-1.73)*
p-value		<0.001	0.89	0.001
1 year mortality (n=180,113)				
Unadjusted OR	1.00 (ref)	0.46 (0.43-0.48)*	0.52 (0.48-0.56)*	0.63 (0.56-0.70)*
p-value		<0.001	<0.001	<0.001
Adjusted value OR	1.00 (ref)	1.07 (0.95-1.20)*	0.67 (0.63-0.71)*	0.81 (0.74-0.89)*
p-value		0.29	<0.001	<0.001
3 year mortality (n=130,190)				
Unadjusted OR	1.00 (ref)	0.56 (0.53-0.58)*	0.60 (0.57-0.65)*	0.75 (0.68-0.82)*
p-value		<0.001	<0.001	<0.001
Adjusted value OR	1.00 (ref)	1.20 (1.09-1.32)*	0.75 (0.72-0.79)*	0.88 (0.81-0.94)*
p-value		<0.001	<0.001	0.001
5 year mortality (n=82,292)				
Unadjusted OR	1.00 (ref)	0.63 (0.60-0.66)*	0.67 (0.63-0.72)*	0.80 (0.73-0.87)*
p-value		<0.001	<0.001	<0.001
Adjusted value OR	1.00 (ref)	1.23 (1.11-1.37)	0.82 (0.78-0.86)*	0.94 (0.87-1.02)
p-value		<0.001	<0.001	0.13
MACE (n=195,577)				
Unadjusted OR	1.00 (ref)	0.67 (0.62-0.72)*	0.66 (0.59-0.74)*	0.79 (0.68-0.92)
p-value		<0.001	<0.001	0.003
Adjusted value OR	1.00 (ref)	1.17 (0.99-1.38)	0.93 (0.85-1.00)	0.95 (0.83-1.07)
p-value		0.061	0.059	0.38
Bleed (n=195,477)				
UnadjustedOR	1.00 (ref)	0.77 (0.72-0.83)*	0.89 (0.80-0.99)*	0.74 (0.63-0.87)*
p-value		<0.001	0.027	<0.001
Adjusted valueOR	1.00 (ref)	0.77 (0.65-0.92)*	0.84 (0.78-0.91)*	0.97 (0.87-1.08)
p-value		0.003	<0.001	0.53

Adjusted for age, gender, year, race, smoker, family history of CAD, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous MI, previous stroke, valvular heart disease, renal disease, previous PCI, previous CABG, lvef, receipt of ventilation, receipt of circulatory support, cardiogenic shock, left main, use of drug eluting stents, radial access, glycoprotein IIb/IIIa inhibitor use and diagnosis.

OR=odds ratio
*=significant

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