Preventive Medicine 107 (2018) 81–89

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Interaction between cardiovascular risk factors and body mass index and 10-year incidence of cardiovascular disease, cancer death, and overall mortality☆

Maria Barroso[a,b], Albert Goday[c,d,e], Rafel Ramos[f,g], Alejandro Marín-Ibañez[h], Maria Jesús Guembe[i,j], Fernando Rigo[k], Maria José Tormo-Díaz[l,m,n,o], Conchi Moreno-Iribas[p,q,r], Joan Josep Cabré[s], Antonio Segura[t], Jose Miguel Baena-Díez[a,b], Agustín Gómez de la Cámara[o,u], José Lapetra[d,v], Miquel Quesada[f], María José Medrano[w], Jesús Berjón[i,r], Guillem Frontera[k], Diana Gavrila[o,x], Aurelio Barricarte[o,p,q], Josep Basora[y], José María García[t], Manel García-Lareo[b], David Lora-Pablos[o,u], Eduardo Mayoral[d,z], María Grau[a,aa,ab,*,1], Jaume Marrugat[a,aa,*,1], On behalf of the FRESCO Investigators

[a] REGICOR Study Group - Cardiovascular Epidemiology and Genetics, IMIM-Hospital del Mar Research Institute, Barcelona, Spain
[b] Primary Care Center La Marina and Primary Health Care Research Institute Jordi Gol, Catalan Institute of Health, Barcelona, Spain
[c] Parc de Salut Mar, Barcelona, Spain
[d] Consortium for Biomedical Research in Obesity and Nutrition (CIBEROBN), Spain
[e] Departament de Medicina, Universitat Autònoma de Barcelona, Spain
[f] Family Medicine Research Unit and Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Girona, Spain
[g] University of Girona, Spain
[h] San Jose Norte Health Centre, Zaragoza, Spain
[i] Vascular Risk in Navarra Research Group (RIVANA), Health Department, Navarra Government, Pamplona, Spain
[j] Knowledge Planning, Evaluation and Management, Health Department, Navarra Government, Pamplona, Spain
[k] Cardiovascular Group of Balearic Islands (REDIAP-IBSALUT), Palma de Mallorca, Spain
[l] Murcian Health Department, Murcia, Spain
[m] University of Murcia, Spain
[n] Murcian Institute of Biomedical Research (IMIMB), Murcia, Spain
[o] Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Spain
[p] Navarre Public Health Institute, Pamplona, Spain
[q] Research Network for Health Services in Chronic Disease (REDISSEC), Pamplona, Spain
[r] Navarra Hospital, IdiSNA–Navarra Institute for Health Research, Pamplona, Spain
[s] Primary Care Center Sant Pere Centre and Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Reus-Tarragona, Spain
[t] Health Science Institute, Department of Health and Social Affairs, Castile – La Mancha Government, Talavera de la Reina, Spain
[u] Clinical Research Department, Hospital 12 Octubre Research Institute, Madrid, Spain
[v] Department of Family Medicine, Research Unit, Primary Care Division of Seville, Spain
[w] Carlos III Health Institute, Madrid, Spain
[x] Health and Consumers Department, Murcia Government, Murcia, Spain
[y] Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Reus-Tarragona, Spain
[z] Diabetes Strategy, Andalusia Health Service, Sevilla, Spain
[aa] CIBERCV CIBER de Enfermedades Cardiovasculares, Spain
[ab] University of Barcelona, Spain

ARTICLE INFO

Keywords:
Body mass index
Cardiovascular disease
Epidemiology
Mortality

ABSTRACT

The effect of above-normal body mass index (BMI) on health outcomes is controversial because it is difficult to distinguish from the effect due to BMI-associated cardiovascular risk factors. The objective was to analyze the impact on 10-year incidence of cardiovascular disease, cancer deaths and overall mortality of the interaction between cardiovascular risk factors and BMI. We conducted a pooled analysis of individual data from 12 Spanish population cohorts with 10-year follow-up. Participants had no previous history of cardiovascular diseases and

☆ A full roster of FRESCO Investigators can be found at www.regicor.org/fresco_inv.

* Corresponding authors at: Research Group on Cardiovascular Epidemiology and Genetics, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain.
E-mail addresses: mgrau@imim.es (M. Grau), jmarrugat@imim.es (J. Marrugat).

[1] Both authors have equally contributed.

https://doi.org/10.1016/j.ypmed.2017.11.013
Received 16 July 2017; Received in revised form 3 November 2017; Accepted 9 November 2017
Available online 16 November 2017

Neoplasms
Obesity

were 35–79 years old at basal examination. Body mass index was measured at baseline being the outcome measures ten-year cardiovascular disease, cancer and overall mortality. Multivariable analyses were adjusted for potential confounders, considering the significant interactions with cardiovascular risk factors. We included 54,446 individuals (46.5% with overweight and 27.8% with obesity). After considering the significant interactions, the 10-year risk of cardiovascular disease was significantly increased in women with overweight and obesity [Hazard Ratio = 2.34 (95% confidence interval: 1.19–4.61) and 5.65 (1.54–20.73), respectively]. Overweight and obesity significantly increased the risk of cancer death in women [3.98 (1.53–10.37) and 11.61 (1.93–69.72)]. Finally, obese men had an increased risk of cancer death and overall mortality [1.62 (1.03–2.54) and 1.34 (1.01–1.76), respectively]. In conclusion, overweight and obesity significantly increased the risk of cancer death and of fatal and non-fatal cardiovascular disease in women; whereas obese men had a significantly higher risk of death for all causes and for cancer. Cardiovascular risk factors may act as effect modifiers in these associations.

1. Introduction

Obesity is a worldwide public health problem due to its high prevalence, the epidemic increase observed in recent decades, and the associated diseases (GBD 2015 Obesity Collaborators, 2017; Finucane et al., 2011; Guh et al., 2009). The World Health Organization (WHO) reports that > 1.9 billion adults were overweight in 2014, and > 600 million of these individuals were obese, doubling the worldwide prevalence of obesity since 1980 (Global Database on Body Mass Index, 2017). Recent projections are that global obesity prevalence will reach 18% in men and surpass 21% in women by 2025; severe obesity will exceed 6% in men and 9% in women (NCD Risk Factor Collaboration, 2016). Finally, overweight and obesity, estimated with body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), have been associated with decreased functional ability and health status and increased risk of chronic conditions in classical observational studies (Guh et al., 2009; Fontaine et al., 2003; Prospective Studies Collaboration, 2009; Stenholm et al., 2016; Flegal et al., 2013) and in Mendelian randomization studies (Carreras-Torres et al., 2017a, 2017b; Holmes et al., 2014; Thrift et al., 2015). Although BMI is well established as a risk factor or indicator, the direct effect of above-normal BMI on health outcomes remains controversial (Gao et al., 2016; Mandviwala et al., 2016). This effect could be secondary, through an influence on the development and severity of cardiovascular risk factors (CRF) such as hypertension, diabetes, and hypercholesterolemia (Bogers et al., 2007; Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014; Jerant and Franks, 2012; Poirier et al., 2006). However, it may also occur in the absence of CRF and may be due to structural and functional changes in excess adipose tissue deposition or to underlying mechanisms that remain unknown (Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014; Mandviwala et al., 2016; Gao et al., 2016). Teasing apart the effect on health outcomes of above-normal BMI from other comorbidities requires a population-based cohort with an appropriate sample size, long follow-up, and an exhaustive register of outcomes. Obtaining this information is essential to design effective preventive measures.

The objectives of the present study are: (1) to ascertain the association of BMI and different BMI cut-off points with 10-year cardiovascular disease (CVD) incidence and with cancer and overall mortality in a population-based cohort of > 54,000 participants, and (2) to describe the interaction of CRF in the association between above-normal BMI values and the risk of all three outcomes.

2. Methods

2.1. Design and participants

We conducted a pooled analysis of anonymized individual data from 12 population cohorts in 7 Spanish regions, examined between 1992 and 2005 with similar methods; the methodology of this cohort study has been explained elsewhere (Marrugat et al., 2014). In summary, all participants in the FRESCO cohorts were randomly selected and included participants without previous symptoms or diagnosis of CVDs, aged 35 to 79 years (Supplementary Table 1). The FRESCO study was approved by the local Ethics Committee of the Parc de Salut Mar (authorization #: 2009/3391/I). All participants were duly informed and signed a consent form to participate in the component studies.

2.2. Measurements

CRF were measured at baseline using standardized methods based on World Health Organization recommendations (Tunstall-Pedoe et al., 1994). A precision scale of easy calibration was used for weight measurement with participants in underwear. Height was measured with a standard measuring rod, with participants standing barefoot. BMI was determined as weight divided by squared height (kg/m^2). Using a standardized smoking questionnaire, participants were classified as smokers (current or quit < 1 year) or nonsmokers (quit ≥ 1 year or never smoked).

Blood was withdrawn after 10–14 h fasting. Total and high-density lipoprotein (HDL) cholesterol concentrations were measured in serum sample aliquots stored at − 80 °C. The Friedewald formula was used to estimate low-density lipoprotein (LDL) cholesterol whenever triglycerides were < 300 mg/dl. A previous study, in which 9 of the 12 FRESCO cohorts participated, obtained good agreement in the measurement of frozen samples from a random subset of participants, establishing that the study's laboratory measurements can be reliably pooled (Grau et al., 2011). Blood pressure was determined from the average of 2 separate readings taken at least 5 min apart. Hypertension, diabetes, hypercholesterolemia and type of treatment were self-reported by the participants in all studies. We also considered hypertension whenever an individual presented with systolic or diastolic blood pressure ≥ 140/90 mm Hg, respectively; diabetic those participants in whom glycemia > 125 mg/dl was observed at the time of baseline examination. In both cases, this condition was assigned regardless of their awareness of such disorders.

2.3. End-points

We defined three end-points for the purpose of our analysis: (1) CVD incidence: fatal or nonfatal myocardial infarction or stroke and angina pectoris; (2) Cancer mortality and (3) Overall mortality. Multiple sources were used to identify potential CVD cases, including self-report, re-examination, and linkages to primary care registers, hospital admissions, and regional and national mortality data. All nonfatal diagnoses were verified by examining the corresponding electronic medical record. Unstable angina during follow-up was diagnosed by the presence of angina symptoms without an abnormal increase in the cardiac enzymes or troponin and with relevant changes in serial electrocardiograms. Alternatively, with or without electrocardiographic changes, a diagnosis was made when suggestive symptoms were recorded during the event and confirmed either by a positive coronary