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Hypertension, obesity and depressed-mood as risk factors for the incidence of type II diabetes and cardiovascular disease

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Seryan Ece Atasoy

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Supervisor: Prof. Dr. Ulrich Mansmann

Second expert: Prof. Dr. med. Karl-Heinz Ladwig

Dean: Prof. Dr. med. dent. Reinhard Hickel

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SUMMARY

Cardiovascular disease (CVD) is the leading cause of mortality among men and women in Europe. Somatic risk factors, including hypertension, obesity and type II diabetes mellitus (T2DM) have been established as having the largest role in the incidence of CVD. However, while research continues to shed light on the pathogenesis, etiology, treatment and management of risk factors, psychosocial factors have not received the required attention.

The current doctoral thesis aims to provide a real-world perspective of the association between somatic risk factors and depressed-mood, and the consecutive impact on the incidence of T2DM and CVD. The investigations were derived from two published manuscripts using population-based prospective data from Augsburg, Southern Germany. The first manuscript examined the 10-year CVD mortality in participants with hypertension cut-off values according to the current European Society of Cardiology (ESC), in comparison to the recently proposed American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Departure from the current ESC to the ACC/AHA hypertension cut-off substantially increased the hypertension prevalence, while capturing a population with lower CVD risk. Furthermore, participants who were aware of their hypertension had higher depressed-mood in comparison to those who were unaware, reflecting a negative labelling effect. The second manuscript examined the interactive effects of obesity and depressed-mood on the 15-year risk of incident T2DM, aiming to understand whether depressed mood had an additional impact for prognosis of morbidity in obese people. The investigation disclosed that despite the significance of obesity as a risk factor for T2DM, presence of depressed-mood heightened the T2DM risk even further in obese people.

The current thesis highlights the relevance of psychosocial factors, namely, depressed-mood, in clinical settings and for public health intervention efforts for CVD and T2DM. Depressed-mood is an essential psychosocial factor to consider in future aetiological conceptualizations of CVD and T2DM because it reveals mortality and morbidity risk beyond the traditional risk factors while simultaneously representing the quality of life of the individual.

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of global mortality, accountable for 32% of all deaths worldwide[1,2], as well as 43.6% of deaths in women and 36.1% of deaths in men in Germany[3]. Beginning with the Framingham Heart Study in 1945, considerable research has been conducted to establish the risk factors of CVD[4]. Ultimately, the INTERHEART case trial found that six major risk factors can be accountable for nine out of ten cases resulting in myocardial infarction; including dyslipidemia, smoking, hypertension, diabetes mellitus, obesity and adverse psychosocial factors[5]. However, despite the advances in the field, the risk prediction of CVD remains low, particularly in individuals with low or intermediate risks[6,7].

Among the classic risk factors of CVD, hypertension takes the lead. Currently, hypertension is defined by the ECS as systolic blood pressures values of 140-159 mmHg and/or diastolic blood pressure values of 90-99 mmHg[8]. Hypertension is independently responsible for 54% of stroke and 47% of ischemic heart disease worldwide[9]. However, despite being a major and modifiable risk factor for the onset of CVD, a review of population studies from 90 countries showed that the prevalence of hypertension increased from 26% in 2000 to 31% in 2010[10]. Additionally, 53.5% of the global population remained unaware of their hypertension, and although this value is 33% in high-income countries, it still remains alarming. Similarly, global antihypertensive treatment increased by only 5% (31.8-36.9%), and by 10% in high-income countries (44.5 to 55.6%). In Germany, treatment of hypertension also showed a comparable increasing trend, and hypertensive patients below 55-years remain largely untreated[11]. Hence, to decrease the global impact of hypertension, the ACC/AHA aimed to reclassify hypertension in 2017 by lowering the hypertension cut-off to systolic blood pressure values of 130-139 mmHg and/or diastolic blood pressure values of 80-89 mmHg[12]. The purpose of the reclassification was to increase awareness and begin earlier antihypertensive treatment; however, real-world consequences remain to be studied. For instance, in a population-based study including 33,105 participants from England, an awareness of hypertension was associated with psychological distress, including depression, irrespective of actual blood pressure values or antihypertensive treatment status[13].

Similarly, detrimental links between CVD and type II diabetes have been revealed by a meta-analysis of 102 prospective studies including data from 698,782 participants, where diabetes increased the risk of CVD by 2-fold, independently of additional risk factors[14] As the global prevalence of T2DM increased from 4.3% to 9.0% in men and 5.0 to 7.9% in women between 1980 and 2014[15], and continues to effect 9.9% of the population in Germany[16], etiological pathways of T2DM require further attention. Moreover, data from the MONICA/KORA cohort used in the current investigations aim to underline the challenge that people with T2DM need intensive preventive interventions to reduce risk of CVD[17]. Obesity, defined as a body mass index of 30 or more, accounts for the majority of T2DM risk[18]. In line with the high prevalence of T2DM in Germany, it corresponds that it is the 8th most obese country in the world[19], with over 23% of the population affected[20]. Furthermore, the prevalence of obesity in Germany has risen by 1.4% in women and 4.4% in men in the last decade, continuing towards an upward trend[20]. However, despite the rising levels of obesity, much remains unknown regarding inter-individual differences for management and treatment for better health prognoses. For instance, recent evidence shows that finding clustered classification

among obese people can allow for individually tailored and more effective interventions – obese people who are considered metabolically healthy might have lower risk of morbidity and mortality[21-23]. Additionally, the many psychosocial facets of obesity[24,25] calls into question the effect of obesity on T2DM risk that can be accounted for by obesity alone. Hence, psychosocial phenotypes of obesity might prove effective in shaping targeted interventions aimed at decreasing the incidence of T2DM and ultimately CVD.

Adverse psychosocial factors have been recognized as significant risk factors of CVD[5]. Among these psychosocial factors, depression has gained utmost attention, increasing CVD risk between 60-90%[26-30] due to multifactorial pathological mechanisms[31]. As depression is a common mental health disorder with a global prevalence of 4.4 % or 300 000 million people [32]) and effecting 10.2% of women and 6.1% of men in Germany[33], further understanding of the connection between depression and other classic risk factors is required. Thus far, depression as a risk factor of CVD and T2DM[34] has three additional implications. Previous research has established that depression additionally increases the risk of hypertension[35] and obesity[36]. Moreover, the relationship is bidirectional - the presence of hypertension[13] and obesity[36] also increases the risk of depression. Lastly, among people with CVD[37]and T2DM[38], a negative impact in prognosis of disease have been found. Despite the implications, depression is not likely to be identified in primary care, and the risks of comorbidity with existing risk factors might go unnoticed due to lack of adequate treatment.

2. RATIONALE AND METHODS

2.1 Aims

The current doctoral thesis aims to investigate the hypothesis that depressed mood is associated with heightened adverse effects of CVD and T2DM, in interaction with or even beyond the major classic risk factors; namely, hypertension and obesity. Specifically, manuscript 1 aims to examine the association of the ECS and AHA classifications of hypertension, corresponding labeling effects as assessed by depressed-mood, and future risk of CVD mortality. Manuscript 2 further aims to examine the association between depressed-mood, obesity and their additive effect on the risk of T2DM.

2.2. Study Population

2.2.1 Baseline Data

The data in the current investigations are derived from 13,426 participants who took part in one of three cross-sectional surveys as part of the Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg (MONICA) project[39], as can be seen in Figure 1. The cross-sectional surveys were conducted by the World Health Organization (WHO) in 1984/85, 1989/90, and 1994/95 through standardized interviews by trained medical staff, a self-administered questionnaire, and medical examination. Written informed consent was obtained from each study participant and the study was approved by the local ethics committee.

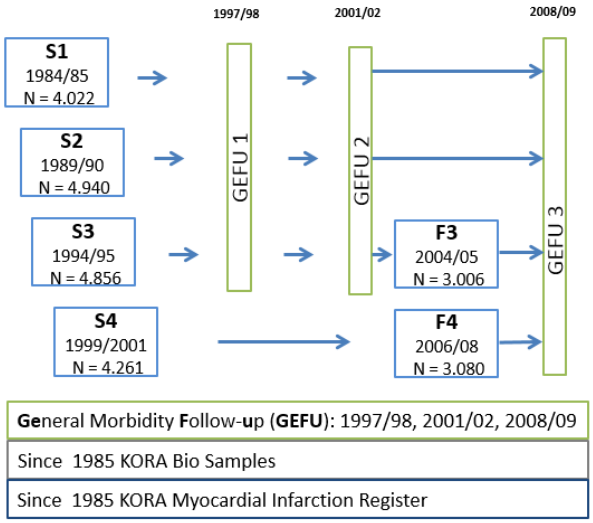

Figure 1. The participant flow from baseline S1-S4 KORA studies to the GEFU follow up.

2.2.2 Follow-up

The General Morbidity Follow up (GEFU) was within the framework of the Cooperative Health Research in the Region of Augsburg and conducted periodically (Figure 1). In Manuscript 1, T2DM incidence was assessed using GEFU 2008/2009 by self-report and further validated through hospital records or by contact with physicians. In Manuscript 2, GEFU 2001/2002 was used to assess CVD mortality. Certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9).

2.2.3. Statistical Analyses

For all analyses, a p value < 0.05 was considered to be statistically significant. All statistical evaluations were performed using SAS (version 9.3). The analyses and descriptions in this manuscript follow the STROBE guidelines for cohort studies.

2.2.4 Descriptive analyses

The proportion of the population with relevant risk factors and group differences were calculated using the Pearson χ^2 and Wilcoxon rank-sum tests. Significance of the obtained results were assessed using Cochran-Armitage Test for Trend.

2.2.5 Absolute and relative risk

The absolute risk of CVD and/or T2DM were calculated across relevant sub-population groups. Proportional hazards models were computed to assess the relative risks of the major risk factors (hypertension, obesity, depression) on CVD and type 2 diabetes endpoints. In both manuscripts, confounders were included in a step-wise manner to present additional risk of associated with the confounders. The step-wise multivariate models were adjusted for (1) age, sex, survey (2) life-style factors (3) metabolic or somatic factors (4) and psychosocial factors. Proportional hazards could be estimated by fitting models stratified by the risk factor categories and plotting the log-log survival curves for each risk factor, which were assessed for parallelism by visual inspection. As severe deviations from parallelism were not observed for any covariates, proportional hazards were assumed. Furthermore, in Manuscript 1, competing risks (additional causes of mortality) were assessed using Fine and Gray's sub-distribution hazard models. On the other hand, in Manuscript 2, multiplicative and additive interaction analyses were included to assess the relative risk of comorbid obesity and depressed mood on the incidence of T2DM.

Robustness of results were scrutinized with additional sensitivity analyses within each manuscript.

3. RESULTS

Manuscript 1: Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/KORA study (S. Atasoy et al., European Heart Journal, 2018)

Manuscript 1 showed that departure from the current ESC hypertension cut-off (Stage 2, or S2) to the ACC/AHA hypertension cut-off (Stage 1, or S1) has increased the hypertension prevalence from 34% to 63% in 11,603 (52% men, 48% women; mean 47.6 years) community dwelling participants from the MONICA/KORA cohort. The cross-sectional analyses showed that only 24% of S2 hypertension patients were under pharmacological treatment. Correspondingly, among S2 participants, there was a significantly higher prevalence of depressed-mood in pharmacologically treated patients (47%) in comparison to non-treated patients (33%) (p<.0001). Furthermore, within a follow-up period of 10 years (70,148 person-years), 370 fatal CVD events were observed. The adjusted CVD-specific mortality rate /1000 persons were 1.61 (95% CI 1.10-2.25) cases in S2 and 1.07 (95% CI 0.71-1.64) cases in S1 hypertension in comparison to normal blood pressure. Cox proportional regression models were significant for the association of S2 and CVD mortality (1.54, 95% CI 1.04-2.28, p=.03), also in the presence of competing risks (1.47, p=.05). However, statistical significance for S1 hypertension was not reached (0.93, 95% CI 0.61-1.44, p=.76).

Manuscript 2: Cumulative Effect of Depressed Mood and Obesity on Type II Diabetes Incidence: Findings from the MONICA/KORA Cohort Study (Atasoy et al. Journal of Psychosomatic Research, 2018)

Manuscript 2 showed that the cumulative effect of having both obesity and depression leads to a significantly higher risk of type 2 diabetes. The study included 9,340 participants (51.6% men, 48.4% women, mean age 49.1 years) from the MONICA/KORA prospective study. Of these participants, 1732 (18.5%) had obesity, 3,816 (37.6%) participants had depressed mood, and 602 (6.4%) had both conditions. After a mean follow up period of 15.4 years (SD ±4.7) there were 968 (10.4%) cases of T2DM incidence. Furthermore, the relative risk of T2DM was over 6 fold higher among obese participants in comparison to normal weight participants (hazard ratio: 6.05; 95% CI 4.82 to 7.59; $p < .0001$). Nonetheless, among participants with obesity, comorbidity of depression was associated with an additional 2-fold risk T2DM (hazard ratio: 8.05, 95% CI 5.90–10.98; $p < .0001$). This finding corresponded to an increase in the 15.4-year absolute risk of T2DM from 15.9 cases per 1000 person-years in participants with obesity but not depression, to 21.4 cases per 1000 person-years for participants with obesity and depression. Further analysis of joint effects and Relative Excess Risk due to Interaction disclosed that depressed mood is associated with significantly higher risk of T2DM in participants with obesity, and to a lesser extent in overweight participants, however an association was not found in normal weight participants.

4. CONCLUSION AND OUTLOOK

In conclusion, the current doctoral thesis highlights the clinical significance of the current ESC hypertension cut-offs for predicting CVD mortality and the risk of obesity for the incidence of T2DM, while accounting for psychosocial risk factors. Within these studies, depressed mood was introduced and examined in both manuscripts in distinctive however clinically relevant ways. In Manuscript 1, depressed mood was associated with an awareness of hypertension at baseline, and implied that a new lower hypertension cut-off would lead to more depressed-mood as a direct result of the increase in hypertension prevalence. However, considering the insignificant risk of CVD mortality in the lower hypertension cut-off, it was unclear whether the potential adverse effects could be justified. On the other hand, in Manuscript 2, depressed-mood had a significant additive effect on the association between obesity and onset of T2DM, showing a clear dose-response relationship with increasing BMI and risk of T2DM in comparison to normal weight participants. Furthermore, this relationship was found to be significant on an additive scale, amplifying the relevance for public health interventions.

The results herein demonstrate that future investigations related to CVD need to include psychosocial factors for real-world applicability of somatic risk factors in terms of the subjective experience of individuals and the consequent effects on their quality of life. With the increasing awareness of the mind-body connection observed in epidemiological research, the expected outlook is that health care professionals will assess CVD risk in light of the individual's mental state. For instance, the next step of Manuscript 1 will be to focus on the trajectory of baseline hypertension with onset psychosocial factors in follow up surveys from MONICA/KORA studies. Finally, the next step of Manuscript 2 will be to take into account additional psychosocial factors in obese people to discover a potential phenotype that exists in parallel to metabolically healthy obesity – a psychologically healthy obesity.

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6. PUBLISHED MANUSCRIPTS

6.1. Manuscript 1

ESC European Society of Cardiology

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CLINICAL RESEARCH
Prevention and epidemiology

Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/KORA study

Seryan Atasoy[1,2], Hamimatunnisa Johar[1,3], Annette Peters[1,4], and Karl-Heinz Ladwig[1,4,5]*

[1]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany; [2]Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 München, Germany; [3]Department of Psychosomatic Medicine and Psychotherapy, University of Gießen and Marburg, Baldingerstraße, D-35043 Marburg, Germany; [4]Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), Partnersite Munich, Biedersteiner Straße 29, 80802 München,, Germany; and [5]Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, Langerstraße 3, 81675 München, Germany

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Aims To investigate the clinical value of a lower blood pressure (BP) cut-off for Stage 1 (S1) hypertension (130–139 mmHg systolic or 80–89 mmHg diastolic) in comparison to the currently established Stage 2 (S2) cut-off (≥140/90 mmHg) in a population-based cohort.

Methods and results We assessed the hypertension prevalence and associated cardiovascular disease (CVD) events in a sample of 11 603 participants (52% men, 48% women; mean 47.6 years) from the MONICA/KORA prospective study. The implementation of the new S1 cut-off increased the prevalence of hypertension from 34% to 63%. Only 24% of S2 hypertension patients were under treatment. Within a follow-up period of 10 years (70 148 person-years), 370 fatal CVD events were observed. The adjusted CVD-specific mortality rate per 1000 persons was 1.61 [95% confidence interval (CI) 1.10–2.25] cases in S2 and 1.07 (95% CI 0.71–1.64) cases in S1 hypertension in comparison to normal BP. Cox proportional regression models were significant for the association of S2 and CVD mortality (1.54, 95% CI 1.04–2.28, $P = 0.03$), also in the presence of competing risks (1.47, $P = 0.05$). However, statistical significance for S1 hypertension was not reached (0.93, 95% CI 0.61–1.44, $P = 0.76$). Among S2 participants, there was a significantly higher prevalence of depressed-mood in treated patients (47%) in comparison to non-treated patients (33%) ($P < 0.0001$).

Conclusion The lower BP cut-off substantially increased hypertension prevalence, while capturing a population with lower CVD mortality. Additionally, participants under treatment were more likely to have depressed-mood in comparison to non-treated participants, which might reflect a negative labelling effect.

Keywords Blood pressure cut-off value • Hypertension prevalence • Cardiovascular risk • Antihypertensive medication • Labelling

Introduction

Among the established somatic and life-style related risk factors for cardiovascular disease (CVD) mortality, the risk of hypertension holds a top rank even surpassing that of smoking.[1] Nevertheless, the exact cut-off values for defining hypertension continue to be a matter of debate. The European Society of Hypertension and the European Society of Cardiology (ESC) currently classifies the cut-off value of systolic blood pressure (SBP) of 120–129 and diastolic blood pressure (DBP) of 80–89 mmHg as 'normal' and the 130–139/

* Corresponding author. Tel: +49 89 3187 3623, Fax: +49 89 3187 3667, Email: ladwig@helmholtz-muenchen.de

85–89 mmHg stratum as 'high normal'.[2] In contrast, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a new guideline in 2017, defining Stage 1 (S1) hypertension at 130–139 mmHg systolic or 80–89 mmHg diastolic, and Stage 2 (S2) hypertension as the former US and current ECS hypertension definition (≥140/90 mmHg).[3] The ACC/AHA estimated that the proportion of US adult population labelled as having hypertension will increase from 32% to 46%.[3,4]

The reclassification was mainly justified by the SBP Intervention Trial (SPRINT), including 9361 adults over 50-year-old with SBP ≥130 mmHg, which showed that lowering SBP to 120 mmHg vs. 130 mmHg led to a substantial relative risk reduction in CVD events and mortality.[5] The reclassification was further supported by two meta-analyses of blood pressure (BP) lowering randomized controlled trials (RCT).[6,7] However, contrary to these findings, the recent and most extended meta-analysis failed to find a favourable effect of BP lowering in subjects with baseline SBP <140 mmHg for CVD events and mortality outcomes.[8]

Apart from highly homogenized patient populations included in RCTs, prospective epidemiological studies have also provided a view into the real-world situation. A meta-analysis of prospective studies supports the 2017 ACC/AHA guideline by showing that 'prehypertension' (defined as SBP 120–139 mmHg) significantly increased the risk of CVD, but not of all-cause mortality.[9] However, the definition of prehypertension used in this study is not in line with the ACC/AHA reclassification of S1 or S2 hypertension.

Given the utmost importance of defining optimal cut-off values for hypertension and the contradictory state of the art, the present investigation used data from the prospective population-based MONICA/KORA study with a random sample of 11 603 participants to assess the proportion of subjects, previously deemed as healthy, who now qualify as hypertensive. Furthermore, considering the adverse effects that labelling people as ill can have,[10] we investigated the occurrence of fatal CVD events based on the 10-year follow-up of participants with S1 and S2 hypertension.

Methods

Participants

The study population was taken from the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)/Cooperative Health Research in the Region of Augsburg (KORA) cohort study.[11] Three independent cross-sectional surveys including 13 427 participants (6725 men and 6702 women aged between 25 and 74-year-old) were conducted in 1984/1985, 1989/1990, and 1994/1995 as part of the multinational WHO MONICA project.[11] In the current analysis, missing data for depressed mood ($N = 939$), cholesterol ($N = 238$), obesity ($N = 129$), and CVD mortality outcome ($N = 26$) lead to a final sample of 11 603 participants (5982 men and 5621 women). A dropout analysis revealed that subjects with missing information were older ($P < 0.001$) compared with subjects with available information.

Assessment of hypertension

Adhering to the WHO MONICA protocol, BP was measured on the right arm in a sitting position using a Hawksley random-zero sphygmomanometer, BP measurements were taken during the clinical interview after approximately half an hour at a 3-min interval. The average readings of the second and third measurement were considered for the analyses.[12] In line with the ACC/AHA Hypertension Guidelines, normal BP was set at SBP <120 mmHg and DBP <80 mmHg, elevated BP at SBP 120/129 mmHg and DBP <80 mmHg, Stage 1 (S1) hypertension at SBP 130–139 mmHg or DBP 80–89 mmHg and Stage 2 (S2) hypertension at SBP ≥140 mmHg or DBP ≥ 90 mmHg. Crude hypertension values were used for analysis; hence, we considered actual BP, irrespective of antihypertensive medication status. Antihypertensive medication was classified as recommended by the German Hypertension Society.

Cardiovascular risk factors

Lifestyle factors

Smoking was defined as currently smoking at least one cigarette per day. Physical activity was defined by engaging in physical activity on average ≥1 h/week throughout the year.

Somatic factors

Total cholesterol (TC) and high-density lipoprotein cholesterol were measured as mg/dL in serum by enzymatic methods (CHOD-PAP, Boehringer Mannheim, Germany) and hypercholesterolaemia was defined as TC ≥ 240 mg/dL. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared and obesity was defined as having a BMI ≥30 kg/m^2. Type 2 diabetes mellitus was self-reported by participants and verified by their medical records.

Depressed mood

Depressed mood was assessed using the depression and exhaustion subscale (DEEX), which combines eight items ranging from 0 to 3, leading to a Likert-like scoring range of 0–24.[13] Participants in the top tertile of the depressive symptom distribution stratified by sex were considered as suffering from depressed mood.

History of cardiovascular disease at baseline and high cardiovascular disease risk group

History of CVD at baseline was defined by self-report of myocardial infarction, heart failure, angina, or stroke. Subjects with high CVD risk were defined by having three or more CVD risk factors.[14]

Follow-up and mortality endpoints

Death certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9). In this study, fatal CVD events (ICD-9: 390-459) were used as the endpoint. In the 10-year follow-up (70 148 person years), there were 370 cases of fatal CVD events. For mortality analyses, event times were calculated as time to death. Subjects without events or with loss to follow-up were censored at the time point of the last follow-up.

Statistical analysis

Descriptive analyses

The proportion of the population with normal BP, elevated BP, S2 and S1 hypertension at baseline were calculated and Pearson's χ^2 test

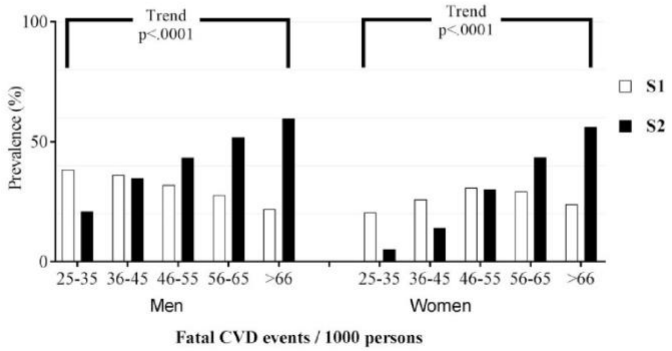


Figure 1 Prevalence of S1 and S2 hypertension in men ($n = 5982$) and women ($n = 5621$) of the MONICA/KORA study, by age group.

and Wilcoxon rank-sum test were used to assess sex, age, treatment, depressed-mood, and additional risk differences. The S1 and S2 hypertension categories were stratified by sex and age groups (10-years), and significance of the obtained results were assessed using Cochran–Armitage test for trend. Similarly, trends in antihypertensive treatment by age groups were assessed.

Fatal cardiovascular disease events

Mortality rates of CVD adjusted for all primary risk factors were calculated for each BP category. Proportional hazards models were computed to assess the association of elevated BP, S2 and S1 hypertension with CVD mortality, where normal BP was considered as the reference group. Four stepwise multivariate models adjusted for (i) age, sex, survey, (ii) life-style factors, (iii) somatic factors, and (iv) depressed mood were calculated. Model 4 included all primary risk factors. A similar step-wise analysis was conducted for the combined S1 + S2 hypertension strata vs. normal BP. In order to ensure power of the analyses was at least 80%, a log-rank test was conducted for comparison of survival rates of CVD mortality in participants with S1 or S2 hypertension vs. normal BP.

Sensitivity analyses calculated the impact of high CVD risk, relative risk of CVD for treated vs. non-treated participants, and the combined S2 + S1 variables vs. normal BP. Proportional hazards could be estimated by fitting models stratified by the risk factor categories and plotting the log–log survival curves for each risk factor, which were assessed for parallelism by visual inspection. As severe deviations from parallelism were not observed for any covariates of CVD events, proportional hazards were assumed. Competing risks were accounted for by cumulative incidence functions using Gray's test. Fine and Gray's sub-distribution hazard model was fitted by specifying event of interest, and by censoring for competing events (non-CVD mortality).[15]

For all analyses, a *P*-value <0.05 was considered to be statistically significant. All statistical evaluations were performed using SAS (version 9.3). The analysis and the description in this manuscript follow the STROBE guidelines for cohort studies.

Results

Baseline characteristics of hypertension

We investigated a population based sample of 11 603 subjects, including 5982 men (51.6%) and 5621 women (48.4%) with a mean age of 47.26 years (±13.3) at baseline. In the total sample, 3914 (33.7%) patients had S2 hypertension. Once the ACC/AHA Guideline's cut-off values for S1 hypertension were applied, an additional 3404 (29.3%) patients were diagnosed with hypertension, almost doubling the prevalence to 7318 (63%).

Sex and age analysis

As shown in *Figure 1*, men had higher S2 (41%) and S1 (33%) hypertension in comparison to women (26% for both S2 and S1 hypertension). The prevalence of S2 hypertension increased with increasing age in both sexes, while the prevalence of S1 hypertension decreased with increasing age for men, and also after 45 years for women ($P < 0.0001$).

Baseline prevalence of cardiovascular disease risk factors

Participants with S2 hypertension presented the most adverse risk factor profile in comparison to other BP groups: they were more likely to be obese, physically inactive, have hypercholesterolaemia, and Type 2 diabetes (*Table 1*; $P < 0.0001$ for all baseline characteristics and BP group associations). The prevalence of S1 criterion resulted in a similar, albeit less pronounced adverse risk factor profile. Correspondingly, the 'high CVD risk' category showed a clear dose–response relationship effect with increasing BP: 7% for normal BP, 10% for elevated BP, 14% for S1, and 21% for S2 hypertensive participants.

Blood pressure lowering treatment

In the S2 hypertension stratum, we identified 948 (24.1%) patients under treatment, while the remaining 2971 (75.9%) did not receive

Table 1 Baseline characteristics of CVD risk factors grouped by BP categories of the 2017 ACC/AHA Guideline in adults between 25 and 74 years old (*N* = 11 603)

		Normal BP ≤120/80	Elevated BP 120–129/<80	Stage 1 hypertension 129–139/80–89	Stage 2 hypertension ≥140/>90	*P*-value
	Total, *n* (%)	2857 (24.62)	1429 12.32)	3403 (29.33)	3914 (33.73)	<0.0001
Age (years), mean (SD)	47.25 (±13.3)	41.18 (±11.7)	45.12 (±13.8)	46.44 (±12.8)	53.32 (±12.2)	<0.0001
Men	5982 (51.6)	872 (30.5)	758 (53.0)	1919 (56.4)	2433 (62.2)	<0.0001
Women	5621 (48.4)	1985 (69.5)	671 (50.0)	1484 (43.6)	1481 (37.8)	<0.0001
Smoking	2807 (24.2)	747 (26.2)	389 (27.2)	826 (24.3)	845 (21.6)	<0.0001
Hyperchol[a]	4687 (40.4)	775 (27.1)	478 (33.5)	1364 (40.1)	2070 (52.9)	<0.0001
Obesity[b]	2123 (18.3)	216 (7.6)	160 (11.2)	605 (17.8)	1142 (29.2)	<0.0001
Physical inactivity	6698 (57.8)	1509 (52.8)	775 (54.2)	1911 (56.2)	2503 (64.0)	<0.0001
Type 2 diabetes	422 (3.6)	26 (0.91)	38 (2.7)	113 (3.3)	245 (6.3)	<0.0001
Depressed mood	4251 (36.6)	1125 (39.4)	520 (36.4)	1201 (35.3)	1405 (35.9)	0.01
High CVD risk[c]	1616 (13.9)	210 (6.9)	118 (9.5)	460 (13.5)	828 (21.2)	<0.0001
History of CVD[d]	961 (8.3)	151 (5.3)	108 (7.6)	238 (7.0)	464 (11.9)	<0.0001
Antihypertensive Medication	1535 (13.2)	130 (4.6)	123 (8.6)	339 (10.0)	943 (24.1)	<0.0001

[a]Hypercholesterolaemia: total cholesterol ≥240 mg/dL.
[b]Obesity: BMI 30 kg/m^2.
[c]High CVD risk: three or more CVD risk factors present.
[d]History of CVD: presents prevalent myocardial infarction, heart failure, angina, or stroke.

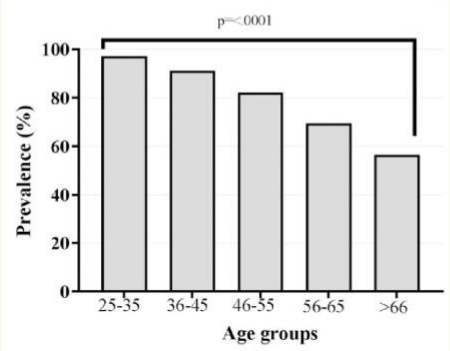


Figure 2 Prevalence of non-treated S2 hypertension participants by age group in the MONICA/KORA cohort (*n* = 2971).

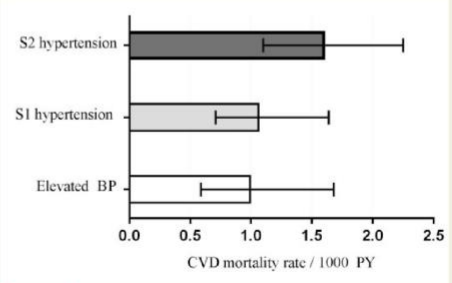


Figure 3 Adjusted cardiovascular disease-specific mortality per 1000 persons with S2 and S1 hypertension in the MONICA/KORA study (*N* = 11 603).

treatment. Further analysis of non-treated participants revealed a clear age related trend, showing that the younger the patient, the less adherent to medication (*Figure 2*). For instance, 325 (97.3%) participants between 25 and 35 years were non-treated, in comparison to 444 (56.4%) of participants over 65 years old.

Blood pressure and depression

In contrast to the other risk factors, higher BP was associated with having lower depressed-mood (*Table 1*). However, S2 patients under treatment, and thus labelled as hypertensive, were the exception to this finding.[16] Among S2 participants, there was a significantly higher prevalence of depressed-mood in treated patients (47%) in comparison to non-treated patients (33%) ($P < 0.0001$).

Cardiovascular disease mortality

In the primary model, the CVD-specific mortality per 1000 persons within the 10-year follow-up period was 1.61 cases in S2 hypertension [95% confidence interval (CI) 1.10–2.25], 1.07 cases in S1 hypertension (95% CI 0.71–1.64), and 1.0 cases in elevated BP (95% CI 0.59–1.68) in reference to normal BP (*Figure 3*).

Table 2 displays the risk of CVD mortality for participants with S2 hypertension, S1 hypertension, and S1 + S2 hypertension combined, in comparison to normal BP. In the S2 hypertension stratum, statistical significance for CVD risk was reached in each stepwise-adjustment

Table 2 Hazard ratios (HR, 95% CI) of fatal CVD events in S2 hypertension (≥140/90 mmHg) ($n = 3914$), S1 hypertension (130–139 mmHg systolic/80–89 mmHg diastolic) ($n = 3403$) and combined S2 and S1 hypertension ($n = 7317$) in comparison to normal BP ($n = 2857$)

Variables	Model 1	Model 2	Model 3	Model 4
S2 vs. normal BP	1.85 (1.26–2.71)**	1.71 (1.16–2.51)**	1.53 (1.04–2.27)*	1.54 (1.04–2.28)*
Smoking	—	2.18 (1.64–2.89)***	2.11 (1.60–2.78)***	2.11 (1.59–2.80)***
Physical inactivity	—	1.23 (0.93–1.63)	1.25 (0.95–1.64)	1.21 (0.96–1.59)
Obesity[a]		1.55 (1.20–2.00)***	1.44 (1.12–1.87)**	1.47 (0.14–1.91)**
Hypercholesterol[b]	—		1.22 (0.95–1.56)	1.22 (0.95–1.57)
Type 2 diabetes	—	—	2.67 (1.96–3.62)***	2.60 (1.92–3.54)***
Depressed mood	—	—	—	1.34 (1.05–1.71)*
S1 vs. normal BP	1.10 (0.72–1.67)	1.08 (0.71–1.65)	0.95 (0.62–1.46)	0.93 (0.61–1.44)
Smoking	—	2.29 (1.48–3.56)***	2.29 (1.47–3.56)***	2.28 (1.46–3.56)***
Physical inactivity	—	1.67 (1.07–2.59)*	1.64 (1.06–2.55)*	1.61 (1.09–2.39)*
Obesity[a]		1.59 (1.04–2.44)*	1.46 (0.95–2.25)	1.48 (0.96–2.28)
Hypercholesterol[b]	—		1.59 (1.08–2.36)*	1.61 (1.09–2.39)*
Type 2 diabetes	—	—	3.32 (1.99–5.57)***	3.10 (1.83–5.26)***
Depressed mood	—	—	—	1.29 (0.87–1.91)
S1+S2 vs. normal BP	1.56 (1.08–2.26)*	1.46 (1.01–2.11)*	1.30 (0.89–1.89)	1.29 (0.89–1.89)
Smoking	—	2.26 (1.78–2.87)***	2.19 (1.73–2.79)***	2.19 (1.73–2.79)***
Physical inactivity	—	1.33 (1.05–1.65)*	1.34 (1.06–1.69)*	1.31 (1.03–1.65)*
Obesity[a]		1.61 (1.30–2.00)***	1.49 (1.20–1.86)***	1.52 (1.22–1.89)***
Hypercholesterol[b]	—		1.36 (1.10–1.68)**	1.36 (1.10–1.68)**
Type 2 diabetes	—	—	2.82 (2.12–3.67)***	2.73 (2.10–3.55)***
Depressed mood	—	—	—	1.29 (1.05–1.60)*

Model 1: crude model (adjusted for age, sex, and survey).
Model 2: adjusted for age, sex, survey, and lifestyle factors.
Model 3: adjusted for age, sex, survey, lifestyle, and somatic factors.
Model 4: adjusted for age, sex, survey, lifestyle factors, somatic factors, and depressed mood.
*$P < 0.05$, $P < 0.01$, $P < 0.001$.
[a]Obesity: BMI ≥30 kg/m^2.
[b]Hypercholesterolaemia: total cholesterol ≥240 mg/dL.

of the Cox regression model, including the primary model adjusted for all risk factors [Model 4: hazard ratio (HR) 1.54, 95% CI 1.04–2.28, $P = 0.03$).

In contrast, the risk of CVD mortality in both S1 hypertension (Model 4: HR 0.93, 95% CI 0.61–1.44, $P = 0.76$) and elevated BP strata (Model 4: HR 0.77, 95% CI 0.44–1.34, $P = 0.36$) vs. normal BP, did not reach statistical significance in any model. Furthermore, combining the S2 and S1 hypertension strata in comparison to normal BP also did not yield significant results between BP >130/80 and CVD mortality in the primary model (HR 1.29, 95% CI 0.89–1.89, $P = 0.18$).

Competing risks analyses showed that in the primary model, S2 hypertension was associated with CVD mortality risk by HR 1.47 ($P = 0.05$), S1 hypertension by HR 1.01 ($P = 0.95$), and elevated BP by HR 0.88 ($P = 0.6$). The effect of competing events (non-CVD related mortality) had a HR of 1.19 ($P = 0.2$) in S2 hypertension and HR of 1.01 ($P = 0.96$) in S1 hypertension.

Sensitivity analyses examining differences of CVD mortality between medically treated vs. non-treated participants with S2 and S1 hypertension were conducted. In the primary model, non-treated S2 participants were at two-fold risk of CVD mortality in comparison to treated S2 participants (HR 2.00, 95% CI 1.14–3.49, $P = 0.01$), whereas a significant difference of CVD mortality was not found in S1 participants who were treated vs. non-treated (HR 1.33, 95% CI 0.73–2.42, $P = 0.35$).

An additional sensitivity analyses considering the effect of CVD history showed HR of 1.54 (95% CI 1.03–2.21, $P = 0.03$) in S2 hypertension, HR 1.03 (0.68–1.57, $P = 0.88$) in S1 hypertension.

Impact of concurrent cardiovascular disease risk factors

As shown in *Table 2*, majority of confounding risk factors had a comparable or higher impact than hypertension on CVD related mortality. For S2 participants, a noteworthy finding was that obesity and depressed mood (HR 1.34, 95% CI 1.05–1.72) showed similar associations to the risk of CVD mortality, demonstrating the high relevance of mental health on CVD related outcomes as comparable to the well-established risk factor of obesity. In comparison, significant associations between depressed mood, obesity, and the risk of fatal CVD events were not found in participants with normal BP.

Discussion

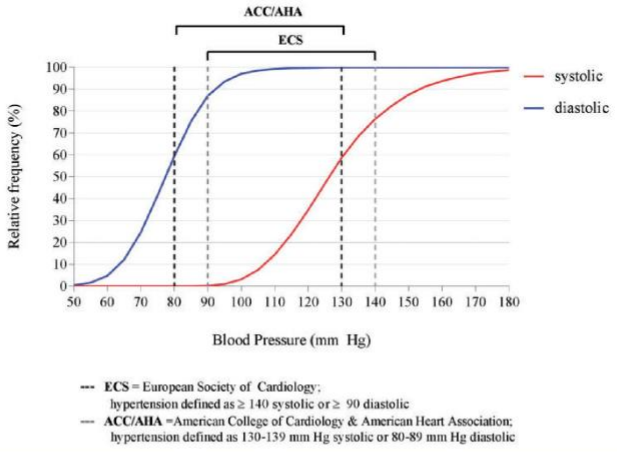
The implementation of the 2017 ACC/AHA Guideline to a German community-dwelling population in the age range of 25–74 years increased the prevalence of hypertension from 34% to 63%. The increase reported herein is notably higher than the recent estimate by Muntner *et al.*,[4] of a rise in hypertension prevalence from 32% to 46%. Nonetheless, given the substantial burden that such high range of new patients would add to health care systems, is it unclear whether the new cut-off points are medically justified.

The present investigation confirms the validity of the S2 hypertension cut-off by showing significant prospective impact in CVD mortality. In contrast, the S1 hypertension cut-off failed to show statistically significant results. However, given the wide boundaries of the CIs, we cannot disprove an increased CVD mortality risk that has been reported in various studies included in previous meta-analyses. Nonetheless, the CVD mortality rates in the S1 hypertension stratum were near the range of elevated BP and normal BP (*Take home figure*).

These results presented here are in contrast to a meta-analysis of 20 prospective studies including 1 129 098 participants performed by Huang *et al.*[9] showing 'prehypertension' (defined as SBP 120–139 mmHg) significantly increased the risk of CVD mortality. However, the significant effect reported in the meta-analysis was driven by four studies, while the remaining 14 studies failed to show significant findings.

The meta-analyses of relevant RCTs also present contradictory findings regarding the optimal BP cut-off for treatment. Our results contradicted the meta-analysis by Ettehad *et al.*[7] including 612 815 participants from 123 RCTs showing that a SBP reduction of 10 mmHg reduced risk of CVD events and mortality across all SBP strata, independently of baseline SBP. A similar finding was achieved by Bundy *et al.*[6] where 42 BP lowering RCTs with 144 220 participants were analysed. Within these studies, the goal of BP reduction was set at SBP of 120–124 mmHg and a linear association between mean achieved SBP reductions and CVD risks was evident, including for subjects with 130 mmHg SBP at baseline (HR 0.71). However, the current investigation confirms the most recent and comprehensive meta-analysis by Brunström *et al.* which included 74 trials with over 300 000 patients. This meta-analysis shows that when baseline SBP is ≥140 mmHg, treatment of hypertension is associated with reduced risk of CVD and death. However, at levels <140, treatment did not lead to observed benefits, with an exception only for coronary heart disease patients.[8]

The ACC/AHA Guidelines aim to decrease the prevalence of hypertension by introducing preventive BP lowering intervention for the S1 population before they reach S2. At first glance, it sounds sensible to target higher-risk individuals for risk factor modification; however, our findings suggest that it is not the optimal approach. First, room for improvement in adherence to antihypertensive medication remains high: 76% of S2 patients remained untreated, and among the medically treated S2 population, only 13% had successfully lowered BP at baseline. Furthermore, the situation remains concerning after follow-up of higher risk individuals identified at baseline. For example, a study by Markus *et al.*, including 1145 subjects from the population based MONICA/KORA S3 survey performed in 1994/1995, and at follow-up in 2004/2005, shows that at baseline, 37.5% of participants were within the S2 hypertension stratum or receiving antihypertensive medication. However, after the 10-year follow-up period, only 8.6% participants had lowered their BP below 140/90 mmHg, despite being aware of their BP status during the initial examination.[17] Second, the baseline prevalence of CVD risk factors showed a clear dose–response relationship with BP; S2 participants led the



Take home figure Departure from the current ECS to the ACC/AHA hypertension cut-off has increased hypertension prevalence, while capturing a population with substantially lower CVD risk.

unhealthiest lifestyle and had the highest CVD risk. This also implies that classifying as hypertensive does not lead to a decrease in unhealthy lifestyle factors, and a lower hypertension classification may not have relevance to initiating lifestyle interventions. Hence, the results demonstrate that having the firmly established ECS hypertension guideline did not lead to higher medical treatment or a healthier lifestyle, and it is doubtful whether a new guideline would lead to higher compliance with BP lowering initiatives.

The relative risk analysis conducted in the present investigation shows that S2 hypertension is not the only significant predictor of CVD risk; and in reality, other risk factors are comparable or present even higher risk. In line with previous findings by Ladwig *et al.*,[18] depressed mood is a significant risk factor to consider, leading to a 34% increase in risk of fatal CVD events in the S2 hypertension stratum. However, based on the cross-sectional baseline analysis, participants in the S2 stratum actually had less depressed mood in comparison to other BP groups, with an exception: among those using antihypertensive medication, half also reported having depressed mood, compared with a third of those not using medication. In line with these findings, Herrmann-Lingen *et al.*[16] showed that a higher BP *per se* was related to less depression, however patients labelled as hypertensive had more depressive symptoms than those without, partially due to medication and awareness of being ill. Hence, high BP could have a protective effect against depression, as suggested by the decrease in depressed mood, however the substantial risk of depressed mood on CVD events is amplified from an awareness of being ill.

Furthermore, labelling has adverse effects on an individual's state of physical and mental health. A review by Pickering shows that diagnoses of hypertension has harmful consequences such as anger, anxiety, depression, deterioration of marital and home life, and worse perception of health in comparison to those without hypertension.[10] The landmark study of this phenomenon, performed by Haynes *et al.*,[19] includes steelworkers recently diagnosed with hypertension, and reports increased work absenteeism by 80% in the following year. Furthermore, an experimental study by Rostrup *et al.*,[20] involving military recruits in Norway shows hypertension labelling leads to increase in BP at the next medical examination. Similarly, labelling of people within the S1 stratum as hypertensive could possibly result in the adoption of sick roles.[21]

Limitation

A limitation of this prospective study is that direct cause and effect relationships cannot be discerned. Furthermore, although we adjusted for a variety of important confounding variables, we cannot exclude that unknown risk factors may have biased the results. Similarly, the wide age range of the population could contribute to the wide CIs in this study, however, this was in line with the ACC/AHA guidelines which do not distinguish between different age groups. The strength of the study is the heterogeneity of a large number of subjects randomly drawn from the population and representative of all hypertensive patients in the community-dwelling population and hence in line with the ACC/AHA guidelines, as opposed to target groups with specific conditions in RCTs. Additional strengths were the availability of data on lifestyle and multiple risk factors, which were measured according to a standardized protocol.

Conclusion

The current prospective epidemiological study has provided a view into the real-world situation of S2 and S1 hypertension patients. The authors of this study recommend a shift of focus back towards BP lowering for patients within the S2 hypertension stratum. As is shown, the departure from the previous US and the current ESC guideline has captured a population that presents lower CVD-specific mortality, and statistically insignificant fatal CVD events. However, participants with S1 hypertension may present clinically significant risk factors that is associated to CVD mortality and should not be overlooked by health care workers (*Table 2*). Nevertheless, the burden on the health care system arising from a lower hypertension cut-off may not be justified considering the potential adverse effects.

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Conflict of interest: none declared.

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Cumulative effect of depressed mood and obesity on type II diabetes incidence: Findings from the MONICA/KORA cohort study

S. Atasoy[a,b], H. Johar[a,c,d], X.Y. Fang[a,e], J. Kruse[c,d], K.H. Ladwig[a,c,e,*]

[a] Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[b] Institute of Medical Informatics, Biometry and Epidemiology (IBE), München, Germany
[c] German Center for Diabetes Research (DZD), München-Neuherberg, Germany
[d] Department of Psychosomatic Medicine and Psychotherapy, University of Gießen and Marburg, Germany
[e] Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, München, Germany

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ABSTRACT

Background: Obesity and depression both individually contribute to the risk of Type II Diabetes (T2DM). The extent to which obesity can be set-off by depression is unknown.
Methods: In a sample of 9340 participants followed for 15.4 years (79,372 person-years) from the prospective MONICA/KORA population-based cohort conducted in Southern Germany, we investigated the impact of obesity, defined as Body Mass Index (BMI) ≥ 30, and depression on the incidence of T2DM using Cox Proportional Hazards Regression.
Results: The relative risk of T2DM was over 6 fold higher among obese participants in comparison to normal weight participants (HR 6.05; 95% CI 4.82 to 7.59; $p < .0001$). Nonetheless, among participants with obesity, comorbidity of depression was associated with an additional 2 fold risk T2DM (HR 8.05, 95% CI 5.90–10.98; $p < .0001$). This finding corresponded to an increase in the 15.4-year absolute risk of T2DM from 15.9 cases per 1000 person-years (py) in participants with obesity but not depression, to 21.4 cases per 1000 py for participants with obesity and depression. Further analysis of joint effects and Relative Excess Risk due to Interaction disclosed that depressed mood is associated with significantly higher risk of T2DM in participants with obesity, and to a lesser extent in overweight participants, however an association was not found in normal weight participants.
Conclusions: The present investigation discloses that despite the overreaching importance of obesity as a risk factor for T2DM, there is room for depressed mood to add measurable risk prediction.

1. Introduction

Even though obesity is established as the leading risk factor for the incidence of type II diabetes mellitus (T2DM), inter-individual differences remain unclear [1–3]. Many observers may assume the existence of a ceiling effect between obesity and subsequent T2DM, however, obesity can be attenuated by psychosocial factors in a real-world setting. Among the current psychosocial etiologies of T2DM, depression as a risk factor has gained uttermost attention. Meta-analytic evidence has confirmed that depression is associated with a 37–60% increase in the incidence of T2DM, despite concurrent lifestyle and metabolic risk factors [2,3].

Surprisingly, there is less research on the involvement of depression in the risk of T2DM among obese people, although epidemiological studies have shown that obesity is also a risk factor for depression [4]. Hence, a higher prevalence of depression among people with obesity may contribute inconsistently to their subsequent T2DM risk [5,6]. Nevertheless, if a cumulative effect between obesity and depression on the onset of T2DM exists, this effect must also remain robust following adjustment for metabolic risk factors to rule out a healthy obesity paradigm [7].

In the current investigation, we aimed to determine the extent to which depression a contributes to an additionally measureable risk of T2DM among participants with obesity using data from a prospective population-based cohort. We anticipate that improved understanding of psychosocial factors among people with obesity, particularly depression, will help advance identification of patients at risk and development of effective treatment options for T2DM.

* Corresponding author at: Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
E-mail address: ladwig@helmholtz-muenchen.de (K.H. Ladwig).

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2. Participants and methods

Data were obtained from 13,426 subjects (30 to 75 years-old) who took part in one of three cross-sectional surveys as part of the Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg (MONICA) project [8]. Baseline information was collected in 1984/85, 1989/90, and 1994/95 through standardized interviews conducted by trained medical staff, a self-administered questionnaire, and medical examination. Participants with prevalent diabetes at baseline (n = 573), without information on diabetes status at follow-up (n = 710) or with incomplete data on all co-variables required for the main analyses (n = 2803) were excluded from the study leading to a final study sample of 9340 participants. A drop-out analysis of excluded participants did not reveal significant age and sex differences in comparison to participants who were included in the study.

Written informed consent was obtained from each study participant and the study was approved by the local ethics committee.

2.1. T2DM

T2DM incidence was assessed using GEFU 2008/2009 (General Morbidity Follow-up) within the framework of the Cooperative Health Research in the Region of Augsburg (KORA) [8]. Self-reported cases and the date of diagnosis were validated through hospital records or by contact with physicians.

2.2. Obesity

Obesity was determined using Body Mass Index (BMI), defined as a person's weight in kilograms divided by the square of her or his height in meters (kg/m^2). Subjects with BMI $<$ 25 were considered to have normal weight, BMI $\geq$ 25 and $<$ 30 were classified as overweight and BMI $\geq$ 30 were classified as obese.

2.3. Depressed mood

Depressed mood was categorized dichotomously into categories of "non-depressed mood" (0–10 for men, 0–12 for women) and "depressed mood" ($\geq$10 for men, $\geq$12 for women) based on the depression and exhaustion subscale (DEEX) that lead to a scoring range of 0–24 [9]. Clinically, the DEEX scale identified symptoms of reduced vitality, weakness and 'vital exhaustion' but without a negative self-concept and feelings of guilt feelings and hence is used as proxy for measuring depression in a large population-based epidemiological study, however is not limited to major depressive disorder.

2.4. Metabolic factors

Metabolic factors consisted of hypertension (systolic/diastolic blood pressure $\geq$ 140/90 mmHg and/or use of antihypertensive medication), and dyslipidemia (total cholesterol to high-density lipoprotein cholesterol ratio $\geq$ 5.0).

2.5. Lifestyle factors

Lifestyle factors consisted of smoking status (regular or non-smoker), alcohol intake (weekday and weekend consumption of beer, wine and spirits) and physical activity (physically active if person regularly participated in sports in summer and winter and was active for at least 1 h/week in at least one season [10].

3. Statistical analyses

Means and proportions of baseline data were computed for participants with depressed mood and non-depressed mood. Baseline differences between categorical variables were tested using the chi-square test and mean differences were assessed using the t-test.

To assess the absolute risk of T2DM, incidence rates of the BMI categories stratified by depressed mood were calculated, and their significance was obtained using Cochran-Armitage Test for trend. The causal interaction of differences between the various absolute risks across the BMI categories and depressed mood as departure from additivity were investigated by testing the incidence rates on the additive scale [11].

The relative risks of T2DM were assessed for each stratum of BMI category and depressed mood with a single reference category (normal weight and without depressed mood) using three subsequent Cox proportional hazards models. Model 1 was adjusted for age, sex, and survey. Model 2 also included lifestyle factors (smoking, physical inactivity, alcohol consumption). Model 3, considered as the primary model, additionally included metabolic risk factors (hypertension, dyslipidemia). The interaction of the relative risks as an amount of departure from additivity was calculated using the Relative Excess Risk due to Interaction (RERI) [12,13].

The assumption of proportional hazards was assessed graphically by checking the log ($-$log (survival)) curves for parallelism. No severe deviations from parallelism were evident. Two-tailed P-values $<$ .05 were considered to be statistically significant. All statistical analyses were performed using SAS (v. 9.3, SAS Institute Inc., Cary, NC, USA). The analyses and description in this article followed the STROBE guidelines for observational cohort studies [14].

4. Results

The present investigation includes 9340 participants (51.6% men, 48.4% women), among whom 1732 (18.5%) were obese, 3816 (37.6%) participants had depressed mood. Additionally, 602 (6.4%) participants suffered from both obesity and depressed mood. After a mean follow up period of 15.4 years (SD ± 6.2, 79,372 person years), there were 968 (10.4%) cases of incident T2DM.

The baseline characteristics, displayed in Table 1, showed that participants with depressed mood were more likely to be older, less educated, and less physically active in comparison to participants without depressed mood. However, clear associations between the BMI categories and depressed mood were not found.

4.1. Incidence and relative risk of T2DM by depressed mood

The T2DM incidence rate per 1000 person-years (py) was 7.6 cases for participants with depressed mood and 6.0 cases for participants without depressed mood. The relative risk analysis showed that in Model 1, depressed mood at baseline was associated with a 17% increased incidence of T2DM (HR 1.17; 95% CI 1.03 to 1.33; p = .01) in comparison to participants without depressed mood. Controlling for lifestyle and metabolic factors did not influence this association (model 2: 1.15, 95% CI 1.01–1.30; p = .04, model 3: HR 1.16; 95% CI 1.06 to 1.02; p = .02).

4.2. Incidence and relative risk of T2DM by BMI status

The T2DM incidence per 1000 py was 18.0 cases in obese participants, 6.8 cases in overweight participants and 1.8 cases in normal weight participants. The relative risk analysis showed that in Model 1, obese and overweight BMI categories were associated with 7.8 fold increased risk (HR 7.80, 95% CI 6.26–9.73, p$<$0001) and 2.9 fold increased risk of T2DM (HR 2.92; 95% CI 2.34–3.63, p $<$ 0001), respectively. In the additional models, the risk of T2DM in obese participants was attenuated due to adjustment for metabolic risk factors (model 2: HR 7.85; 95% CI 6.30–9.80, p $<$ 0001, model 3: HR 6.0; 95% CI 4.80–7.50, p $<$ 0001). On the other hand, the risk of T2DM in overweight participants was not largely effected by further adjustments (model 2: HR 2.94; 95% CI 2.36–3.70, p $<$ 0001, model 3: HR 2.50;

Table 1
Prevalence of baseline characteristics, according to depressed mood, in the MONICA/KORA Cohort (N = 9340).

Baseline characteristics	Total, N (%)	Non-depressed mood (n = 5824)	Depressed mood (n = 3516)	p
Age (yr.) (SD)	49.13 (11.76)	48.3 (11.8)	50.5 (11.6)	< 0.0001
Men	4816 (51.6)	3002 (51.56)	1814 (51.6)	0.96
Women	4524 (48.4)	2822 (48.5)	1702 (48.4)	
Education (> 12 yrs.)	2603 (27.9)	1687 (29.0)	916 (26.1)	0.002
BMI				
Normal	3360 (36.0)	2117 (36.4)	1243 (35.4)	0.003
Overweight	4248 (45.5)	2577 (44.3)	1671 (47.5)	
Obese	1732 (18.5)	1130 (19.4)	602 (17.1)	
Hypertension	3642 (39.0)	2225 (38.2)	1417 (40.3)	0.04
[3]Dyslipidemia	3001 (32.1)	1828 (31.4)	1173(33.4)	0.04
Regular smoking	2424 (26.0)	1502 (25.8)	922 (26.2)	0.64
Alcohol intake				
None	2466 (28.3)	1619 (27.8)	1025 (29.2)	0.34
[1]Moderate	4134 (44.3)	2588 (44.4)	1546 (44.0)	
[2]High	2562 (27.4)	1617 (27.8)	945 (26.8)	
Physically active	3911 (41.9)	2613 (44.9)	1298 (36.9)	< 0.0001

Data represent (N, %) except for age (mean [SD]).
[1] Moderate alcohol consumption: 0.1–39.9 g/day for men and 0.1–19.9 g/day for women.
[2] Heavy alcohol consumption: ≥ 40 g/day for men and ≥ 20 g/day for women).
[3] Dyslipidemia: ratio of total cholesterol to high-density lipoprotein cholesterol ≥ 5.0.

95% CI 2.00–3.11, p < 0001).

4.3. Incidence and relative risk of T2DM by BMI status and depressed mood

As shown in Fig. 1, the incidence of T2DM according to the BMI categories and depressed mood revealed a substantially increasing trend. In the total population, obese participants with depressed mood had the highest absolute risk of T2DM, followed by obese participants without depressed mood (21.4 vs. 15.9 cases per 1000 py; Cochran-Armitage test: p = .01). On the other hand, overweight participants with depressed mood had slightly higher absolute risk of T2DM than without depressed mood (7.73 vs. 6.28 cases per 1000 py; Cochran-Armitage test: p = .05). Lastly, normal weight participants did not present significant differences of absolute T2DM risk with or without depressed mood (2.25 vs 1.59; Cochran-Armitage test: p = .11). Additionally, the absolute risk of T2DM for participants obesity and depressed mood indicated an interaction on the additive scale, as their combined effect was larger than the sum of their effects (21.4 vs 17.15).

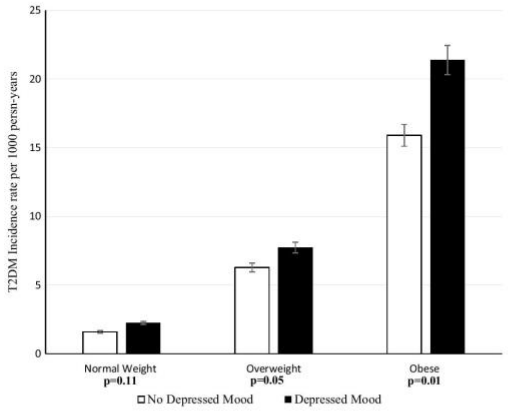

Fig. 1. Incidence rates of T2DM, according to categories of BMI and depressed mood (N = 9340).
*The I bars represent 95% CI.
p values show the association of trend between specific BMI category and depressed mood for the incidence of T2DM. Shown are the unadjusted incidence rates reported per 1000 person-years.

Table 2
Adjusted hazard ratios for T2DM, according to BMI and depressed mood in the MONICA/KORA Cohort (N = 9340).

BMI groups		Non-depressed mood (n = 5824)	Depressed mood (n = 3516)
		(HR, 95% CI)	(HR, 95% CI)
Normal weight (n = 3360)	Model 1	1.00[‡]	1.31 (0.90–1.91)
	Model 2	1.00[‡]	1.29 (0.90–1.91)
	Model 3	1.00[‡]	1.30 (0.90–1.91)
Overweight (n = 4248)	Model 1	3.04 (2.27–4.07)	3.61 (2.68–4.88)
	Model 2	3.07 (2.29–4.11)	3.61 (2.67–4.88)
	Model 3	2.67 (2.00–3.58)	3.11 (2.30–4.21)
Obese (n = 1732)	Model 1	7.89 (5.89–10.57)	10.50 (7.72–14.26)
	Model 2	7.99 (5.96–10.71)	10.35 (7.61–14.10)
	Model 3	6.12 (4.55–8.23)	8.05 (5.90–10.98)

*P values < .0001 for overweight and obese BMI groups.
Model 1: adjusted for age, sex and survey.
Model 2: additionally adjusted for lifestyle risk factors (smoking, alcohol consumption, physical inactivity).
Model 3: additionally adjusted for metabolic risk factors (hypertension, dyslipidemia).
[‡] Participants with a normal BMI and no depressed mood serve as the reference group.

The relative risks of incident T2DM associated with the joint effect of BMI categories and depressed mood is presented in Table 2. As shown, participants with either obese or overweight BMIs presented a significantly higher risk of developing T2DM irrespective of depressed mood, whereas normal weight participants did not. However, obese and overweight participants presented an even higher risk of T2DM when they also had depressed-mood. This cumulative effect on the risk of T2DM was substantially more pronounced in obese participants; a finding in line with the RERI of 1.68 (95% CI: 0.16–3.30) in obese subjects with depressed mood, in contrast to the RERI of 0.14 (95% CI: -0.50-3.20) in overwight participants with depressed mood. On the other hand, there was no evidence of a significant interaction on the multiplicative scale between obesity and depressed mood (p = .44). Furthermore, an in-depth analysis focussing on participants with obesity showed that depressed mood is a significant predictor of their T2DM risk; having depressed mood was associated with a 32% higher risk of T2DM among obese participants than not having depressed

mood (HR: 1.32, 95% CI 1.08–1.61, $p = .007$).

5. Discussion

In this study, we investigated the impact of obesity and depression on the risk of T2DM, with a focus on the cumulative effect between these two risk factors. Based on our results, three conclusions are supported.

First, there was a significant risk gradient between a higher BMI and incidence of T2DM that was demonstrated in both the absolute and relative risk models; indeed, obesity increased the relative risk of T2DM by a HR of 6, confirming prior findings [15]. Second, the presence of depressed mood was associated with an increased relative risk of T2DM by a HR of 1.16, a finding that also confirms and extends prior studies that demonstrate a link between depression and onset T2DM [2,3]. The most important finding, however, was that despite the relatively lower risk of depression in the total sample in comparison to obesity, there was a significant cumulative effect between these two risk factors. Specifically, the incidence of T2DM in participants with obesity and depressed mood was increased by a HR of 8.05 in comparison to the HR of 6.12 in obese participants without depressed mood.

This cumulative effect between obesity and depression may reflect shared or additive biological pathways that, when combined, lead to detrimental effects. For instance, in a recent review by Milaneschi et al., it is thought that obesity causes inflammation related alterations in the insulin pathway that lead to T2DM [5]. This insulin dysregulation also could play a role in the development of depression [16,17]. Our data supports this theory because the effect of depression is most predictive of T2DM in participants within the obese BMI category. On the other hand, normal and overweight participants presumably have lower levels of inflammation, which does not play an additive role in the development of depression. Likewise, the RERI suggested that the joint effect estimated between obesity and depressed mood is greater than the sum of the estimated effects of obesity or depressed mood alone.

The results presented herein confirm a recent study with 919 participants showing a significant interaction between depression, continuous waist-to-hip ratio (WHR) in the risk of diabetes [6]. However, this study had several shortcomings as WHR was self-reported, measure of diabetes was not limited to type 2, and confounding metabolic risk factors beyond WHR were not considered. The current study attains to overcome these limitations and additionally extends the findings to the effect of obesity defined by BMI. Thus, we show that body fat percentage as measured by BMI promotes the increased risk of T2DM in depressed participants independently of fat distribution. This finding is in paralel to purely the intra-abdominal fat stores, which have already been linked to endocrine abnormalities [18]. In summary, this finding suggests that the additional effect of depression remains robust in participants with obesity, and is independent of metabolic risk factors.

The present study has limitations that need to be addressed. Patients who might have prediabetes were not removed at baseline, although it has been shown that undiagnosed prediabetes is not significant associated with depression [19]. Furthermore, depressed mood was assessed by the DEEX scale, which is among the less rigorous options to assess depressive mood although a recent re-examination of its validity and reliability is promising [9].

Additionally, depressed mood was measured at one time point, however, recurrence rates of depression are thought to be over 85% within a decade of an episode [20]. Despite the limitations, depression as a risk factor for T2DM was much more conservative in our study in comparison to similar studies; hence the effects mentioned herein are thought to be robust. Lastly, we have not included possible associations between antidepressants use and obesity because the population using antidepressants was very low; for example, in a follow-up study of 3184 participants who participated in the S3 survey, only 4% used antidepressant medication [21].

In conclusion, an increase in the level of depressed mood was associated with an escalated risk of T2DM within obese participants in the KORA/MONICA prospective cohort. Hence, the present investigation discloses that despite the overreaching importance of obesity as a risk factor for T2DM, there is still room for depressed mood to add measurable risk prediction. The departure from risk additivity that was observed in this study implies that among people with obesity, depressed participants would benefit from a greater risk reduction from an intervention [22].In this way, depression should be included in part of the risk assessment and treatment of obese individuals in clinical settings, particularly by keeping in mind the magnitude of the layered stigma of having both conditions [23].

Declarations of interest

None.

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Dean's Office
Medical Faculty

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Atasoy, Seryan

Surname, first name

Lipperheidestr. 21

Street

81245, Munich

Zip code, town

Germany

Country

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