Metabolically healthy obesity and cardiovascular events

A nationwide cohort study

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Metabolically Healthy Obesity and Cardiovascular Events. A Nationwide Cohort Study.

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Short title: Metabolically Healthy Obesity and CV events

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Abstract

Aims. Whether obesity is associated with a higher risk of cardiovascular events in the absence of metabolic risk factors is a matter of debate. We evaluated the associations among metabolically healthy obesity (MHO) and different types of incident cardiovascular events in a contemporary population.

Methods: All patients discharged from French hospitals in 2013 with at least 5 years of follow-up and without a history of major adverse cardiovascular event (myocardial infarction, heart failure [HF], ischemic stroke or cardiovascular death, MACE-HF) or underweight/ malnutrition were identified. They were categorized by phenotypes defined by obesity and 3 metabolic abnormalities (diabetes mellitus, hypertension, and hyperlipidemia). Hazard ratios for cardiovascular events during follow-up were adjusted on age, sex and smoking status at baseline.

Results: In total, 2,873,039 individuals were included in the analysis, among whom 272,838 (9.5%) had obesity. During a mean follow-up of 4.9 years, when pooling men and women, individuals with MHO had a higher risk of MACE-HF (multivariate-adjusted hazard ratio [HR] 1.22, 95% confidence interval [CI]: 1.19-1.24), new-onset HF (HR 1.34, 95%CI 1.31-1.37), and AF (HR 1.33, 95%CI 1.30-1.37) compared with individuals with no obesity and 0 metabolic abnormalities. By contrast, risks were not higher for myocardial infarction (HR 0.92, 95%CI 0.87-0.98), ischemic stroke (HR 0.93, 95%CI 0.88-0.98) and cardiovascular death (HR 0.99, 95%CI 0.93-1.04). MHO in men was associated with higher risk of clinical events compared to MH men with normal weight (HR 1.12 to 1.80) while women with MHO had lower risk for most events than MH women with normal weight (HR 0.49 to 0.99).

Conclusions. In a large and contemporary analysis of patients seen in French hospitals, individuals with MHO did not have a higher risk of myocardial infarction, ischemic stroke or cardiovascular death than metabolically healthy individuals with no obesity. By contrast they had a higher risk of new-onset HF and new onset AF. Notable differences were however observed in men and women in the sex-stratified analysis.

Keywords: Obesity, diabetes, myocardial infarction, ischemic stroke, atrial fibrillation, heart failure.

Introduction

Obesity is a risk factor for cardiovascular disease (CVD) and has been increasing globally over the past 40 years in many countries worldwide [1,2]. Metabolic abnormalities such as hypertension, dyslipidemia, and diabetes mellitus are commonly associated and may mediate some of the deleterious effects of obesity [3]. However, the clustering of obesity related metabolic abnormalities varies widely among individuals with obesity. A subset of individuals with obesity without related metabolic abnormalities may be classified as having "metabolically healthy obesity" (MHO) [4–7]. Cardiovascular diseases are generally considered the major component of the excess death risk in subjects with obesity. Even when they have no metabolic abnormalities, men and women with obesity may be at increased risk of coronary heart disease, cerebrovascular disease, and heart failure (HF) compared to people of normal weight with no metabolic abnormalities. Similarly, men and women who are normal weight can have metabolic abnormalities and be at high risk of cardiovascular disease events[7]. However, there have been conflicting in previous studies to establish whether obesity is associated with CVD in the absence of metabolic risk factors[8]. To evaluate the associations among MHO individuals and different types of incident cardiovascular events, we performed a longitudinal nationwide cohort study of a contemporary population.

Methods

Study design

This longitudinal cohort study was based on the national hospitalization database covering hospital care from the entire French population. The data for all patients admitted in French hospitals in France from January to December 2013 with at least 5 years of complete follow-up (or dead earlier) were collected from the national administrative PMSI (*Programme de Médicalisation des Systèmes d'Information*) database, which was inspired by the US Medicare

system. Through this program, which was implemented in 2004, medical activity is recorded in a database, computed, and rendered anonymous. It includes more than 98% of the French population (67 million people) from birth (or immigration) to death (or emigration), even if a person changes occupation or retires. This process allows the determination of each hospital's budget, in 1,546 French healthcare facilities for both public and private hospitals. Each hospitalization is encoded in a standardized dataset, which includes information about the patient (age during first hospitalization in 2013 and sex), hospital, stay (date of admission, date of discharge, and modes of discharge), pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux (CCAM). The PMSI contains individual anonymized information on each hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for each patient. Patients had a period of 3 years (2010 to 2013) to determine medical history. The reliability of PMSI data has already been assessed and this database has previously been used to study patients with cardiovascular conditions [9–14]. Use of medication was identified from a 1/97 permanent random sample of the complete French nationwide claims database (Echantillon Généraliste de Bénéficiaires, EGB – general sample of healthcare beneficiaries). This is another database not linked to the PMSI database, which has been previously used to study patients with diabetes in France [15]. We enrolled patients with same inclusion criteria than in the PMSI database (patients seen in 2013 with at least 5 years of follow-up). Patients were considered to be included in a treatment group if they received a treatment from that class of drugs for ≥60 days within 6 months after enrolment.

The medical information contained in the database is anonymous and protected by professional

confidentiality. Consequently, ethics review was not required. Patient consent was not sought. The study was conducted retrospectively and as patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, as all data were anonymized. This type of study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 1, 2015, and registered as a clinical audit. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés (CNIL), the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139).

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Because this study used data from human subjects, the data and everything pertaining to the data are governed by the French Health Agencies and cannot be made available to other researchers.

Study population

From 1 January 2013 to 31 December 2013, 3,381,472 adults (age ≥18 years) were hospitalized for any reason in French hospitals and then had at least 5 years of complete follow-up (or suffered in-hospital death earlier). Patient information (demographics, comorbidities, medical history, and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined diagnoses at discharge were obtained. Each diagnosis was identified using ICD-10 codes. Obesity was identified with ICD-10 codes E65. Exclusion criteria were age <18 years, previous hospitalisation for in-hospital cardiovascular death, myocardial infarction, ischemic stroke or new-onset HF (MACE-HF)

events recorded over the period 2010 to 2013, and underweight or malnutrition (identified with the following ICD-10 codes: E41, E43, E44, E46, F508, K912, R636). After exclusion of underweight patients or those with poor nutrition (n= 80,777) and those with history of MACE-HF (n=427,656), the study finally included 2,873,039 patients (figure 1). We defined MHO as obesity being free from hypertension, dyslipidemia and diabetes identified with their respective ICD codes. Metabolically unhealthy individuals were defined as having at least one metabolic abnormality among hypertension, dyslipidemia and diabetes.

Outcomes

Patients were followed until 31 December 2019 for the occurrence of outcomes. We aimed to evaluate the incidence of first MACE-HF events. The endpoints were evaluated with follow-up starting from the date of entry of the first hospitalization in 2013 until the date of each specific outcome or date of last news in the absence of the outcome. Information on outcomes during the follow-up was obtained by analysing the PMSI codes for each patient. All-cause death, cardiovascular death, myocardial infarction, ischemic stroke, HF and atrial fibrillation (AF) were identified using their respective ICD-10 codes. The mode of death (cardiovascular or non-cardiovascular) was identified based on the main diagnosis during hospitalization resulting in in-hospital death. The combined endpoint of MACE-HF (cardiovascular death, myocardial infarction, ischemic stroke or new-onset HF) was evaluated for the long-term follow-up.

Statistical analysis

Qualitative variables are described as frequency and percentages and quantitative variable as means (standard deviations [SDs]). Comparisons were made using chi-square tests for categorical variables and the student's t-test for continuous variables. Incidence rates (IR) with 95% Confidence Interval (95%CI) were calculated for outcomes of interest in each subgroup.

A multivariable analysis for clinical outcomes during the whole follow-up in the groups of interests was performed using a Cox model with age, sex and smoking at baseline to calculate the relative hazard ratio (HR) and 95%CI for each subgroup, the reference category being individuals with no obesity and 0 metabolic abnormalities. We also tried to identify independent predictors for each of the clinical outcomes using a fully adjusted model taking into account all baseline characteristics from table 1 that may have interdependencies or possible causal paths with these cardiovascular outcomes (confounders or mediators, see directed-acyclic-graph using dagitty.net in Supplemental Figure 1). The proportional hazard assumption was checked by plotting the log-log Kaplan Meier curves and scaled Schoenfeld residuals against time plots. All analyses were performed using Enterprise Guide 7.1, (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina), USA and STATA version 12.0 (Stata Corp, College Station, TX.

Results

Among 2,873,039 patients seen in French hospitals in 2013 with no past history of MACE-HF, 272,838 (9.5%) had obesity and 2,600,201 (90.5%) had no obesity (Table 1 and Figure 1). Among these individuals, 65.8% were classified as non-underweight and had no obesity with no metabolic abnormalities and 3.1% were classified as having obesity with no metabolic abnormalities (Supplemental Table 1).

Population characteristics at baseline showed that individuals with obesity were younger and had higher levels for several comorbidities than individuals with no obesity. This was seen whether one compared subgroups of individuals with obesity and individuals with no obesity based on the metabolically healthy or unhealthy profile at baseline (Table 1 and Supplemental Table 2). Baseline characteristics of patients with obesity according to metabolic health status

are in Table 2.

During 14.1 million person-years of follow-up, 510,439 patients with new-onset MACE-HF events were identified, which included 77,924 patients with myocardial infarction, 391,637 patients with HF, 84,042 patients with ischemic stroke, and 100,633 cardiovascular deaths. There were 257,289 patients with new onset AF during follow up. The incidence rates (IRs) of MACE-HF, cardiovascular death, myocardial infarction, ischemic stroke, new onset HF and new onset AF increased with increasing number of metabolic abnormalities for both groups of individuals with obesity and no obesity (Figure 2, Figure 3 and Figure 4).

Individuals with obesity and no metabolic abnormalities had a higher risk of MACE-HF (multivariate-adjusted hazard ratio [HR] 1.22, 95% confidence interval [CI]: 1.19-1.24), new-onset HF (HR 1.34, 95%CI 1.31-1.37), and AF (HR 1.33, 95%CI 1.30-1.37) compared with individuals with no obesity and 0 metabolic abnormalities. By contrast, risk was not higher for myocardial infarction (HR 0.92, 95%CI 0.87-0.98), ischemic stroke (HR 0.93, 95%CI 0.88-0.98) and cardiovascular death (HR 0.99, 95%CI 0.93-1.04) (Figure 2, Figure 3 and Figure 4). Considering individuals with no obesity and 0 metabolic abnormalities as the reference category, those with obesity and metabolic abnormalities did not have statistically higher adjusted risks of myocardial infarction, ischemic stroke and cardiovascular death than their non-counterparts with no obesity and the same number of metabolic abnormalities. By contrast, they had a higher risk of new-onset HF resulting in higher risk of MACE-HF. This was also the case for new-onset AF with a very marked effect, since MHO individuals had a higher adjusted risk of AF (HR 1.33, 95%CI 1.30-1.37) than individuals with no obesity and 3 metabolic abnormalities (HR 1.21, 95%CI 1.18-1.24) (Figure 4).

Supplemental table 3 presents an interaction analysis into the models including "Obesity * Metabolic status" with adjusted HRs (95% CI) for unhealthy vs healthy metabolic status related to each outcome of the study in patients with obesity or no obesity, including obesity to no obesity ratios and p for interaction. These ratios were all statistically significant (ranging from 1.06 to 1.18). This suggested an interaction for the effects due to obesity or metabolic status on clinical outcomes and made sense to look into each combination strata for metabolic healthy obese patient and metabolically non-healthy obese patients.

Associations between body size phenotypes and clinical outcomes during follow-up adjusted for age, sex, smoking status, alcohol and illicit drug abuse are presented in Supplemental Table 4 and indicated similar results.

The fully adjusted model analyses taking all baseline characteristics listed in table 1 for independent predictors of outcomes are reported in Supplemental Table 5 for MACE-HF events, Supplemental Table 6 for cardiovascular death, Supplemental Table 7 for MI, Supplemental Table 8 for ischemic stroke, Supplemental Table 9 for new-onset HF and Supplemental Table 10 for new-onset AF. Obesity was independently associated with a higher risk of MACE-HF events (HR 1.13, 95%CI 1.12-1.14), of new-onset HF (HR 1.19, 95%CI 1.18-1.20) and new-onset AF (HR 1.29, 95%CI 1.28-1.31). This was not the case for the association of obesity with cardiovascular death (HR 0.96, 95%CI 0.94-0.98), myocardial infarction (HR 0.93, 95%CI 0.91-0.95) and ischemic stroke (HR 0.93, 95%CI 0.91-0.96). Hypertension and diabetes mellitus were independent predictors of all types of outcomes whilst dyslipidemia was associated with a lower risk for all outcomes.

Considering that sex difference may exist on these issues, the sex-specific prevalence of obesity

and metabolically healthy or unhealthy status and a sex-stratified analysis are presented in supplemental tables 11 to 14. We found that the results were somewhat different in men and women since MHO in men was associated with higher risk of clinical events compared to MH men with normal weight (HR 1.12 to 1.80) while women with MHO had lower risk for most events than MH women with normal weight (HR 0.49 to 0.99).

Discussion

In our large contemporary nationwide analysis adjusted on age, sex and smoking, MHO individuals had a higher adjusted risk of new-onset HF and new onset AF. By contrast, they did not have a higher adjusted risk of myocardial infarction, ischemic stroke or cardiovascular death than metabolically healthy individuals with no obesity. Our analysis also indicated that individuals with no obesity can have metabolic abnormalities and be at high risk of cardiovascular disease events.

Several meta-analyses have reported that, compared with metabolically healthy normal weight individuals, MHO individuals are at increased risk for cardiovascular events[8,16]. Another meta-analysis that examined the association between MHO and cardiovascular events limited to studies using the strictest definition for metabolic health (absence of all metabolic abnormalities) found an insignificant association between MHO and CVD events.[5] The relationship between MHO and clinical outcomes may vary depending on the definition of MHO used.[17] Risk factors used to define metabolic health may differ according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF). Main limitations in some of these studies were the lack of adjustment on some confounding factors such as age, sex or history of smoking and the lack of separate analysis of the different subtypes of incident CV events. Whether MHO is associated with excess risk of CVD thus remains a matter of debate because of limitations to the global evidence base and our results provide new insights on some of these issues.

When studying obesity, several studies defined metabolic abnormalities as diagnoses of diabetes, hypertension, hyperlipidemia (and not blood pressure, blood glucose, triglycerides, HDL cholesterol, waist circumference that may not be available in administrative database).[7,8]

We used this strategy and acknowledge that we do not know whether the results would be fully similar in case these more precise measurements would have been available, although we do not see clear reason why this would not be the case.

The finding that obesity was associated with a slightly lower risk of MI and ischemic stroke than metabolically healthy individuals with no obesity may be surprising, considering that obesity may influence the atherosclerotic process. The different findings reported by others might be related to selection bias at inclusion and information bias during follow-up[18] while our study analysed unselected patients seen at a nationwide level with systematic identification of events during follow-up. The relationship between MHO and clinical outcomes may also vary depending on the definition of MHO used.[17] In a large analysis, Caleyachetty et al. reported that obesity was associated with a lower risk of peripheral vascular disease [7], which was similarly unexpected and they suggested residual confounding by cigarette smoking, which is strongly associated with both peripheral vascular disease and lower body mass index. However, the lower risk in our analysis was obtained after adjustment on smoking. One might suggest that obesity is a phenotype that is easy to identify and that it may flag an at-risk status associated in a modern era with more aggressive measure with cardiovascular drugs and lipid lowering drugs (as seen with medication use among patients from the representative sample in our analysis), resulting in a lower risk for atherothrombotic events [19].

Lee et al also reported in a nationwide analysis in South Korea that MHO individuals were not at increased risk for ischemic stroke [20]. Our findings in a larger and more recent dataset confirm these results, by contrast to other findings obtained in far smaller dataset with pooled analyses of cardiovascular events [8]. The large analysis by Caleyachetty et al reported a marginally higher risk of cerebrovascular disease in MHO individuals compared to normal weight MHO (HR

1.07, 95%CI 1.04-1.11) [7] but their definition for this outcome was less specific than that in our study on ischemic stroke focused on ischemic stroke.

The most obvious risk associated with obesity in our results was for the incidence of new-onset AF. Individuals with MHO had a higher adjusted risk of AF than individuals with no obesity and 3 metabolic abnormalities. This may explain why MHO individuals had a higher risk of new-onset HF than individuals with no obesity and the same number of metabolic abnormalities, considering that AF at baseline was also a powerful predictor of new-onset HF during FU. This is also a plausible reason for the higher risk of MACE-HF events in MHO individuals since the adjusted analysis did not find a higher risk of myocardial infarction or ischemic stroke in these patients. Obesity may be a direct link for the higher risk of AF [21], which may be less likely to be adequately reversed in daily practice [22]. The "critical mass" hypothesis suggests that smaller individuals with smaller hearts are less able of sustaining a fibrillatory rhythm [23]. We have no echocardiographic data, but it is plausible that the relationship between higher body weight (usually associated with higher body surface area) and AF in our analysis is mediated through effects on atrial size. Body weight variability may also be associated with AF development, which may in addition affect MHO in case they obtain a significant weight loss [24]. AF screening in individuals with obesity and its potential clinical benefits might be studied in the future but is not for now included in current guidelines [25].

A similarly direct association may be suggested for obesity and HF, particularly when considering HF with preserved ejection fraction where cardiovascular drugs recommended in case of reduced ejection fraction might be somewhat less efficient [26]. In a dynamic longitudinal analysis, a recent study indicated that even if metabolic health was maintained, obesity was a risk factor for HF [27]. However, transition from MHO to non-obesity may have a protective

effect against HF [27]. The prevention and control of obesity while maintaining metabolic health would be relevant in preventing HF although this may be difficult to obtain with primary care management [28].

Our findings suggest that early detection and management of individuals with obesity may therefore be beneficial in the prevention of AF and of HF, whilst an appropriate management of individuals with no obesity and metabolic abnormalities may be beneficial in the prevention of ischemic events. Among these measures, one might propose different pharmacologic strategies in appropriate subgroups based on their phenotype, which might significantly reduce cardiovascular atherosclerotic events (intensive lipid lowering therapies, antithrombotic agents, and antidiabetic drugs such as glucagon-like peptide 1 (GLP1) or HF events (angiotensin converting enzyme inhibitors, mineralocorticoid-receptor antagonists and SGLT2 inhibitors for type 2 diabetes) [26,29]. Based on our results, one might suggest that these latter should be more appropriate for MHO individuals since they may bring a more specific benefit in terms of or progression of HF.

Finally, one should mention that our results were somewhat different in men and women: higher risk of clinical events in men with MHO compared to MH men with normal, but lower risk for most events in women with MHO than in MH women with normal weight. The recent meta-analysis by Opio et al investigated the association between MHO and risk of CVD and reported results with high heterogeneity was high but gender was not a cause of heterogeneity. Men and women with obesity carry excess adipose mass in different anatomical locations, known to differently influence cardiovascular risk. Due to the oestrogens, women accumulate more subcutaneous adipose tissue than men. Adipose tissue depots influence oppositely cardiovascular risk, visceral adipose conferring an increased risk while subcutaneous may be

neutral or protective[30], which may partly explain our different results in men and in women.

Limitations

We acknowledge several limitations to our work. A main limitation is inherent to the retrospective, observational nature of the study and its potential biases. Further, the study was based on administrative data, with limitations inherent to such methodology. The PMSI database contains diagnoses coded using ICD-10, which are obtained at hospital discharge and are the physician's responsibility, therefore only hospitalised patients were included in our analysis. Data were not systematically externally checked, and this could have caused information bias. However, the large scale of the database may partly compensate some of these biases and, as coding of complications is linked to reimbursement and is regularly controlled, it is expected to be of good quality. Events included were only in-hospital and we were not able to analyze data for out-of-hospital deaths, but most of the major cardiovascular events analyzed in our study are not managed out of hospitals. Our large population of hospitalized patients likely represents a heterogeneous group of patients admitted with various kinds of illnesses and severities, which may have affected prognosis. Another limitation is the lack of complete information in terms of therapies recommended for diabetes or cardiovascular conditions beyond the representative sample from our analysis. Thus, medication information may not be included in the full model for confounder adjustment. Some of these therapies may be associated with a lower risk of CV events, but the addition of therapy to models may not improve discrimination in statistical analyses [19]. Further, the observational design of the analysis leaves a risk of residual confounding factors. Our analysis was restricted to the variables present in the database, which meant that characteristics such as information on the socioeconomic status, some of the lifestyle factors (physical activity level or diet), metabolic control (glucose levels, lipids, body mass index and blood pressure) or imaging

(echocardiography including measures of systolic function) were not available for analysis. Thus, we were not able to distinguish among hyperlipidemia high LDL, high triglycerides and low HDL. Considering that body mass index was not available, we did not specifically analyse outcomes for overweight patients among individuals with no obesity. The majority of the French population is white Caucasian and our results may not be generalizable to non-Caucasian people. Finally, although the number of person-years in our study is one of the highest in the literature, the follow-up period of 5 years was relatively short. Previous studies suggested that MHO may be a transition process to metabolically unhealthy obesity. Hence, longer follow-up may be warranted to confirm some of our negative results.

Conclusions

In our contemporary nationwide cohort study, we found that MHO individuals do not have a higher risk of myocardial infarction, ischemic stroke or cardiovascular death than metabolically healthy individuals with no obesity. By contrast they have a higher risk of new-onset HF and new onset AF. Individuals with no obesity can have metabolic abnormalities and be at high risk of cardiovascular disease events. Our observations suggest that specific studies investigating different aggressive preventive measures in specific subgroups of patients are warranted.

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Conflict of interest

None directly related to the matter of this article. DA: consultant and speaker for Amgen, Sanofi, Novartis, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Pfizer, and Servier. GYHL: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo; No fees are received personally. LF: consultant and speaker activities for

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Figure legends.

Figure 1. Flow chart of studied patients

Figure 2. Incidences and associations between body size phenotypes and metabolic status for combined major cardiovascular events (in-hospital cardiovascular death, myocardial infarction, ischemic stroke or new-onset heart failure, top panel), for cardiovascular death (median panel) and for myocardial infarction (lower panel) during follow-up.
Analyses for hazard ratios are adjusted for age, sex and smoking status. The reference category is normal weight, 0 metabolic abnormalities.

Figure 3. Incidences and associations between body size phenotypes and metabolic status for ischemic stroke (top panel), new-onset HF (median panel) and for new-onset AF (lower panel) during follow-up.
Analyses for hazard ratios are adjusted for age, sex and smoking status. The reference category is normal weight, 0 metabolic abnormalities.

Table 1. Baseline characteristics of patients seen in French hospitals in 2013 with at least 5 years of follow-up (mean follow-up 4.9±1.7 years, median 5.5, IQR 5.1-5.8 years) according to obesity and metabolic health status.

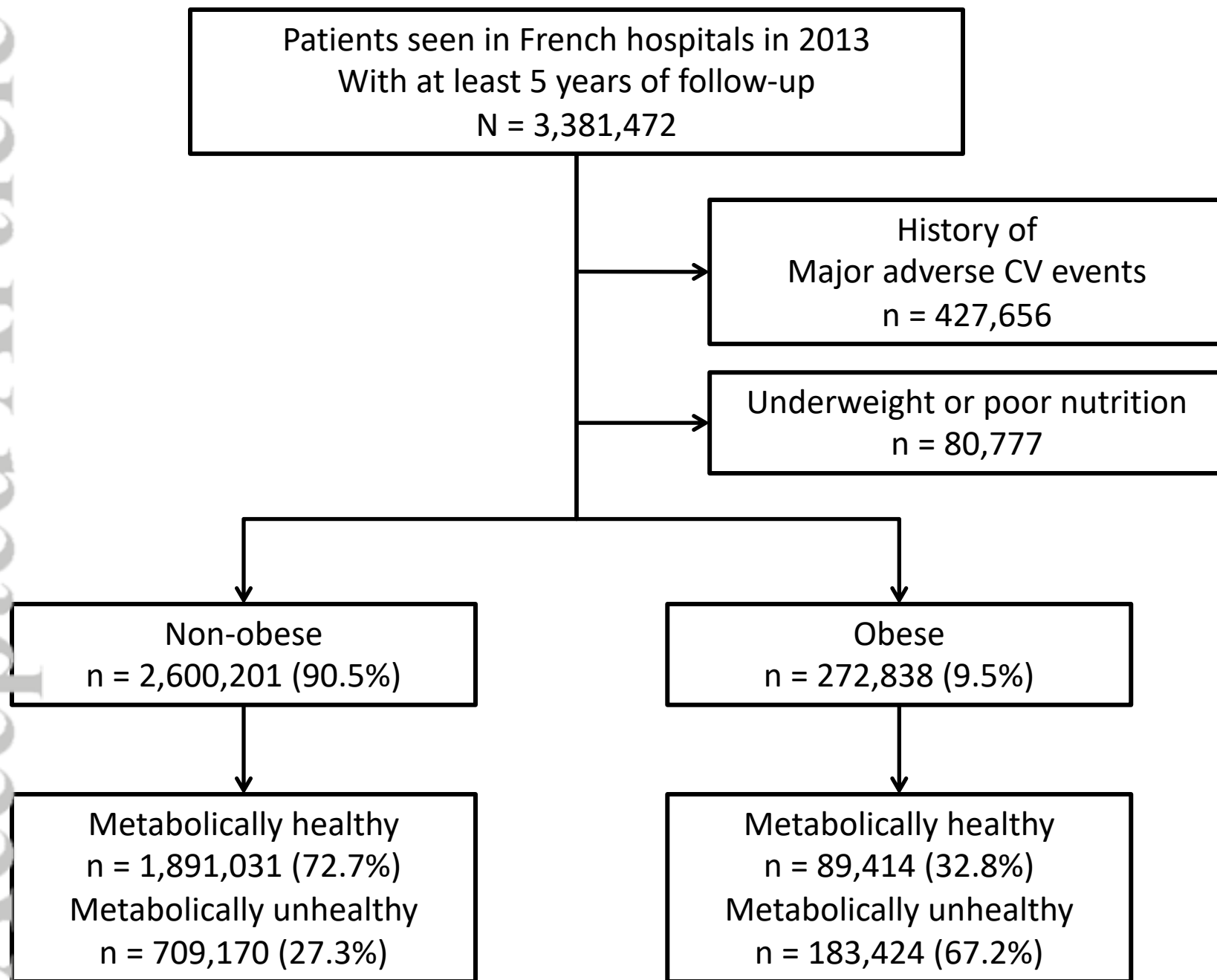|	No Obesity and Metabolically Healthy (n=1891031)	No-Obesity and Metabolically Unhealthy (n=709170)	Obesity and Metabolically Healthy (n=89414)	Obesity and Metabolically Unhealthy (n=183424)	Overall p value
Age, years	51.5±22.2	69.4±14.7	48.8±17.1	63.7±13.6	<0.0001
Sex (male)	822136 (43.5)	363943 (51.3)	26577 (29.7)	82674 (45.1)	<0.0001
Obesity	0 (0.0)	0 (0.0)	89414 (100.0)	183424 (100.0)	<0.0001
Hypertension	0 (0.0)	551590 (77.8)	0 (0.0)	148127 (80.8)	<0.0001
Diabetes mellitus	0 (0.0)	235925 (33.3)	0 (0.0)	100252 (54.7)	<0.0001
Dyslipidemia	0 (0.0)	217160 (30.6)	0 (0.0)	77118 (42.0)	<0.0001
Smoker	83434 (4.4)	56014 (7.9)	8833 (9.9)	19917 (10.9)	<0.0001
Alcohol related diagnoses	83377 (4.4)	41986 (5.9)	3668 (4.1)	12412 (6.8)	<0.0001
Valve disease	12955 (0.7)	25179 (3.6)	803 (0.9)	6496 (3.5)	<0.0001
Coronary artery disease	30404 (1.6)	81993 (11.6)	1968 (2.2)	23856 (13.0)	<0.0001
Previous PCI	5998 (0.3)	17668 (2.5)	327 (0.4)	4793 (2.6)	<0.0001
Previous CABG	311 (0.0)	1861 (0.3)	29 (0.0)	699 (0.4)	<0.0001
Vascular disease	27971 (1.5)	81263 (11.5)	1482 (1.7)	21371 (11.7)	<0.0001
Atrial fibrillation	41842 (2.2)	78976 (11.1)	2864 (3.2)	19463 (10.6)	<0.0001
Previous pacemaker or ICD	13298 (0.7)	24309 (3.4)	601 (0.7)	4532 (2.5)	<0.0001
Chronic kidney disease	12541 (0.7)	35069 (4.9)	548 (0.6)	10090 (5.5)	<0.0001
Lung disease	89152 (4.7)	82571 (11.6)	10119 (11.3)	32624 (17.8)	<0.0001
Sleep apnea syndrome	25977 (1.4)	25077 (3.5)	9793 (11.0)	36072 (19.7)	<0.0001
Liver disease	34706 (1.8)	28081 (4.0)	3652 (4.1)	15588 (8.5)	<0.0001
Thyroid diseases	43699 (2.3)	57167 (8.1)	6167 (6.9)	22953 (12.5)	<0.0001
Inflammatory disease	78041 (4.1)	39849 (5.6)	4484 (5.0)	12678 (6.9)	<0.0001
Anaemia	75265 (4.0)	71028 (10.0)	5323 (6.0)	19894 (10.8)	<0.0001
Previous cancer	224589 (11.9)	138024 (19.5)	9370 (10.5)	29085 (15.9)	<0.0001
Cognitive impairment	26217 (1.4)	33805 (4.8)	750 (0.8)	4155 (2.3)	<0.0001
Illicit drug use	8966 (0.5)	1548 (0.2)	433 (0.5)	471 (0.3)	<0.0001

Values are n (%) or mean±SD. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SD = standard deviation.
Using data about medications from a 1/97 sample of patients in the French healthcare system for those with the same inclusion criteria, those with (obesity) were slightly more frequently treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blockers, diuretics, statins and antidiabetic drugs than patients without obesity (Supplemental Table 2).

Table 2. Baseline characteristics of patients with obesity according to metabolic health status.
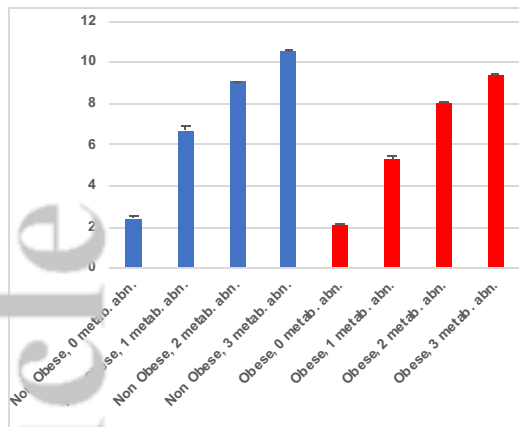
	Obesity, Metabolically Healthy (n=89414)	Obesity, 1 metabolic abnormality (n=80066)	Obesity, 2 metabolic abnormalities (n=64643)	Obesity, 3 metabolic abnormalities (n=38715)	Overall p value
Age, years	48.8±17.1	61.3±15.5	65.7±12.2	65.2±10.5	<0.0001
Sex (male)	26577 (29.7)	31948 (39.9)	30795 (47.6)	19931 (51.5)	<0.0001
Hypertension	0 (0.0)	51052 (63.8)	58360 (90.3)	38715 (100.0)	<0.0001
Diabetes mellitus	0 (0.0)	20084 (25.1)	41453 (64.1)	38715 (100.0)	<0.0001
Dyslipidemia	0 (0.0)	8930 (11.2)	29473 (45.6)	38715 (100.0)	<0.0001
Smoker	8833 (9.9)	7849 (9.8)	6903 (10.7)	5165 (13.3)	<0.0001
Alcohol related diagnoses	3668 (4.1)	4763 (5.9)	4638 (7.2)	3011 (7.8)	<0.0001
Valve disease	803 (0.9)	2237 (2.8)	2658 (4.1)	1601 (4.1)	<0.0001
Coronary artery disease	1968 (2.2)	5902 (7.4)	9590 (14.8)	8364 (21.6)	<0.0001
Previous PCI	327 (0.4)	1055 (1.3)	1980 (3.1)	1758 (4.5)	<0.0001
Previous CABG	29 (0.0)	107 (0.1)	311 (0.5)	281 (0.7)	<0.0001
Vascular disease	1482 (1.7)	4718 (5.9)	8500 (13.1)	8153 (21.1)	<0.0001
Atrial fibrillation	2864 (3.2)	7646 (9.5)	7762 (12.0)	4055 (10.5)	<0.0001
Previous pacemaker or ICD	601 (0.7)	1625 (2.0)	1860 (2.9)	1047 (2.7)	<0.0001
Chronic kidney disease	548 (0.6)	2396 (3.0)	4058 (6.3)	3636 (9.4)	<0.0001
Lung disease	10119 (11.3)	13587 (17.0)	11978 (18.5)	7059 (18.2)	<0.0001
Sleep apnea syndrome	9793 (11.0)	13126 (16.4)	12956 (20.0)	9990 (25.8)	<0.0001
Liver disease	3652 (4.1)	4990 (6.2)	5599 (8.7)	4999 (12.9)	<0.0001
Thyroid diseases	6167 (6.9)	8829 (11.0)	8223 (12.7)	5901 (15.2)	<0.0001
Inflammatory disease	4484 (5.0)	5230 (6.5)	4619 (7.1)	2829 (7.3)	<0.0001
Anaemia	5323 (6.0)	7345 (9.2)	7632 (11.8)	4917 (12.7)	<0.0001
Previous cancer	9370 (10.5)	12696 (15.9)	10824 (16.7)	5565 (14.4)	<0.0001
Cognitive impairment	750 (0.8)	1630 (2.0)	1683 (2.6)	842 (2.2)	<0.0001
Illicit drug use	433 (0.5)	236 (0.3)	162 (0.3)	73 (0.2)	<0.0001

Values are n (%) or mean±SD. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SD = standard deviation.
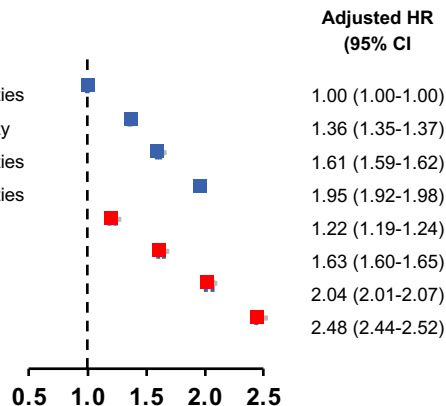
Patients seen in French hospitals in 2013
With at least 5 years of follow-up
N = 3,381,472

History of
Major adverse CV events
n = 427,656

Underweight or poor nutrition
n = 80,777

Non-obese
n = 2,600,201 (90.5%)

Obese
n = 272,838 (9.5%)

Metabolically healthy
n = 1,891,031 (72.7%)
Metabolically unhealthy
n = 709,170 (27.3%)

Metabolically healthy
n = 89,414 (32.8%)
Metabolically unhealthy
n = 183,424 (67.2%)

MACE-HF

Incidence (%/year)

	Adjusted HR (95% CI
Non Obese, 0 metabolic abnormalities	1.00 (1.00-1.00)
Non Obese, 1 metabolic abnormality	1.36 (1.35-1.37)
Non Obese, 2 metabolic abnormalities	1.61 (1.59-1.62)
Non Obese, 3 metabolic abnormalities	1.95 (1.92-1.98)
Obese, 0 metabolic abnormalities	1.22 (1.19-1.24)
Obese, 1 metabolic abnormality	1.63 (1.60-1.65)
Obese, 2 metabolic abnormalities	2.04 (2.01-2.07)
Obese, 3 metabolic abnormalities	2.48 (2.44-2.52)

0.5   1.0   1.5   2.0   2.5

Cardiovascular Death

Incidence (%/year)
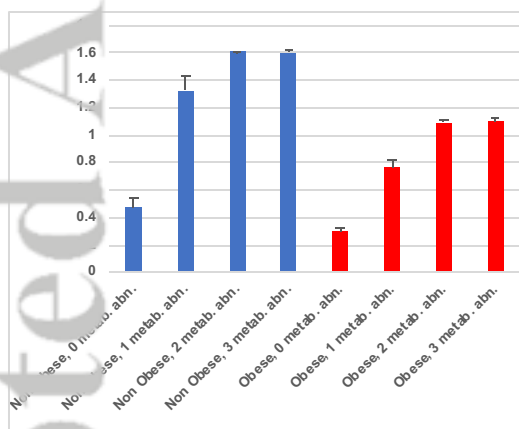
	Adjusted HR (95% CI
Non Obese, 0 metabolic abnormalities	1.00 (1.00-1.00)
Non Obese, 1 metabolic abnormality	1.26 (1.24-1.28)
Non Obese, 2 metabolic abnormalities	1.36 (1.33-1.38)
Non Obese, 3 metabolic abnormalities	1.47 (1.42-1.52)
Obese, 0 metabolic abnormalities	0.99 (0.93-1.04)
Obese, 1 metabolic abnormality	1.19 (1.14-1.23)
Obese, 2 metabolic abnormalities	1.40 (1.35-1.45)
Obese, 3 metabolic abnormalities	1.51 (1.44-1.58)

0.8   1.0   1.2   1.4   1.6
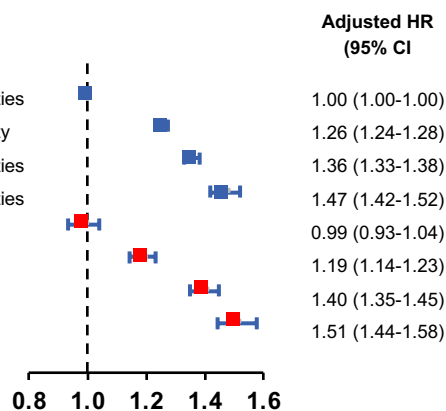
Myocardial Infarction

Incidence (%/year)
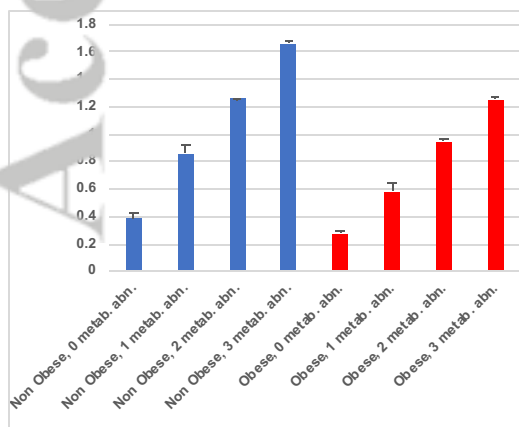
	Adjusted HR (95% CI
Non Obese, 0 metabolic abnormalities	1.00 (1.00-1.00)
Non Obese, 1 metabolic abnormality	1.25 (1.23-1.28)
Non Obese, 2 metabolic abnormalities	1.56 (1.53-1.60)
Non Obese, 3 metabolic abnormalities	2.00 (1.93-2.07)
Obese, 0 metabolic abnormalities	0.92 (0.87-0.98)
Obese, 1 metabolic abnormality	1.15 (1.10-1.20)
Obese, 2 metabolic abnormalities	1.53 (1.47-1.59)
Obese, 3 metabolic abnormalities	1.98 (1.90-2.07)

0.5   1.0   1.5   2.0
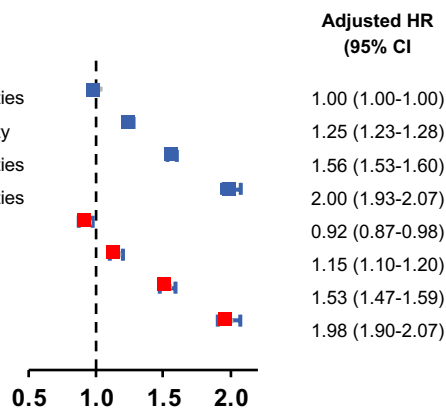
Ischemic Stroke

Incidence (%/year)
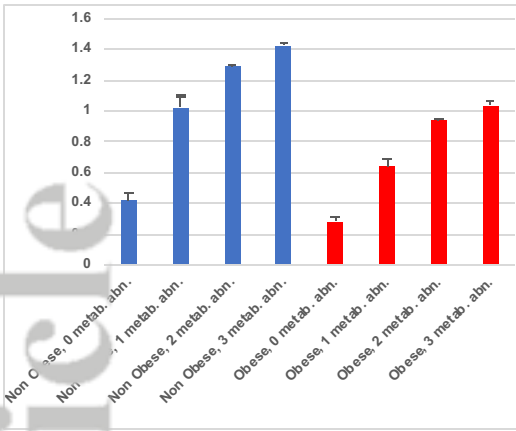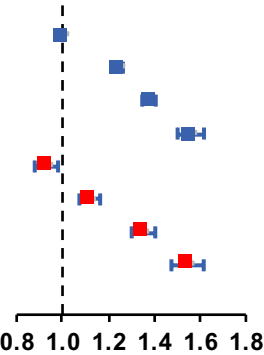
	Adjusted HR (95% CI)
Non Obese, 0 metabolic abnormalities	1.00 (1.00-1.00)
Non Obese, 1 metabolic abnormality	1.24 (1.22-1.26)
Non Obese, 2 metabolic abnormalities	1.38 (1.35-1.41)
Non Obese, 3 metabolic abnormalities	1.56 (1.50-1.62)
Obese, 0 metabolic abnormalities	0.93 (0.88-0.98)
Obese, 1 metabolic abnormality	1.12 (1.07-1.16)
Obese, 2 metabolic abnormalities	1.35 (1.30-1.41)
Obese, 3 metabolic abnormalities	1.54 (1.48-1.62)

New-onset Heart Failure

Incidence (%/year)
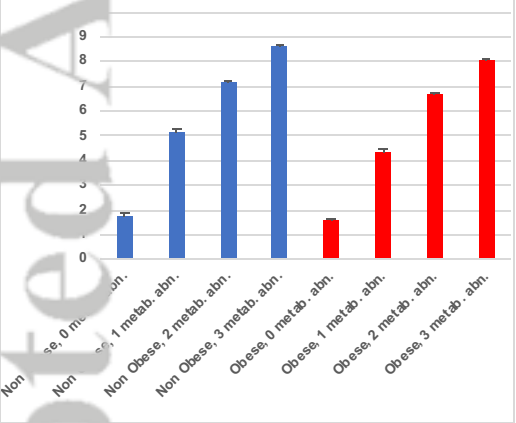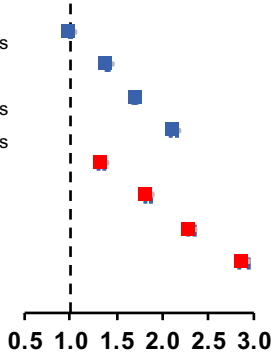
	Adjusted HR (95% CI)
Non Obese, 0 metabolic abnormalities	1.00 (1.00-1.00)
Non Obese, 1 metabolic abnormality	1.41 (1.39-1.42)
Non Obese, 2 metabolic abnormalities	1.70 (1.69-1.72)
Non Obese, 3 metabolic abnormalities	2.13 (2.09-2.16)
Obese, 0 metabolic abnormalities	1.34 (1.31-1.37)
Obese, 1 metabolic abnormality	1.85 (1.82-1.88)
Obese, 2 metabolic abnormalities	2.32 (2.28-2.36)
Obese, 3 metabolic abnormalities	2.89 (2.84-2.94)

New-onset Atrial Fibrillation

Incidence (%/year)

	Adjusted HR (95% CI)
Non Obese, 0 metabolic abnormalities	1.00 (1.00-1.00)
Non Obese, 1 metabolic abnormality	1.10 (1.09-1.11)
Non Obese, 2 metabolic abnormalities	1.15 (1.14-1.17)
Non Obese, 3 metabolic abnormalities	1.21 (1.18-1.24)
Obese, 0 metabolic abnormalities	1.33 (1.30-1.37)
Obese, 1 metabolic abnormality	1.55 (1.51-1.58)
Obese, 2 metabolic abnormalities	1.64 (1.61-1.67)
Obese, 3 metabolic abnormalities	1.68 (1.64-1.73)