Is hypertension the link between depression and cardiovascular disease?

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SUMMARY

English

Both cardiovascular disease (CVD) and depression contribute a great deal to the disease burden around the world, and particularly in Kosovo. There is strong evidence that depression and CVD are causally linked. Several hypotheses support the notion of hypertension as a causal mediator of the association between depression and CVD. However, the mechanisms underlying the prospective relationship between depression and CVD remains poorly understood. Identifying mechanisms of this relationship is of great public health relevance towards improved CVD prevention and would greatly contribute towards cardiovascular epidemiology.

The overarching purpose of this dissertation was to elucidate the prospective association between depressive symptoms and blood pressure-related outcomes. Specifically, the dissertation aims to assess the potential effects of depression and depressive symptoms on change in blood pressure, hypertension diagnosis and hypertension control. Further, the dissertation will provide novel and updated evidence of the burden of depression, CVD and their risk factors in Kosovo.

Part of the dissertation work involved implementing a cohort study in Kosovo. Primary healthcare users aged 40 years and above were recruited consecutively between March and October 2019 from 12 Main Family Medicine Centers across Kosovo. Cohort data were collected annually in two phases, approximately 6 months apart, with an expected total follow-up time of 5 years. The dissertation also uses longitudinal data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults from waves 2, 3 and 4. Multivariable censored regression was used to assess the prospective association between depression or depressive symptoms and change in systolic and diastolic blood pressure. Multivariable logistic regression was used to assess the prospective association between depression or depressive symptoms with hypertension diagnosis.

The dissertation provides evidence on the burden of hypertension, CVD risk factors and depression in Kosovo. Poor nutrition (85%), physical inactivity (70%), obesity (53%), and smoking (21%) were common risk factors among PHC users, contributing to the CVD burden in the country. Although mental health in Kosovo appears to have improved since reports from

the early 2000s, moderate to very severe depressive symptoms were still highly prevalent (12.1%) in 2019. These findings highlight the importance of CVD-centered epidemiological studies in the Kosovo context for stakeholders and policy-makers.

We found that, within the same sample, depression was associated with both smaller age-related increases in blood pressure and an increase in odds of hypertension diagnosis. The dissertation, therefore, contributes to cardiovascular epidemiology by further elucidating the prospective association between depression and CVD through different pathways involving blood pressure. These findings can be explained first by shared biology between depression and lower blood pressure, while higher healthcare utilization among people with depression may explain the observed increase in odds of having underlying hypertension diagnosed.

Taken together, hypertension is not a likely causal mediator in the association between depression and CVD. The findings of this dissertation help explain the mixed evidence on the prospective association between depression and hypertension. The dissertation also provides evidence that depression and hypertension are still important disease burdens in Kosovo which need improved prevention. This thesis points to the important need for further research into other possible pathways between depression and CVD given their high contribution to disease burden and disability.

Deutsch

Sowohl Herz-Kreislauf-Erkrankungen als auch Depressionen tragen weltweit und insbesondere im Kosovo in hohem Masse zur Krankheitslast bei. Es gibt starke Hinweise darauf, dass Depression und Herz-Kreislauf-Erkrankungen kausal miteinander verbunden sind. Mehrere Hypothesen unterstützen die Ansicht, dass Bluthochdruck ein kausaler Vermittler des Zusammenhangs zwischen Depressionen und Herz-Kreislauf-Erkrankungen ist. Die Mechanismen, die dem prospektiven Zusammenhang zwischen Depressionen und Herz-Kreislauf-Erkrankungen zugrunde liegen, sind jedoch nach wie vor kaum bekannt. Die Mechanismen dieses Zusammenhangs aufzuzeigen ist von grosser Bedeutung für die öffentliche Gesundheit, um die Prävention von Herz-Kreislauf-Erkrankungen zu verbessern, und würde einen wichtigen Beitrag zur kardiovaskulären Epidemiologie leisten.

Das übergeordnete Ziel dieser Dissertation ist es, den prospektiven Zusammenhang zwischen depressiven Symptomen und blutdruckbezogenen Folgen zu erforschen. Insbesondere sollen die potenziellen Auswirkungen von Depressionen und depressiven Symptomen auf

Veränderungen des Blutdrucks, die Diagnose von Bluthochdruck und die Kontrolle des Bluthochdrucks untersucht werden. Darüber hinaus wird die Dissertation neue und aktualisierte Erkenntnisse über die Krankheitslast durch Depressionen und Herz-Kreislauf-Erkrankungen sowie deren Risikofaktoren im Kosovo liefern.

Ein Teil der Arbeit an der Dissertation bestand in der Durchführung einer Kohortenstudie im Kosovo. Nutzer der primären Gesundheitsversorgung im Alter von 40 Jahren und älter wurden zwischen März und Oktober 2019 konsekutiv aus 12 grossen Zentren für Familienmedizin im Kosovo rekrutiert. Kohortendaten wurden jährlich in zwei Phasen im Abstand von etwa 6 Monaten erhoben, mit einer erwarteten Gesamtnachbeobachtungszeit von 5 Jahren. Die Dissertation verwendet auch Längsschnittdaten aus den Wellen 2, 3 und 4 der Schweizerischen Kohortenstudie über Luftverschmutzung und Lungen- und Herzkrankheiten bei Erwachsenen. Mittels multivariabler zensierter Regression wurde der prospektive Zusammenhang zwischen Depression oder depressiven Symptomen und Veränderungen des systolischen und diastolischen Blutdrucks untersucht. Mittels multivariabler logistischer Regression wurde der prospektive Zusammenhang zwischen Depression oder depressiven Symptomen und der Diagnose von Bluthochdruck untersucht.

Die Dissertation gibt Aufschluss über die Krankheitslast durch Bluthochdruck, Herz-Kreislauf-Erkrankungen-Risikofaktoren und Depressionen im Kosovo. Schlechte Ernährung (85 %), Bewegungsmangel (70 %), Fettleibigkeit (53 %) und Rauchen (21 %) waren häufige Risikofaktoren unter Nutzern der primären Gesundheitsversorgung und trugen zur Krankheitslast durch Herz-Kreislauf-Erkrankungen im Land bei. Obwohl sich die psychische Gesundheit im Kosovo seit den Berichten aus den frühen 2000er Jahren verbessert zu haben scheint, waren mässige bis sehr schwere depressive Symptome im Jahr 2019 immer noch weit verbreitet (12,1 %). Diese Ergebnisse machen deutlich, wie wichtig epidemiologische Studien zu Herz-Kreislauf-Erkrankungen im Kosovo für Interessengruppen und politische Entscheidungsträger sind.

Wir fanden heraus, dass Depressionen in derselben Stichprobe sowohl mit einem geringeren altersbedingten Anstieg des Blutdrucks als auch mit einer höheren Wahrscheinlichkeit einer Hypertonie-Diagnose verbunden waren. Die Dissertation leistet damit einen Beitrag zur kardiovaskulären Epidemiologie, indem sie den prospektiven Zusammenhang zwischen Depressionen und Herz-Kreislauf-Erkrankungen über verschiedene Blutdruckverläufe weiter aufklärt. Diese Ergebnisse lassen sich einerseits durch die gemeinsame Biologie von

Depressionen und niedrigerem Blutdruck erklären, während andererseits eine höhere Inanspruchnahme der Gesundheitsfürsorge bei Menschen mit Depressionen den beobachteten Anstieg für die Diagnose einer zugrunde liegenden Hypertonie erklären könnte.

Insgesamt ist Bluthochdruck kein kausaler Vermittler für den Zusammenhang zwischen Depression und Herz-Kreislauf-Erkrankungen. Die Ergebnisse meiner Dissertation tragen dazu bei, die uneinheitlichen Erkenntnisse über den prospektiven Zusammenhang zwischen Depression und Bluthochdruck zu erklären. Die Dissertation liefert auch Hinweise darauf, dass Depressionen und Bluthochdruck im Kosovo nach wie vor eine große Krankheitslast darstellen, die einer verbesserten Prävention bedarf. Diese Arbeit zeigt auf, wie wichtig es ist, andere mögliche Zusammenhänge zwischen Depressionen und Herz-Kreislauf-Erkrankungen weiter zu erforschen, da sie in hohem Masse zu Krankheitslast beitragen.

Shqip

Sëmundjet kardiovaskulare (CVD) dhe depresioni kontribuojnë shumë në barrën e sëmundjeve në mbarë botën, dhe veçanërisht në Kosovë. Ka prova të forta që depresioni dhe CVD janë të lidhura në mënyrë shkakësore. Disa hipoteza mbështesin nocionin e hipertensionit si një shkaktar ndërmjetës i lidhjes midis depresionit dhe CVD. Megjithatë, mekanizmat që qëndrojnë në themel të marrëdhënies së mundshme midis depresionit dhe CVD mbeten pak të kuptuara. Identifikimi i mekanizmave të kësaj marrëdhënieje ka një rëndësi të madhe për shëndetin publik për përmirësimin e parandalimit të CVD dhe do të kontribuonte shumë në epidemiologjinë kardiovaskulare.

Qëllimi kryesor i këtij disertacioni është të sqarojë lidhjen e mundshme midis simptomave të depresionit dhe rezultateve të lidhura me presionin e gjakut. Në mënyrë të veçantë, disertacioni synon të vlerësojë efektet e mundshme të depresionit dhe simptomave depresive në ndryshimin e presionit të gjakut, diagnozën e hipertensionit dhe kontrollin e hipertensionit. Më tej, disertacioni do të ofrojë dëshmi të reja dhe të përditësuara të barrës së depresionit, CVD dhe faktorëve të tyre të rrezikut në Kosovë.

Një pjesë e punës së disertacionit përfshiu implementimin e një studimi kohort në Kosovë. Përdoruesit e kujdesit parësor shëndetësor të moshës 40 vjeç e lart u rekrutuan në mënyrë të njëpasnjëshme midis marsit dhe tetorit 2019 nga 12 Qendrat Kryesore të Mjekësisë Familjare në mbarë Kosovën. Të dhënat e kohortit u mblodhën çdo vit në dy faza, në një distance kohore prej 6 muajsh, me pritshmërinë e një kohë ndjekjeje totale prej 5 vjetësh. Disertacioni përdor

gjithashtu të dhëna longitudinale nga studimi i kohortit zviceran mbi ndotjen e ajrit dhe sëmundjet e mushkërive dhe të zemrës tek të rriturit nga valët 2, 3 dhe 4. Regresioni logjistik shumëvariabël u përdor për të vlerësuar lidhjen e mundshme midis depresionit ose simptomave depresive me diagnozën e hipertensionit.

Disertacioni ofron dëshmi mbi barrën e hipertensionit, faktorët e rrezikut për CVD dhe depresionin në Kosovën në tranzicion. Nutricioni i varfër (85%), pasiviteti fizik (70%), obeziteti (53%) dhe duhani (21%) ishin faktorë të zakonshëm rreziku tek përdoruesit e KSHP, duke kontribuar në barrën CVD në vend. Megjithëse shëndeti mendor në Kosovë duket se është përmirësuar që nga raportet e fillimit të viteve 2000, simptomat depresive të moderuara deri në shumë të rënda ishin ende shumë të përhapura (12.1%) në vitin 2019. Këto gjetje theksojnë rëndësinë e studimeve epidemiologjike të përqendruara në CVD në kontekstin e Kosovës për palët e interesuara dhe politikëbërësit.

Ne zbuluam se, brenda të njëjtit kampion, depresioni është i lidhur si me rritjen e presionit të gjakut në moshë të vogël, ashtu edhe me një rritje në shanset e diagnozës së hipertensionit. Disertacioni, pra, kontribuon në epidemiologjinë kardiovaskulare duke sqaruar më tej lidhjen e mundshme midis depresionit dhe CVD përmes rrugëve të ndryshme që përfshijnë presionin e gjakut. Këto gjetje mund të shpjegohen së pari nga biologjia e përbashkët midis depresionit dhe presionit të ulët të gjakut, ndërsa përdorimi më i lartë i kujdesit shëndetësor midis njerëzve me depresion mund të shpjegojë rritjen e vërejtur në rrezikun e të pasurit diagnostikim të hipertensionit bazë.

Të marra së bashku, hipertensioni nuk është një ndërmjetës i mundshëm në lidhjen midis depresionit dhe CVD. Gjetjet e disertacionit tim ndihmojnë në shpjegimin e evidencës të përzier mbi lidhjen e mundshme midis depresionit dhe hipertensionit. Disertacioni gjithashtu ofron evidencë se depresioni dhe hipertensioni janë ende barra të rëndësishme sëmundjesh në Kosovë të cilat kanë nevojë për parandalim të përmirësuar. Kjo temë tregon nevojën e rëndësishme për kërkime të mëtejshme për rrugë të tjera të mundshme midis depresionit dhe CVD duke pasur parasysh kontributin e tyre të lartë në barrën e sëmundjes dhe paaftësinë.

Srpski

I kardiovaskularne bolesti (KVB) i depresija doprinose velikom opterećenju bolesti širom sveta, a posebno na Kosovu. Nekoliko hipoteza podržava koncept hipertenzije kao uzročnog posrednika veze između depresije i KVB. Međutim, mehanizmi koji leže u osnovi

potencijalnog odnosa između depresije i KVB i dalje su slabo istraženi. Identifikovanje ovih mehanizama je od velike važnosti za javno zdravlje i poboljšanje prevencije KVB i u velikoj meri bi doprinelo kardiovaskularnoj epidemiologiji.

Sveobuhvatna svrha ove disertacije je da razjasni moguću povezanost između simptoma depresije i ishoda povezanih sa krvnim pritiskom. Konkretno, disertacija ima za cilj da proceni potencijalne efekte depresije i simptoma depresije na promenu krvnog pritiska, dijagnozu hipertenzije i kontrolu hipertenzije. Takodje, disertacija će pružiti nove i ažurirane dokaze o opterećenju depresije, KVB i njihovim faktorima rizika na Kosovu.

Deo rada na disertaciji uključivao je sprovođenje kohortne studije na Kosovu. Korisnici primarne zdravstvene zaštite starosti 40 i više godina regrutovani su uzastopno između marta i oktobra 2019. iz 12 glavnih centara porodične medicine širom Kosova. Podaci o učesnicima su prikupljani godišnje u dve faze, u razmaku od približno 6 meseci, sa očekivanim ukupnim vremenom praćenja od 5 godina. Disertacija takođe koristi longitudinalne podatke iz Švajcarske kohortne studije o zagađenju vazduha i bolestima pluća i srca kod odraslih iz faze 2, 3 i 4. Multivarijabilna cenzurisana regresija je korišćena za procenu potencijalne povezanosti između simptoma depresije ili depresije i promene sistolnog i dijastolnog krvnog pritiska. Multivarijabilna logistička regresija je korišćena za procenu potencijalne povezanosti depresije ili simptoma depresije sa dijagnozom hipertenzije.

Disertacija pruža dokaze o opterećenju hipertenzije, faktorima rizika za KVB i depresije na Kosovu. Loša ishrana (85%), fizička neaktivnost (70%), gojaznost (53%) i pušenje (21%) su bili uobičajeni faktori rizika među korisnicima PZZ, doprinoseći opterećenju KVB u zemlji. Iako se čini da se mentalno zdravlje na Kosovu poboljšalo od izveštaja iz ranih 2000-ih, umereni do veoma teški depresivni simptomi su i dalje bili veoma rasprostranjeni (12,1%) u 2019. Ovi nalazi naglašavaju važnost epidemioloških studija koje se bave KVB u kontekstu Kosova za zvaničnike i kreatore politike.

Otkrili smo da je, u okviru istog uzorka, depresija bila povezana i sa manjim porastom krvnog pritiska u vezi sa godinama i povećanjem šanse za dijagnozu hipertenzije. Ova disertacija, stoga, doprinosi kardiovaskularnoj epidemiologiji daljim razjašnjavanjem potencijalne veze između depresije i KVB kroz različite puteve koji uključuju krvni pritisak. Ovi nalazi se prvo mogu objasniti zajedničkom biologijom između depresije i nižeg krvnog pritiska, dok češće korišćenje zdravstvene zaštite među osobama sa depresijom može objasniti uočeno povećanje rizika za dijagnozu osnovne hipertenzije.

Uzeto zajedno, hipertenzija nije verovatan posrednik u vezi između depresije i KVB. Nalazi moje disertacije pomažu da se objasne mešoviti dokazi o mogućoj povezanosti između depresije i hipertenzije. Disertacija takođe pruža dokaze da su depresija i hipertenzija i dalje važan teret bolesti na Kosovu, i da je potrebna bolja prevencija. Ova teza ukazuje na značajnu potrebu za daljim istraživanjem drugih mogućih puteva između depresije i KVB s obzirom na njihov visok doprinos opterećenju bolesti i invalidnosti.

LIST OF ARTICLES

ARTICLE 1

Obas KA, Gerold J, Bytyçi-Katanolli A, Jerliu N, Kwiatkowski M, Ramadani Q, Statovci S, Zahorka M, Probst-Hensch N. Study protocol: a prospective cohort on non-communicable diseases among primary healthcare users living in Kosovo (KOSCO). BMJ Open. 2020 Sep 1;10(9):e038889. doi: 10.1136/bmjopen-2020-038889. PMID: 32963070; PMCID: PMC7509972.

ARTICLE 2

Obas KA, Bytyci-Katanolli A, Kwiatkowski M, Ramadani Q, Fota N, Jerliu N, Statovci S, Gerold J, Zahorka M, Probst-Hensch N. Strengthening Primary Healthcare in Kosovo Requires Tailoring Primary, Secondary and Tertiary Prevention Interventions and Consideration of Mental Health. Front Public Health. 2022 Apr 5;10:794309. doi: 10.3389/fpubh.2022.794309. PMID: 35480592; PMCID: PMC9037373.

ARTICLE 3

Obas KA, Kwiatkowski M, Schaffner E, Lang UE, Stolz D, Eze IC, Imboden M, Probst-Hensch N. Depression and cardiovascular disease are not linked by high blood pressure: findings from the SAPALDIA cohort. Sci Rep. 2022 Apr 1;12(1):5516. doi: 10.1038/s41598-022-09396-2. PMID: 35365701; PMCID: PMC8975826.

ARTICLE 4

Obas KA, Kwiatkowski M, Bytyci-Katanolli A, Statovci S, Jerliu N, Ramadani Q, Fota N, Gerold J, Zahorka M, Probst-Hensch N. Prospective association between depressive symptoms and blood-pressure related outcomes in Kosovo. PLOS Glob Public Health. 2023 Apr 7;3(4):e0000851. doi: 10.1371/journal.pgph.0000851. PMID: 37027380; PMCID: PMC10081745.

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ABBREVIATIONS

AQH	Accessible Quality Healthcare Project
BEN	Balkan Endemic Nephropathy
BP	Blood pressure
CAD	Coronary artery disease
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CRH	Corticotropin-releasing hormone
CVDs	Cardiovascular Diseases
DALY	Disability Adjusted Life-Years
DASS	Depression Anxiety Stress Syndrome
DM	Diabetes Mellitus
DSM-5	The Diagnostic and Statistical Manual for Mental Disorders, fifth edition
FMA	Family Medicine Ambulantas
FMC	Family Medicine Center
GHQ	General Health Questionnaire
HbA1c	glycosylated haemoglobin
HIS	Health Information System
HPA	Hypothalamic–pituitary–adrenal axis
HSCL	Hopkins Symptoms Checklist
KOSCO	Kosovo Non-Communicable Disease Cohort
LMIC	Low- and middle-income country
MDD	Major Depressive Disorder
MFMC	Main Family Medicine Center
MR	Mendelian Randomization
N06AA	Non-selective monoamine reuptake inhibitors
N06AB	Selective serotonin reuptake inhibitors
N06AX	other antidepressants and/or using a combination of antidepressants
NCD	Non-communicable diseases
NIPH	National Institute of Public Health
ODK	Open Data Kit
OOP	Out-of-pocket

PEN	Packages of Essential Non-communicable Disease Interventions for Primary Healthcare in Low Resource Settings
PHC	Primary Healthcare
PHQ	Patient Health Questionnaire
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
RAE	Roma, Ashkali, Egyptian ethnicity
RCT	Randomized Controlled Trial
SAPALDIA	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults
SDC	Swiss Agency for Development and Cooperation
SF36MH	36-item Medical Outcomes Study Short Form, Mental Health domain, version 1
SOP	Standard Operating Procedures
SPs	Service Packages
SSRI	Selective serotonin reuptake inhibitor
STEPS	Stepwise approach to surveillance survey
Swiss TPH	Swiss Tropical and Public Health Institute
TCA	Tricyclic antidepressant
UP	University of Prishtina
WCH	White coat hypertension
WHO	World Health Organization
YLD	Years lived with disability

DEFINITIONS

There are subtle differences in predictor and outcome definitions in this dissertation that need to be defined. The term **depression** was used in this dissertation to indicate a depression diagnosis from a healthcare professional, usually determined using criteria from the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5). However, in the SAPALDIA study (article 3), depression was expanded to include three criteria: (1) depression diagnosis by a healthcare professional, (2) antidepressant treatment, and (3) depressive symptoms as defined by the 36-item Medical Outcomes Study Short Form, Mental Health domain (SF36MH) using cut-off score below 50. On the other hand, the term **depressive symptoms** was used in this dissertation to indicate the presence of depressive symptoms according to recommended score cut-offs from the questionnaire developer and do not necessarily denote a diagnosis of depression, although the two are not mutually exclusive. For the KOSCO Study using the 21-item Depression Anxiety Stress Scale (DASS-21), this means moderate to very severe depressive symptoms in the last 4 weeks before data collection.

The dissertation also assessed different blood pressure-related outcomes which are closely linked but distinct. The term **hypertension** was considered too broad because it could be understood as having high systolic or diastolic blood pressure, which had evolving cut-offs over the last decades, or it could be considered the state of being diagnosed with hypertension. As per the guidelines from the European Society of Cardiology, hypertension can be diagnosed when systolic blood pressure is equal to or above 140mmHg or diastolic blood pressure is equal to or above 90mmHg. However, several measurements above this threshold are often needed to obtain a diagnosis from a healthcare professional. Clinical guidelines may also differ across cultures and institutions. To improve the clarity in potential effects of depression on blood pressure-related outcomes, the articles in this dissertation differentiate between systolic and diastolic blood pressure measurements and the state of being diagnosed with hypertension by a healthcare professional. **Systolic and diastolic blood pressure** are the measured resting values of pressure in the arteries expressed in millimetres of mercury. We measured the change of systolic and diastolic blood pressure over time. When the term "**attenuated age-related blood pressure increase"** is used, it means that although blood pressure increases on average in a population over time, the indicated group has a smaller increase over time. **Hypertension diagnosis** is simply the self-reported diagnosis of hypertension by a healthcare professional, regardless of blood pressure measurement.

CHAPTER 1 – INTRODUCTION

1.1 Global burden of non-communicable diseases

1.1.1 Epidemiology

Non-communicable diseases (NCDs) kill over 42 million people each year, equivalent to 74% of all deaths globally (1). Cardiovascular disease (CVD) is the leading cause of annual NCD deaths (18.6 million deaths), followed by cancers (10.1 million deaths), chronic respiratory diseases (4.0 million deaths), and diabetes (1.6 million deaths) (1). These four groups of diseases account for over 80% of all NCD deaths. More than 15 million of these NCD deaths (36%) are premature (between the ages of 30 and 69 years) (1). In addition to premature death, NCDs cause a great deal of disability. NCDs account for over 692 million years lived with disability (YLDs).

NCDs are the result of a combination of genetic, physiological, environmental and behavioural factors, and therefore are in large part highly preventable. The leading modifiable risk factors globally in terms of attributable deaths are elevated systolic blood pressure (to which 10.4 million deaths globally are attributed), followed by smoking (7.1 million deaths), high fasting glucose (6.5 million deaths) and obesity (4.7 million deaths) (2).

There has been a discernable shift of disease burden dominated by communicable disease to NCDs in Low- and middle-income countries (LMICs) (3,4). Premature death due to NCDs disproportionally affects LMICs, accounting for over 85% of global premature deaths due to NCDs (1). This is related to the increase of modifiable behavioural risks in these settings such as tobacco use and unhealthy diets in parallel to the reduction of infectious diseases (3). One study found that LMICs are expected to see dramatic increases in the burden of premature death and disability from NCDs by 2040 because over the next 25 years, these countries are expected to have the greatest increases in death and disability from NCDs as well as projected to have the smallest increases in health spending (3). This poses a huge financial strain on people with NCDs in LMICs because NCDs require long-term treatment thus high healthcare costs which are often paid out-of-pocket (OOP) due to insufficient state-funded insurance schemes in LMICs. In addition to the burden on individuals, NCDs also pose a burden on health systems in LMICs who strain to meet the increasing demands for NCD care with limited funding.

Economies also suffer due to work absenteeism from illness. Thus, LMICs are particularly vulnerable to the adverse impact of NCDs and make them poorly equipped to manage NCDs in the next decades.

1.1.2 Current efforts for the prevention and control of non-communicable diseases in low and middle-income countries

NCDs threaten progress towards the 2030 Agenda for Sustainable Development, which includes a target of reducing premature deaths from NCDs by one-third by 2030 (5). The World Health Organization (WHO) monitors and promotes global action against NCDs. The WHO developed a Global Action Plan for the prevention and control of NCDs 2013-2020 (6), which includes nine global targets that impact global NCD mortality. These targets address the prevention and management of NCDs. There are low-cost interventions for governments and other stakeholders to reduce common modifiable risk factors. For example, the WHO has prepared Packages of Essential Non-communicable Disease Interventions for Primary Healthcare in Low Resource Settings (PEN) (7) to strengthen early detection and timely treatment. Evidence shows such interventions are excellent economic investments because, if provided early to patients, they can reduce the need for more expensive treatment (8). However few LMICs implement such tools. Major challenges for primary and secondary prevention in LMICs include lack of health data, limited national resources, and NCDs having a relatively low priority in their health agenda.

In summary, NCDs are the biggest threat to global health and disproportionately affect LMICs. Vigilant surveillance of the NCD burden in LMICs and further investment into low-cost approaches to support health systems respond to the NCD burden in LMICs are needed.

1.2 Global burden of cardiovascular disease

1.2.1 Epidemiology

CVDs remain the leading cause of mortality in the world and a major contributor to disability (9). CVDs account for over 393 million disability-adjusted life-years (DALY) (15.5% of all DALYs globally), over 523 million prevalent cases and 18.6 million deaths annually (1). CVD consists of a group of diseases that affect the heart and blood vessels, including coronary artery disease (CAD), also called ischemic heart disease or coronary heart disease, cardiomyopathy, cerebrovascular disease, peripheral vascular disease, rheumatic heart disease, arrhythmias, hypertensive heart disease, and endo/myocarditis. End-stage CVD includes congestive heart

failure. Important and often fatal CVD events include myocardial infarction and stroke (ischemic and hemorrhagic). CVD and CVD events that caused the most deaths in 2019 include CAD (49.2%), ischemic stroke (17.7%), hemorrhagic stroke (17.5%) and hypertensive heart disease (cardiomyopathy caused by hypertension) (6.2%) (9). The CVD burden was higher in men compared to women up until the age of 80, from which the pattern reverses (9).

CVD also disproportionately burdens LMICs. About 80% of all cardiovascular-related deaths occur in LMIC and at a younger age in comparison to high-income countries (10). The highest burden of cardiovascular death is in Eastern Europe and Central Asia (10–12), as shown in **Figure 1 (Chapter 1)**.

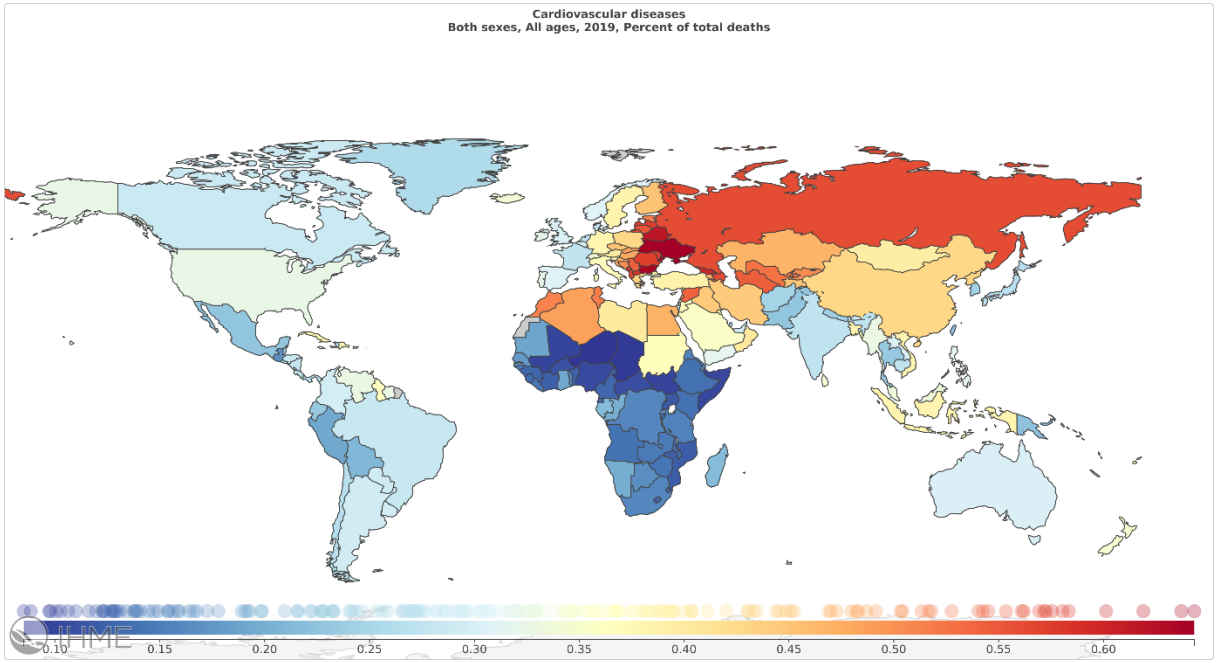

Figure 1. Distribution of the global burden of cardiovascular diseases (12)

In addition to the well-known risk factors of CVD, LMIC face novel risk factors that affect them disproportionately (10). This includes air pollution, climate change, and psychological/economic stressors. **Figure 2 (Chapter 1),** reproduced from Gersh et al. (2010), shows the "perfect storm" of predisposing environmental, genetic and economic factors for CVD in LMICs.

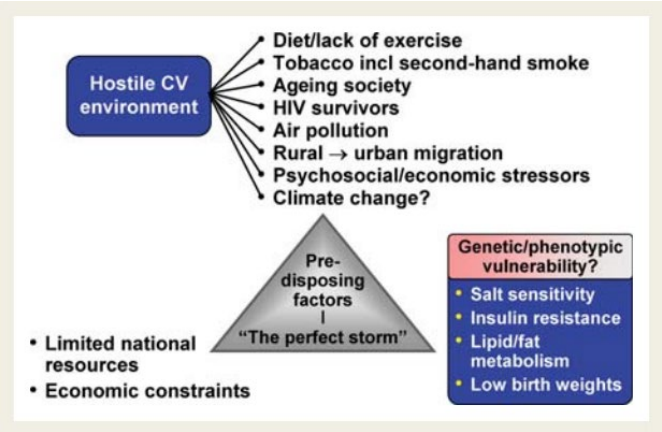

Figure 2. Factors contributing to the epidemic of cardiovascular disease in low- and middle-income countries (10)

CVD has also been associated with adverse outcomes of communicable diseases like the coronavirus disease 2019 (COVID-19). In light of the COVID-19 pandemic, emerging evidence has shown that people with CVD risk factors or CVD have an increased risk of severe COVID-19 (13,14). Challenges in vaccine rollout (15) and adherence to COVID-19 prevention measures due to overcrowding, limited resources and economic pressure to return to work make people in LMICs all the more vulnerable to the adverse effects of COVID-19 related to CVD.

1.2.2 Etiology and pathophysiology

As many diseases fit under the umbrella term CVD, there are also several causes. A common denominator in the pathophysiology of several CVDs however is atherosclerosis. Atherosclerosis is the formation of fibro-fatty lesions in the artery wall, which is a slow, lifelong process. Atherogenesis is thought to involve dyslipidemia, immunologic phenomena, inflammation, and endothelial dysfunction (16). These factors trigger lesions in the endothelium and low-density lipoproteins (LDL) deposit where the lesions occur. The endothelium progressively thickens and becomes calcified, narrowing the channel within the artery and reducing blood flow (17,18). The reduced blood flow limits the amount of oxygen and other nutrients reaching the body. Angina and myocardial infarction occur when there is insufficient oxygen transported to the heart tissue, and stroke occurs when insufficient oxygen is transported to the brain tissue.

Risk factors for atherosclerosis include smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, low consumption of fruits and vegetables, regular alcohol consumption, and physical inactivity as was found in several longitudinal studies like

the INTERHEART study (19), NHANES III (20) and Framingham Heart study (21). Identifying these risk factors has played a crucial role in CVD prevention. Population-based strategies for primary prevention are effective in CVD mortality risk reduction, as seen in Finland who saw a reduction of smoking, cholesterol and blood pressure in parallel to population-based primary prevention interventions and subsequently a 66% reduction in CVD mortality risk (22). Risk factor modification in other earlier observational studies was associated with 44% of the decline in CVD risk in Finland (23) and the United States of America (24). CVD risk factor modification can also be facilitated through a Health-in-All Policy approach to enable lifestyle change (25). For example, ensuring green spaces and safe sidewalks are important environmental factors that promote healthy lifestyles such a physical activity (26). These environmental enablers are often not available in LMICs.

Due to shared risk factors between NCDs, people with CVD also often have comorbidities. One study found that 77% of people with CVD had at least a second morbidity, which was also associated with increased healthcare utilization (27). Diabetes and COPD were among the most common comorbid conditions for CVD patients in another study (28). CVD can also lead to other NCDs. For example, CVD and CVD risk factors are associated with an increased risk of dementia later in life (29). Thus, people with CVD require holistic and integrated care which addresses all NCDs.

In summary, CVD is the most important disease contributing to poor health globally and greatly affects people in LMIC, especially in Eastern Europe. Risk factor modification plays an important role in the reduction of CVD risk as well as for other NCDs.

1.3 Global burden of depression

1.3.1 Epidemiology

Mental health is recognized as an integral part of overall health (30). The Sustainable Development Goal Target 3.4 to reduce premature mortality from NCDs by 2030 also includes the promotion of mental health and well-being. Mental disorders were the second leading cause of disability globally in 2019 (1), with 970 million prevalent cases, which corresponds to an increase in cases of 48% between 1990 and 2019 (31). Mental disorders accounted for 125 million YLDs or 14.6% of global YLDs in 2019 (31). Among mental disorders, depressive disorders were the most common (over 279 million cases) and contributed nearly 47 million DALYs globally in 2019 (1). Anxiety was the second leading disorder. In a study of over

36 000 participants, the 12-month prevalence of major depressive disorder (MDD) was 10.4% and the lifetime prevalence was 20.6% (32). Depressive and anxiety disorders were more common in females (31). Men and women were triggered by different adverse life events: men were more likely to have depressive episodes following divorce, separation, and work difficulties, whereas women were more sensitive to events in their proximal social network, such as difficulty getting along with an individual, serious illness, or death (33).

The emergence of the COVID-19 pandemic in the year 2020 created an environment where many determinants of poor mental health outcomes were exacerbated. One British study found that the prevalence of mental health problems using the 12-item General Health Questionnaire (GHQ-12 score ≥3) increased by 13.5% from pre-pandemic to April 2020. Mental health issues improved between April and June 2020 but remained still poorer than pre-pandemic levels thereafter (34). In another study, there was an estimated 53.2 million additional cases of major depressive disorder globally due to the COVID-19 pandemic (an increase of 27.6%) (35). The long-term mental health effects of COVID-19 are not yet revealed.

Two-thirds of all DALYs in 2019 attributable to depressive disorders were from LMICs (1). Of note, lower-income countries had the least coverage of epidemiological data on depressive symptoms (36) and therefore the burden may be underestimated. Stigma is a major problem in LMICs for those with mental illness wanting to seek help. Further, governments from LMICs spend the lowest percentages on mental health worldwide (37) and often model their mental health systems based on care that is primarily delivered through psychiatric institutions. These barriers often make adequate mental healthcare inaccessible in this low-resource setting. This can explain why many people that require mental health care do not receive any kind of intervention in LMICs. The treatment gap for serious mental disorders was 35–50% in developed countries and 76–90% in LMICs (38).

1.3.2 What is depression?

Those who suffer from depression experience persistent feelings of sadness, hopelessness and lose interest in activities they once enjoyed (39). Aside from the emotional problems caused by depression, individuals can also present with physical or somatic symptoms such as chronic pain or digestive issues (40). In addition to the emotional and physical impacts of depression, there are also important economic impacts: Depressive symptom severity has a linear relationship with productivity loss (41), leading to lowered work functioning, absences, impaired productivity, and decreased job retention.

Clinicians use the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria to diagnose major depressive disorder (MDD) (39), which is a pathological form of depression: "The individual must be experiencing five or more symptoms during the same 2-week period from the following list of symptoms: (1) Depressed mood most of the day, nearly every day; (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day; (3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day; (4) A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down); (5) Fatigue or loss of energy nearly every day; (6) Feelings of worthlessness or excessive or inappropriate guilt nearly every day; (7) Diminished ability to think or concentrate, or indecisiveness, nearly every day; (8) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide." These symptoms must cause the individual significant distress or impairment in social, occupational, or other important areas of functioning. As well as not be a result of substance abuse or another medical condition. At least one of the symptoms should be either a depressed mood or loss of interest or pleasure.

There is however a growing argument in favour of looking at mental health as a spectrum (42,43), rather than distinct categories. The concept of a mental health spectrum includes first the idea of symptoms spectrum relating to the severity within a single disorder, and secondly, the idea of spectra of different disorders sharing overlapping collections of symptoms. This is reflected also in the hundreds of screening tools used by clinicians and researchers alike which place depressive symptoms on a severity scale and acknowledge the overlapping symptoms of depression, anxiety and stress.

1.3.3 Etiology and pathophysiology

The etiology and pathophysiology of depression are still not fully elucidated. Many questions remain about the biology underlying the disorder. Several theories of the pathophysiology of depression have been put forward, however, one review concluded that "the many theories of depression and the relatively low response rate of all available antidepressant treatments argue against a unified hypothesis of depression" and suggested that depression is a clinically and etiologically heterogeneous disorder" (44). The strengths and weaknesses of the prominent depression pathophysiology theories are summarized in **Table 1.** The first three, with the

strongest evidence, are discussed in further detail. These hypotheses are not mutually exclusive, for example, genetic variants could modify the hypothalamic-pituitary-adrenal (HPA) axis.

Table 1. Clinically relevant neurobiological hypotheses of major depressive disorder (MDD), reproduced from Hasler, 2010.

Hypothesis	Main strength	Main weakness
Genetic vulnerability	Solid evidence from twin studies that 30-40% of MDD risk is genetic	No specific MDD risk gene or gene-environment interaction has been reliably identified
Altered HPA axis activity	Plausible explanation for early and recent stress as MDD risk factor	No consistent antidepressant effects of drugs targeting the HPA axis
Deficiency of monoamines	Almost every drug that inhibits monoamine reuptake has antidepressant properties	Monoamine deficiency is likely a secondary downstream effect of other, more primary abnormalities
Dysfunction of specific brain regions	Stimulation of specific brain regions can produce antidepressant effects	Neuroimaging literature in MDD provides limited overlap of results
Neurotoxic and neurotrophic processes	Plausible explanation of "kindling" and brain volume loss during the course of depressive illness	No evidence in humans for specific neurobiological mechanisms
Reduced GABAergic activity	Converging evidence from magnetic resonance spectroscopy and post-mortem studies	No consistent antidepressant effect of drugs targeting the GABA system
Dysregulation of glutamate system	Potentially rapid and robust effects of drugs targeting the glutamate system	Questionable specificity, since glutamate is involved in almost every brain activity
Impaired circadian rhythms	Manipulation of circadian rhythms (e.g., sleep deprivation) can have antidepressant efficacy	No molecular understanding of the link between circadian rhythm disturbances and MDD

HPA – hypothalamic-pituitary-adrenal; GABA – gamma-aminobutyric acid

The genetic theory of depression vs non-genetic factors

So far, there is solid and consistent evidence that MDD is a familial disorder and the influence of genetic factors is about 30-40% (45), thus non-modifiable. However, the remaining 60-70% are explained by non-genetic factors and therefore are modifiable. Non-genetic factors include individual-specific environmental effects such as adverse events in childhood, ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce. Such adverse life events are associated with the onset of depression (46). Another study (47) found that the type of adverse life event was associated with different types of depressive symptoms: Deaths and romantic breakups were associated with high levels of sadness, anhedonia, appetite loss, and guilt. Chronic stress and failures were associated with fatigue and hypersomnia. Those who reported that no adverse life events caused their depressive episodes reported fatigue, appetite gain, and thoughts of self-harm. The large influence of modifiable factors for depression suggests that there is great potential for prevention through psychosocial interventions in schools and workplaces, as well as treatment through empirically validated psychotherapy (48,49). It is important to understand the cause of the depressive symptoms for personalized health approaches.

Hypothalamic–pituitary–adrenal axis dysfunction

A meta-analysis found that depressed people had higher levels of cortisol (50). It is thought that the perception of psychological stress from adverse life events can cause chronic stress, which is perceived by the cortex of the brain and transmitted to the hypothalamus, where corticotropin-releasing hormone (CRH) is released onto pituitary receptors, ultimately resulting in the release of cortisol into the blood (44). These hormones cause physiological and behavioural changes typical of depression such as decreased appetite, disrupted sleep, decreased libido, and psychomotor changes. Chronic activation of the stress response can therefore lead to a depressive state (51). Women show generally greater stress responsiveness than men (52), which is in line with higher rates of depression in women.

Monoamine theory

The monoamine deficiency theory of depression is supported by the evidence that almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant (53). There is some evidence that increased levels of monoamine oxidase in the brain, which metabolizes serotonin, may cause serotonin deficiency (54).

In summary, depression contributes a great deal to the global burden of disease, and people in LMICs are particularly affected by the adverse effects of depression. There are several theories on the pathophysiology of depression, but no consensus has yet been made. It is clear however that adverse life events and the environment are important contributing factors.

1.4 Association between depression and cardiovascular disease

Depression and CVD both independently contribute a great deal to the global burden of disease. In addition to their discrete impact on health, there is overwhelming evidence through meta-analyses that depression is an independent risk factor for CVD (55–60) and that the two conditions exist in a bidirectional relationship (61,62). Several other authors hypothesize on potential causal mediating mechanisms underlying the association between depression and CVD (63–69), which can be classified into genetic, biological and behavioural mechanisms. The genetic correlation between depression and CVD is 42% (70). A meta-analysis of Genome-Wide Association Studies (meta-GWAS) found 24 pleiotropic candidate genes that are likely shared between mood disorders and cardiometabolic risk (71). The hypotheses of biological mechanisms derive from basic science research. The behavioural mechanisms are behaviours

associated with depressive states which are also risk factors for CVD. Hypothesized causal mediating mechanisms between depression and CVD are summarized in **Table 2.**

***Table 2. Summary of potential mechanisms linking depression to increased cardiovascular risk* (65)**

Causal mediating mechanisms	
Unhealthy lifestyle	Smoking
	Excessive alcohol use
	Physical inactivity
	Unhealthy diet
	Lower treatment compliance and worse medical care
Pathophysiology	Metabolic dysregulations
	Immuno-inflammatory dysregulations
	Autonomic dysregulations
	HPA-axis dysregulations
Alternative mechanisms	
Residual cConfounding	Depression picks up or is a prodrome of not yet discovered or not measured (sub)clinical conditions
Iatrogenic effects	Pharmacological impact of antidepressants increase cardiovascular risk
'Third underlying factors'[a]	Childhood stressors
	Personality
	Genetic pleiotropy

[a] Factors that influence in parallel both cardiovascular risk as well as depression risk, but potentially independently from each other.

Although the theoretical underpinnings of the hypothesized mechanisms of the depression - CVD association are sound, no consistent evidence on potential mechanisms has been observed in epidemiological studies. In one meta-analysis of 10 Danish population-based cohort studies (median follow-up time = 20.6 years, n=93 076), the bidirectional association between CVD and depression was not explained by shared risk factors (socioeconomic factors, smoking, physical inactivity, alcohol use, body mass index, systolic blood pressure, total cholesterol), misclassification or non-response (61).

In summary, the mechanisms underlying the prospective relationship between depression and CVD remains poorly understood. Identifying mechanisms of this relationship is of great public health relevance towards improved CVD prevention and would greatly contribute towards cardiovascular epidemiology.

1.5 Hypertension as a potential causal mediator of the prospective association between depression and cardiovascular disease

Numerous epidemiological studies have focused on the association between depression and hypertension as a potential causal pathway to CVD because of the importance of hypertension in the development of CVD as well as the biological and behavioural overlap between depression and hypertension. Hypertension is the risk factor with the highest attributable DALYs (1). As previously discussed in this chapter, hypertension plays an important role in propagating atherosclerosis. Although the definition for hypertension has evolved throughout the past decades, a widely accepted definition currently is systolic blood pressure equal to or above 140mmHg or diastolic blood pressure equal to or above 90mmHg as per the guidelines of the European Society of Cardiology (72). According to a meta-analysis of 41 cross-sectional studies (73), the prevalence of depression in patients with hypertension was much higher than in the general population (26.8% compared to 4.4%), suggesting that the two are strongly connected.

1.5.1 Potential behavioural mediators between depression and hypertension

Depression is associated with an increased risk for unhealthy behaviours such as smoking, physical inactivity, increased alcohol consumption, poor nutrition, and poor sleep (74–76), all of which are known risk factors for raised blood pressure and CVD. Insomnia and short sleep duration, which are typical symptoms of some forms of depression, have been found to significantly increase the risk of hypertension incidence (75,77). Little sleep can activate the HPA axis, which raises blood pressure in the short term, and can lead to long-term structural adaptation that gradually reset the cardiovascular system to operate at an elevated pressure equilibrium. Depression was associated with poorer adherence to hypertension treatment (78). Additionally, one study found that physicians were more cautious with augmenting antihypertensive treatment in people with depression (79) as antihypertensive medication may worsen depression (80). Both factors suggest that depressed persons may be less likely to receive adequate treatment for their high blood pressure.

1.5.2 Potential biological effects of depression on blood pressure

Genetic links

The genetic correlation of depression with hypertension is estimated to be 19% (70).

Biological response to stressors

Depression is thought to be caused in part by environmental factors or adverse events which cause an individual to perceive stress. Perceived stress associated with depression can cause the activation of several biological stress responses. First, stress can activate the autonomic nervous system which stimulates sympathetic activities thereby elevating blood pressure, increasing heart rate, and decreasing heart rate variability (81). Secondly, stress can activate the HPA axis. Through this axis, cortisol is released, which is a well-known stress hormone that increases glucose in the bloodstream and increases blood pressure (65).

Monoamines

A less popular theory links depression to lower blood pressure. The monoamine theory of depression suggests that depletion of monoamines is involved in the pathogenesis of depression (82). Monoamines such as serotonin, epinephrine and norepinephrine play important roles in raising blood pressure. Therefore in the instance of depletion of monoamines, both depressive symptoms and lower blood pressure can be observed.

Antidepressant medication

There is evidence that antidepressant treatments themselves may independently increase blood pressure (83,84). A recent review summarized the literature on the effect of each class of antidepressants on blood pressure (85). Some classes have stronger effects on blood pressure than others. Selective Serotonin Reuptake Inhibitors (SSRIs or ATC code N06AB) were considered the safest class of antidepressants in terms of risk of increasing blood pressure given their limited effects on the autonomic nervous system. Tricyclic antidepressants and dopamine (TCAs or ATC code N06AA) have been associated with both increases in blood pressure and orthostatic hypotension.

1.5.3 Epidemiological studies on the prospective association between depression and hypertension

Epidemiological studies thus far explore the association of depression with three main facets of hypertension: the incidence of hypertension among those with previously normal blood pressure, the control of blood pressure among those with a previous diagnosis of hypertension, and the course of blood pressure as a continuous variable.

Evidence on depression and hypertension incidence

According to a meta-analysis of nine longitudinal studies, depression significantly increased the risk of incident hypertension (RR, 1.42; 95% CI, 1.09-1.86) (86). However, the authors cautioned that the limited number of longitudinal studies available may have impacted conclusions. Although some studies detected hypertension with blood pressure measurements alone (87,88) or in combination with hypertension diagnosis or antihypertensive medication use (83,89–94), several others relied solely on physician-diagnosed hypertension and the use of antihypertension medication to assess the presence of hypertension (95–98). However, many people remain unaware that they have high blood pressure, especially if they do not experience symptoms and fail to get a diagnosis. Depression is associated with higher healthcare utilization (99), thus people living with depression might be more likely to have underlying hypertension diagnosed than those without depression.

The inverse relationship (hypertension as a risk factor for incident depression) was assessed in another meta-analysis, which did not find a significant association (100). One possible explanation is that hypertension is often asymptomatic, having less impact on quality of life and mental health when compared to more advanced stages of CVDs.

Evidence on depression and uncontrolled hypertension

The goal of hypertension control in secondary prevention is to reduce and maintain blood pressure at a normal level through lifestyle changes and/or adhering to prescribed medication. Uncontrolled hypertension is the persistence of high blood pressure after a diagnosis of hypertension, which is a risk factor for developing CVDs. Despite being of great relevance for secondary and tertiary prevention in the public health sector, few studies have assessed the effect of depression on the control of hypertension among hypertensive patients. Depression was found to be positively associated with uncontrolled hypertension in a small cross-sectional study (RR, 15.5; 95% CI, not reported; n=40) (101), and a case-control study's adjusted model (RR, 1.94; 95% CI, 1.31-2.85; n=590) (102). In a large retrospective cohort study (n=210 482), the authors found a significant association between depression and uncontrolled hypertension in their secondary analysis (OR, 1.21; 95% CI, 1.16-1.26) (103).

Evidence on depression and the course of blood pressure

Taking direct blood pressure measurement into consideration is important in epidemiological studies on depression and hypertension. Looking at blood pressure on a continuous scale is also

of interest to better understand the magnitude depression can impact blood pressure. Yet, few longitudinal studies have assessed the association between depression and blood pressure as a continuous variable. A recent longitudinal study in Germany (n=1887) found that after 12 years of follow-up, a moderate level of MDD among hypertensive people was associated with a decrease in both systolic and diastolic blood pressure (104). Since depressive symptoms vary over time, this study was limited by its definition of depression (a lifetime history of depression) because conclusions about the relative effect of short and long-term depressive symptoms could not be made. The importance of evaluating depressive symptoms in parallel to blood pressure over time was noted in another longitudinal study in Norway (105) with follow-ups at 11 and 22 years, which found that a high symptom level of depression and anxiety at baseline and year 11 was more strongly associated with a decrease in blood pressure at year 22, and associated with an even stronger decrease in blood pressure if there were high levels of symptoms at all three examinations. Other population-based studies reported that blood pressure increased with increasing (106) or consistently high (93) depressive symptoms.

In summary, several hypotheses support the notion of hypertension as a causal mediator of the association between depression and CVD. However, there is insufficient epidemiological evidence on the association between depression and hypertension and the existing evidence is mixed. Additional studies that can disentangle the different effects of depression on blood pressure outcomes are warranted.

1.6 Background in the context of Kosovo

Kosovo is an LMIC located on the European continent, in the Balkan region (map in **Figure 3 of Chapter 1**). In 2020, Kosovo had an average gross monthly wage of 466 Euros according to the Kosovo Agency of Statistics (107). Kosovo had the lowest life expectancy in Europe, with 72 years (tied with Moldova) (108). This is well below neighbouring countries such as Albania (79 years), Montenegro (77 years), Macedonia (76 years), and Serbia (76 years) (108).

Figure 3. Map of Kosovo (109)

1.6.1 Limited epidemiological evidence

Good governance in health care requires reliable and timely information to plan, manage, and measure progress in attaining health objectives. Given that the country's Health Information System (HIS) is still in its initial developmental phase (110), it is a challenge to get a better understanding of the main culprits of Kosovo's disease burden due in part to limited epidemiological evidence available. The Ministry of Health in collaboration with the World Bank has been developing/implementing an integrated information system for healthcare providers (110,111). As of 2020, Kosovo has a mixture of paper-based patient record keeping and limited use of the HIS within healthcare facilities (111). In some facilities, no written or electronic record of patient care is maintained. Although the HIS Department has progressed with the implementation of a comprehensive nationwide information system, an audit report in 2017 indicated that the HIS implementation was met with difficulties and had not achieved the goal of 30% coverage in the country (110). Having limited health data in healthcare facilities is a barrier for public health stakeholders in Kosovo to tailor services to the needs of the patients. This additionally makes epidemiological evidence on NCDs in Kosovo scarce, as few studies on NCDs have been conducted in the country.

Another potential cause for limited epidemiological evidence on NCDs in Kosovo is the fact that Kosovo is not recognized as an independent state by many nations. Only half (97 out of 193) of United Nations member states, 22 out of 27 (81.5%) European Union member states, 26 out of 30 (86.7%) NATO member states, and 31 out of 57 (54.4%) Organisation of Islamic Cooperation member states have recognized Kosovo (112). Switzerland is one of the nations which recognizes Kosovo, and the dissertation is therefore written from this stance. Kosovo

comprises an ethnically diverse population, with an ethnic-Albanian majority, with ethnic-Serbian, Roma, Ashkali, Egyptian minorities. In terms of ecological studies, Kosovo is often grouped with Serbia (formally a state of Serbia), as with the Global Burden of Disease data. The life expectancy at birth in Serbia is significantly higher than in Kosovo (108), indicating that the burden of disease differs. The economic, governmental, and healthcare structures also vary greatly so the aggregation of Serbian and Kosovar health statistics thus hides the Kosovo burden of disease. Being unrecognized as an independent state can also create challenges in qualifying for international aid, international support, and research grants. Finally, because of its geographical location in the continent of Europe which is often regarded as a high-income area, Kosovo may be overlooked as an LMIC.

1.6.2 The burden of cardiovascular disease in Kosovo

The Kosovo Agency of Statistics reports that CVDs were responsible for 57.9% of deaths in 2012; 18% of these occurring under the age of 60 (113). In a population-based study in Kosovo (n=1890), 63% of adults aged 65 or more had CVD (114). Progress in Kosovo over the last decade for the reduction of CVD is visible given that the proportion of deaths attributable to CVD in 2019 went down to 51.1% (more women (54.2%) affected than men (48.5%)), and premature deaths (under the age of 60) due to CVD was reduced to 12% (115). Still, 26.8% of all deaths did not receive an ICD-10 code. The large proportion of missing data thus compromises the strength of this evidence.

1.6.3 The burden of depression in Kosovo

Depression and Post-Traumatic Stress Disorder (PTSD) in Kosovo have been studied extensively in the early 2000s as a result of the scientific interest to study psychological effects following the war in the late 1990s. In the first decade after the war, one nationally representative study (n=1161) of persons aged 15 years or older found that 41.7% had moderate to severe depressive symptoms and 41.6% had severe anxiety, measured by the Hopkins Symptoms Checklist (HSCL) (116). PTSD was present in 22% of respondents, measured by the Harvard Trauma Questionnaire, and was predictive of suicidal ideation which was measured with a suicidal ideation index created using items from the General Health Questionnaire and HSCL (116). In the years following the declared independence in 2008, other studies focusing on specific regions of the country or specific subgroups found a prevalence of depression that ranged from 29.7% to 66.5% (117–120). Clearly, depression is common in Kosovo. Some interpret the high rates of depression as an aftermath of the stressful conditions following the

war (121). However, as relative peace and economic development grow in Kosovo, the mental health of inhabitants is expected to improve.

1.6.4 Primary healthcare in Kosovo

In Kosovo, the primary healthcare (PHC) system is divided into three tiers: Each municipality has one Main Family Medicine Center (MFMC), several Family Medicine Centers (FMC) and several Family Medicine Ambulantas (FMA). MFMCs are the largest facilities at the highest level of PHC, which offer more services, staff, and medical equipment and therefore have a higher patient flow compared to the second level FMCs and third-level FMAs.

The Accessible Quality Healthcare (AQH) implementation project, which is funded by the Swiss Agency for Development and Cooperation (SDC) and led by the Swiss Tropical and Public Health Institute (Swiss TPH), started in 2016 and is now one of the prominent projects in Kosovo working within the PHC system. The AQH project has been devoted to working with local stakeholders to improve the quality of PHC in the public health sector through a health system strengthening approach, with a focus on the prevention of NCDs. The three project outcomes are as follows: 1) PHC providers deliver quality services that respond better to communities' needs, 2) Health managers improve their performance in guiding service delivery towards continuous quality improvement, and 3) The population improves its health literacy and is empowered to demand the right to quality services and better access to care.

Health systems strengthening interventions implemented by the AQH project in Kosovo are broad and complex. One of the AQH interventions for the improvement of PHC services is the implementation of service packages (SPs). An important aspect of the SPs is improving the quality of care by setting standards that should be provided at PHC facilities, based on the WHO PEN Protocols (122) which have been adapted to the Kosovo context by national experts. The SPs ensure a continuum of care with the family physician in a gatekeeper role, where patients who are at risk of developing diabetes or hypertension, or those who have already been diagnosed are referred to a health educator for one-to-one motivational counselling sessions to facilitate behaviour change.

1.6.5 Mental healthcare in Kosovo

Providing care for people with mental illness in Kosovo is a challenge. There are only 2.68 psychiatrists, 0.49 psychologists, 0.11 social workers, 4.92 social counsellors, and 15.35 psychiatric nurses per 100,000 inhabitants (123). Mental health services are far less accessible

compared to Switzerland, which has 30 psychiatrists per 100,000 inhabitants (124). There are eight Community-Based Mental Health Centres in Kosovo, each covering approximately 250,000 inhabitants. The implementation of new community mental health services in Kosovo is still characterized by considerable shortages, including financial and human resources, capacity building, stakeholder involvement and service availability (125). Additionally, the psychiatry clinic of the University Clinical Centre of Kosovo in Pristina provides the majority of psychiatric inpatient capacities of Kosovo (88 beds), and regional psychiatric wards are equipped with 10–25 beds on average, for a total of 166 psychiatric beds excluding Prishtina (123). This is a psychiatric bed rate (8.3 per 100,000 population) which is roughly 10 times less than in Central European or Scandinavian countries. There are no specialized psychiatric hospitals in Kosovo.

In addition to insufficient human resources, seeking professional support for mental health is associated with 'tremendous shame' in the country, thus, support is rarely requested or is kept within the family circle (126). Only 15.8% of people who stated they needed help for their mental health sought help from a psychologist or psychiatrist due to fear of being stigmatized (120). If help for mental illness is sought outside the home, families often consult with traditional healers or local religious persons instead of mental health professionals (126). A further obstacle is that people with depressive symptoms often consult healthcare services for somatic symptoms of depression rather than psychological symptoms of depression (127). Depression is therefore more likely to be overlooked by clinicians not trained in mental healthcare when they are preoccupied with treating a comorbid somatic disorder rather than focusing on the patient as a whole (128). This has important implications for PHC, indicating that screening for depression should be included as usual care when a person consults a general practitioner. This can improve the provision of adequate mental healthcare to those who need it.

In summary, both CVD and depression contribute a great deal to the disease burden in Kosovo. Important progress has been made in CVD prevention, however, several barriers still exist in obtaining mental health services in Kosovo. Firstly, mental health services are scarce. Secondly, stigmatization of mental illness such as depression in Kosovo prevents people from seeking care. Finally, PHC providers in Kosovo are not trained for screening for depression. These factors together lead to untreated mental illness.

1.7 Rational for thesis

Depression and CVD are both highly prevalent and contribute immensely to the global burden of disease. They disproportionately affect people in LMICs. Kosovo is among the poorest European countries and has the lowest life expectancy. There is evidence that depression and CVD are highly prevalent in Kosovo, however, studies on these topics are few and outdated.

In addition to their individual burden, depression is also a risk factor for CVD. Understanding the mechanisms underlying the association is of public health relevance for CVD prevention. Mechanisms through blood pressure have been the focus of recent research because of plausible behavioural and biological links. The few existing evidence on the effect of depression on blood pressure is currently mixed. A meta-analysis of 9 prospective studies concluded that depression was associated with the incidence of hypertension (86). The studies included in this meta-analysis had heterogeneous definitions of hypertension, such as blood pressure measurement of different cut-offs, physician diagnosis or antihypertension treatment. The latter two are highly subject to the influence of the health system and health-seeking behaviour. For this reason, studies that include change in blood pressure as an outcome variable provide better insight into the longitudinal biological effects of depression on blood pressure and should be assessed separately from the effect of depression on hypertension diagnosis incidence. Few studies have assessed the prospective association between depressive symptoms and change in blood pressure (88,93,104–106), and the findings are inconsistent. Thus, there is insufficient evidence on the association between depression and the course of blood pressure to conclude the direction of the association. To the best of our knowledge, no study to date has assessed separately the effects of depression on blood pressure change and hypertension diagnosis incidence in the same sample, which could help elucidate the mixed evidence and potential differing effects of depression on blood pressure-related outcomes.

1.8 Chapter References

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CHAPTER 2 – OBJECTIVES

The overarching purpose of this dissertation is to elucidate the prospective association between depression and blood pressure-related outcomes. Specifically, the dissertation aims to assess the potential effects of depression and depressive symptoms on change in blood pressure, hypertension diagnosis and uncontrolled hypertension. Further, the dissertation will provide novel and updated evidence of the burden of depression, CVD and their risk factors in Kosovo.

Specific objectives:

1. Establish a non-communicable disease cohort in Kosovo to provide epidemiological evidence for scientific research, policy and decision making
2. Assess the burden of depressive symptoms and CVD risk factors among PHC users in Kosovo as well as gaps in primary, secondary and tertiary prevention
3. Assess first the prospective association between depression and change in blood pressure as well as hypertension diagnosis in a long-term Swiss cohort with over 10 years of follow-up in preparation for a replication analysis in the Kosovo cohort with a shorter follow-up period
4. Assess the prospective association between depressive symptoms and change in blood pressure as well as hypertension diagnosis and uncontrolled hypertension in Kosovo after one year of follow-up in the Kosovo Non-Communicable Disease Cohort (KOSCO)

CHAPTER 3 – ARTICLE 1

Study Protocol: A prospective cohort on non-communicable diseases among primary healthcare users living in Kosovo (KOSCO)

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ABSTRACT

Introduction With the lowest life expectancy in the Balkans, underlying causes of morbidity in Kosovo remain unclear due to limited epidemiological evidence. The goal of this cohort is to contribute epidemiological evidence for the prevention and control of non-communicable diseases such as depression, hypertension, diabetes and chronic respiratory disease in Kosovo as the basis for policy and decision-making, with a spotlight on the relationships between non-experimental primary healthcare (PHC) interventions and lifestyle changes as well as between depression and the course of blood pressure.

Methods and analysis PHC users aged 40 years and above were recruited consecutively between March and October 2019 from 12 main family medicine centres across Kosovo. The data collected through interviews and health examinations included: sociodemographic characteristics, social and environmental factors, comorbidities, health system, lifestyle, psychological factors and clinical attributes (blood pressure, height, weight, waist/hip/neck circumferences, peak expiratory flow and HbA1c measurements). Cohort data were collected annually in two phases, approximately 6 months apart, with an expected total follow-up time of 5 years.

Ethics and dissemination Ethical approvals were obtained from the Ethics Committee Northwest and Central Switzerland (Ref. 2018-00994) and the Kosovo Doctors Chamber (Ref. 11/2019). Cohort results will provide novel epidemiological evidence on non-communicable diseases in Kosovo, which will be published in scientific journals. The study will also examine the health needs of the people of Kosovo and provide evidence for health sector decision-makers to improve service responsiveness, which will be shared with stakeholders through reports and presentations.

Strengths and limitations of this study

- As the first prospective cohort covering different areas of Kosovo, the study will provide important evidence on the course of non-communicable diseases in a country with limited epidemiological evidence.
- The longitudinal study design will allow us to observe changes in non-communicable diseases and their determinants over time in individuals and analyse the temporal sequence of changes, thus providing stronger evidence in investigating causal relationships.
- Study results can be immediately applied in designing or adapting existing targeted behaviour change interventions by healthcare stakeholders.
- This study is not population based due to the recruitment scheme in primary healthcare facilities, which limits its generalisability and may overestimate the prevalence of health conditions; however, healthy persons are included in the study because primary healthcare patients visit centres for an array of conditions including general check-ups.

INTRODUCTION

Burden of non-communicable diseases in Kosovo

The burden of disease in the Balkan region falls heaviest on Kosovo, suggested by a life expectancy of 72 years,[1] which is lower than neighbouring countries such as Albania (78 years), Montenegro (77 years), Macedonia (76 years) and Serbia (76 years).[1] It is a challenge, however, to get a better understanding of the main culprits of Kosovo's disease burden due in part to limited epidemiological evidence given the country's health information system is still in its initial developmental phase.[2]

Although it is well known that non-communicable diseases (NCDs) are the greatest contributor to health loss in the world, accounting for 61% (or 1.5 billion) of disability-adjusted life years (DALY), only a few estimates on NCDs in Kosovo are available. A national population-based study conducted in 2010 in Kosovo of adults over the age of 65 (n=1890) indicated that the most common self-reported NCDs were cardiovascular diseases (CVDs), with a prevalence of

63%, followed by stomach and liver disease (21%), then diabetes mellitus (DM; 18%).[3]

CVDs are a major health concern globally, accounting for 353 million DALYs (14.8% of all DALYs globally), over 471 million prevalent cases and 17.6 million deaths annually.[4] The situation is dire in the Balkans, where the burden of CVDs is nearly double that of the global prevalence (27.7% of all DALYs for the Balkans). CVDs include coronary artery disease, cardiomyopathy, cerebrovascular disease, peripheral vascular disease, rheumatic heart disease, arrhythmias and endo/myocarditis. Acute CVDs events include myocardial infarctions and strokes. The Kosovo Agency of Statistics reports that CVDs were responsible for 57.9% of deaths in 2012; 18% of these occurring under the age of 60.[5]

Although CVDs are the principal causes of death worldwide, mental disorders are now among the leading causes of disability.[4] Among mental disorders, depression is the most common with over 300 million prevalent cases worldwide (4.4% global prevalence).[6] Depression results from a complex interaction of social, psychological and biological factors and is characterised by persistent sadness, loss of interest in activities a person normally enjoys and inability to carry out daily activities. People who have gone through adverse life events (unemployment, bereavement, psychological trauma) are more likely to develop depression as well as post-traumatic stress disorder (PTSD). PTSD differs from depression in that the person must have experienced a traumatic event and experiences intense, disturbing thoughts and feelings related to their trauma that last long after the event has ended.

Depression and PTSD in Kosovo have been studied more extensively in the past two decades as a result of the scientific interest to study psychological effects following the war in the late 1990s. One nationally representative study (n=1161) of persons aged 15 years or older found that 41.7% had moderate-to-severe depressive symptoms and 41.6% had severe anxiety, measured by the Hopkins Symptoms Checklist (HSCL).[7] PTSD was present in 22% of respondents, measured by the Harvard Trauma Questionnaire, and was predictive of suicidal ideation which was measured with a suicidal ideation index created using items from the General Health Questionnaire and HSCL.[7] Other studies, which focused on specific regions of the country or specific subgroups, found a prevalence of depression which ranged from 29.7% to 66.5%.[8–11] It is clear that depression is common in Kosovo, far exceeding the global average. Some interpret the high rates of depression as an aftermath to the stressful conditions following the war.[12]

In summary, CVD and depression are among the NCDs which cause the greatest burden to global health and may be important starting points for NCDs research in Kosovo.

NCD prevention and control in Kosovo

Primary healthcare (PHC) plays a key role in the prevention and control of CVDs and other NCDs.[13] Primary prevention includes interventions which avert the occurrence of disease, whereas secondary prevention includes interventions which stop or slow the progression of disease once it has started.[14] Many PHC interventions aim to reduce common risk factors of NCDs, such as smoking, physical inactivity and poor diet, in both healthy people and patients with NCDs. In Kosovo, the PHC system is divided into three tiers: each municipality has one main family medicine centre (MFMC), several family medicine centres (FMC) and several family medicine ambulantas (FMA). MFMCs, which formed the basis for the recruitment of the study participants, are the largest facilities at the highest level of PHC, which offer more services, staff and medical equipment and therefore have a higher patient flow compared with the second level FMCs and third level FMAs.

The Accessible Quality Healthcare (AQH) implementation project, which is funded by the Swiss Agency for Development and Cooperation and led by the Swiss Tropical and Public Health Institute (Swiss TPH), started in 2016 and is now one of the prominent projects in Kosovo working within the PHC system. The AQH project has been devoted to working with local stakeholders to improve the quality of PHC in the public health sector through a health system strengthening approach, with a focus on the prevention of NCDs. The three project outcomes are as follows: (1) PHC providers deliver quality services that respond better to communities' needs, (2) health managers improve their performance in guiding service delivery towards continuous quality improvement, and (3) the population improves its health literacy and is empowered to demand the right to quality services and better access to care.

Health systems strengthening interventions implemented by the AQH project in Kosovo are broad and complex. One of the AQH interventions for improvement of PHC services is the implementation of service packages (SPs). This intervention aims to improve the quality of care by setting standards that should be provided at PHC facilities, based on the WHO 'Packages of Essential Non-Communicable Disease (PEN) Protocols,'[15] which have been adapted to the Kosovo context by national experts. The SPs ensure a continuum of care *with the family physician in a gatekeeper role*, where patients who are at risk of developing diabetes or hypertension, or those who have already been diagnosed are referred to a health educator for one-to-one motivational counselling sessions to facilitate behaviour change. Behaviour change is facilitated through lifestyle medicine, which is 'evidence-based practice of assisting individuals and families to adopt and sustain behaviours that can improve health and quality of life (QoL). Healthy behaviours could greatly influence future health and well-being, especially among patients with NCDs'.[16] In the long run, improving the health of populations means that individuals, communities and organisations need to change their behaviour to become healthier.[17] The principal modifiable risk factors for CVDs and other NCDs include: tobacco use, an unhealthy diet

and physical inactivity (which together result in obesity), hypertension, dyslipidaemia and diabetes.[18] Prevention, management or reversal of the modifiable risk factors can be achieved through leading a healthier lifestyle.[19]

When considering the reduction of CVDs, the most damaging risk factor in terms of attributable DALYs is hypertension.[4] Hypertension is defined as blood pressure of above 140/90 mm Hg according to the European Society of Cardiology.[20] The prevalence of hypertension is available in a few Kosovar studies, but no data on hypertension control is yet available. One cross-sectional study (n=423, mean age 51 years) of two rural predominantly ethnic-Serb communities in Kosovo found a hypertension prevalence of 42%.[21] Another cross-sectional study of PHC users (n=1793, mean age 51 years) in the capital city of Pristina found a prevalence of hypertension at 33.6% (39% in men and 29% in women).[22] A third cross-sectional study in 20 villages with a mixture of ethnic-Serbs and ethnic-Albanians found a hypertension prevalence of 30.6% (mean age men=62 years, women=49 years).[23]

The state of other risk factors for CVDs in Kosovo is even less well known. Although one study showed that 18% of older adults self-reported a diagnosis of DM,[3] it is suspected that DM is highly underdiagnosed in Kosovo, indicating a large diagnostic gap. For example, another population study (n=423) conducted in 2006 assessing the prevalence of kidney disease (a positive family history for Balkan Endemic Nephropathy, mild proteinuria, alpha 1-microglobulinuria, eGFR <60 mL/min/1.73 m^2, anaemia, low specific gravity of urine and reduced kidney length) in adults aged 18 years and older living in 2 Serbian settlements in the municipality of Rahovec found that 13% of participants had a previous diagnosis of diabetes but 21% (n=89) still had a pathological glycaemia finding (fasting blood glucose >6.1 mmol/L).[24] Although all residents aged 18 years and above in the two settlements were eligible to participate in the study, the methodology in recruitment was not specified. Some studies on physical activity are available on Kosovar adolescents,[25] but no evidence is available for adults. Similarly, evidence on tobacco use in Kosovo has been focused on school children and adolescents. However, a recent publication on the WHO Stepwise approach to surveillance (STEPS) survey of persons aged 15–64 years conducted in 2010 (n=6400) showed that 37% of men and 20% of women in Kosovo smoke.[26] The prevalence increased with age until it dropped at age 45. The results from the same STEPS survey on physical activity, diet and cholesterol have not yet been published. The AQH project conducted a population-based study in 12 municipalities, with the aim to collect primary data on project indicators for a baseline against which the impact of the project activities will be measured. The study found that 20.6% of respondents smoked, 15% had ever consumed alcohol and 46% did not meet WHO recommendations on physical activity.[27]

In summary, more information is needed about NCD risk factors in the context of Kosovo and the impact of current interventions aimed at their reduction for a better understanding of where to target PHC services.

Mental disorders and their relationship with hypertension

CVDs and mental disorders are among the most burdensome NCDs to global health. It is furthermore disconcerting that there is a well-established bidirectional relationship between CVDs such as coronary artery disease and mental disorders like depression.[28] In PHC, the prevention of CVDs is a high priority. Thus, the relationship between depression and risk factors of CVDs such as hypertension is of great relevance for the public health sector. According to a meta-analysis of 41 cross-sectional studies,[29] the prevalence of depression in patients with hypertension was much higher than in the general population (26.8% compared with 4.4%), suggesting that the two are strongly connected.

Potential mechanisms linking depression and hypertension

Some mechanisms have been proposed to explain how depression is linked to hypertension. First, people living with depression tend to have unhealthy lifestyles which include habits such as smoking, alcohol abuse and physical inactivity,[30] all of which are risk factors for hypertension and CVDs. Second, depression can cause autonomic nervous system dysfunctions which activates sympathetic activities[31] thereby elevating blood pressure. Insomnia and short sleep duration, which are typical symptoms of some forms of depression, have been found to significantly increase the risk of hypertension incidence.[32 33] Little sleep can activate the hypothalamic–pituitary–adrenal axis, which raises blood pressure in the short term, and can lead to long-term structural adaptation that gradually reset the cardiovascular system to operate at an elevated pressure equilibrium. Finally, beyond its role in the aetiology of hypertension and CVDs, the presence of depression may also affect the treatment of hypertension. It was found that physicians were more cautious with augmenting antihypertensive treatment in people with depression[34] because some antihypertensive medications have been found to cause or worsen depression.[35] This means that depressed persons may be less likely to receive adequate treatment from their physician for their blood pressure. In another sense, depression is a risk factor for poor adherence to antihypertensive medication.[36]

The literature thus far explores the association of depression with three main facets of hypertension: the incidence of hypertension among those with previous normal blood pressure, the control of blood pressure among those with a previous diagnosis of hypertension and the course of blood pressure on a continuous scale.

Evidence on depression and hypertension incidence

The goal of primary prevention in PHC in terms of blood pressure is to prevent people from developing hypertension. According to a meta-analysis of longitudinal studies, depression significantly increased the risk of incident hypertension (RR 1.42; 95% CI 1.09 to 1.86).[37] However,

authors cautioned that the limited number of longitudinal studies available may have impacted conclusions. It should also be noted that definitions of hypertension differed among studies, which included either high blood pressure measurement (with differing cut-offs such as ≥140/90 mm Hg or ≥165/95 mm Hg), prescribed antihypertensive medication, physician diagnosis, self-reported hypertension or a combination of these. The inverse relationship (hypertension as a risk factor for incident depression) was assessed in another meta-analysis, which did not find a significant association.[38] One possible explanation is that hypertension is often asymptomatic, having less impact on QoL and thus depression when compared with more advance stages of CVDs.

Evidence on depression and hypertension control

The goal of hypertension control in secondary prevention is for people with hypertension to reduce and maintain their blood pressure at a normal level through lifestyle changes and/or adhering to prescribed medication. Uncontrolled hypertension is the persistence of high blood pressure after a diagnosis of hypertension, which is a risk factor for developing CVDs. Despite being of great relevance for secondary and tertiary prevention in the public health sector, few studies have assessed the effect of depression on the control of hypertension among patients with hypertension. Depression was found to be positively associated with uncontrolled hypertension in a small cross-sectional study (RR 15.5; 95% CI, not reported; n=40),[39] and a case-control study's adjusted model (RR 1.94; 95% CI 1.31 to 2.85; n=590).[40] In a large retrospective cohort study (n=210 482), the authors found a significant association between depression and uncontrolled hypertension in their secondary analysis (OR 1.21; 95% CI 1.16 to 1.26).[41]

Evidence on depression and the course of blood pressure

Looking at blood pressure on a continuous scale is also of interest to better understand the magnitude depression can impact blood pressure. One cross-sectional study (n=2981) found that depressed subjects had lower mean systolic blood pressure than controls, and tricyclic antidepressant users had higher mean systolic and diastolic blood pressure.[42] A recent longitudinal study in Germany (n=1887) also found that after 12 years of follow-up, a history of moderate major depressive disorder was associated with a decrease in both systolic and diastolic blood pressure.[43] Since depressive symptoms vary over time, this study was limited by its definition of depression (a lifetime history of depression) because conclusions about the relative effect of short-term and long-term depressive symptoms could not be made. The importance of evaluating depressive symptoms in parallel to blood pressure over time was noted in another longitudinal study in Norway,[44] which also found that baseline depression predicted lower blood pressure at year 22, but further found that a high symptom level of depression and anxiety at baseline and year 11 was more strongly associated with a decrease in blood pressure at year 22, and associated with an even stronger decrease in blood pressure if there were high levels of symptoms at all three examinations.

Other emotional states such as anxiety and stress have overlapping symptomology with depression but are distinct negative emotional states. The independent associations between anxiety and stress with hypertension have been studied.

Evidence on anxiety and hypertension

According to the Depression Anxiety Stress Scale (DASS), which differentiates the three emotional states, symptoms of anxiety include autonomic arousal (heart rate increase, mouth dryness, etc), skeletal muscle effects (trembling), feelings of panic, faintness or being terrified for no good reason.[45] A meta-analysis which pooled 13 cross-sectional studies with 151 389 subjects found a significant positive association between anxiety and hypertension (OR 1.40, 95% CI 1.20 to 1.62).[46] Although significant publication bias was detected, the OR remained significant after trim and fill analysis (OR 1.18, 95% CI 1.02 to 1.37). In the same meta-analysis, eight prospective studies on baseline anxiety and incident hypertension were pooled (n=80 146) and presented a HR by random effect model of 1.55 (95% CI 1.24 to 1.94) with strong heterogeneity ($p<0.001$, $I^2=84.6\%$) but no publication bias was detected (p=0.663). Although there are clear relationships, the mechanisms for them are not yet well understood.

Evidence on stress and hypertension

Symptoms of stress included in the DASS are difficulty relaxing, nervous arousal, getting easily upset or agitated, irritable/over-reactive and impatience.[45] In a recent meta-analysis (n=5696) of 11 studies, domains of mental stress were defined as psychological stress, anxiety/depression or work stress.[47] Two studies (n=622) looked at the association of mental stress on the risk of hypertension (OR 2.40, 95% CI 1.65 to 3.49, $I^2=0\%$, p=0.33) and the other nine studies looked at the association of hypertension on the risk of mental stress (OR=2.69, 95% CI 2.32 to 3.11). The limitation of studies on stress and hypertension, as seen in the meta-analysis, are that they are few in numbers and have varying definitions of stress, which in some cases include depression and anxiety. Therefore, more studies are needed on the relationship between stress and hypertension, with a clear definition of stress as a distinct emotional state.

Mental healthcare in Kosovo

Supporting persons with mental illness in Kosovo is a challenge. This is because mental health services are only available on referral to a specialist, which may deter persons with mental illness from seeking care as it remains highly stigmatised in the country. Seeking professional support to address mental health problems is associated with 'tremendous shame' in the country; thus, support is rarely requested or is kept within the family circle.[48] Indeed, only 15% of people who stated they needed help

actually sought the help from a psychologist or psychiatrist due to fear of being stigmatised.[11] If help for mental illness is sought outside the home, families often consult with traditional healers or local religious persons instead of mental health professionals.[48]

In summary, further research is needed to make sense of the inconsistencies in the literature between depression and the different facets of hypertension. Understanding potential mutual influences between depression and hypertension in Kosovo is highly relevant, as it could indicate the need for integrated mental health services in PHC, especially given that both depression and hypertension are common and standalone mental health services are stigmatised. Integrated mental health services have been found to be effective in another setting[49] for more effective control of both depression and hypertension.

Objectives of the KOSCO study

The overarching goal of the 5-year KOSCO study is to contribute epidemiological evidence to the prevention and control of NCDs in Kosovo as the basis for policy and decision-making, which is currently lacking in the country. Specific objectives include:

1. To assess the prevalence and temporal change of NCDs such as hypertension, depression, diabetes and chronic obstructive pulmonary disease (COPD), as well as the prevalence and temporal change of aetiological risk factors, disease control and underdiagnosis of these NCDs among PHC users.
2. To evaluate the longitudinal relationship of PHC non-experimental interventions such as motivational counselling sessions with adherence to healthy lifestyles (physical activity, nutrition, smoking, alcohol consumption), clinical measurements (blood pressure, BMI and HbA1c) and the stage of health behaviour change.
3. To assess the predictive association between depression and the course of blood pressure in adult PHC users living in Kosovo, as well as the mediators of the association.

METHODS AND ANALYSIS

Study design

This prospective 5-year longitudinal study of PHC users in Kosovo conducted follow-ups annually in two phases, spaced by approximately 6 months. Part 1 included an in-person interview and health examination, while part 2 included a telephone interview. Part 1 of baseline data collection began in March 2019 and part 2 began in October 2019. The second follow-up started in March 2020. Annual follow-ups during a 5-year cohort allows for potential mediation analysis.

Setting

The study was conducted in Kosovo, which is located in the centre of the Balkans and the newest independent state in Europe, although not accepted as such by all countries. It has a population of 1.8 million and is divided into 38 municipalities over a surface area of nearly 11 000 km^2. The country has mainly rural settlements (62%), ethnic-Albanians with minorities of Serbian, Roma, Ashkali, Egyptian (RAE), Bosnians and Turkish ethnicities and has a male-to-female ratio of 1.06.[5] Study sites included the 12 MFMCs from the following municipalities in Kosovo: Fushë Kosovë, Drenas, Gračanica, Gjakovë, Junik, Lipjan, Malishevë, Mitrovicë, Obiliq, Rahovec, Skënderaj and Vushtrri. There exists only one MFMC per municipality.

The study was embedded within the AQH project and the selection of municipalities was based on the project's established stakeholder collaboration. The AQH project engaged with these municipalities based on nine indicators: RAE population as percentage of total population, per capita public expenditure, per capita total PHC financing, social welfare beneficiaries per 100 inhabitants, female lone parent as percentage of female population, doctors per 1000 inhabitants, nurses per 1000 inhabitants, total PHC visits per capita, diarrhoea per 1000 inhabitants and applying a convenience sample to ensure geographical clustering and representation of ethnic-Serbs.

Participants

The study population included adults aged 40 years or older who consulted healthcare services at one of the 12 study sites on the day of recruitment. Persons were excluded from participating in the study if (1) they had a terminal illness, (2) were not able to understand or respond to prescreening questions, (3) did not live in 1 of the 12 study municipalities or (4) live abroad for more than 6 months of the year. Patients exiting the 12 participating MFMCs were approached consecutively and screened for inclusion and exclusion criteria. Informed consent was obtained from participants in a quiet room of the MFMC. Research nurses alternated municipalities in their study clusters each week of recruitment (Cluster 1: Gračanica, Drenas, Skënderaj. Cluster 2: Malishevë, Rahovec, Gjakovë, Junik. Cluster 3: Fushë Kosovë, Vushtrri, Mitrovicë. Cluster 4: Lipjan, Obiliq). Clusters were developed based on the proximity of municipalities to each other and the number of participants to be recruited per municipality to balance the workload of each research nurse.

Incentive

As a participant of the cohort, one was entitled to the following incentives: waived copayments of one health consultation and associated blood tests once per year, and an HbA1c test was free of charge to the participant on the day of each in-person interview.

Study preparation

Four research nurses were hired to conduct the data collection. They participated in a 3-day training certified by the Kosovo Nursing Chamber which covered standard operating procedures (SOP) to perform interviews and health assessments. One week prior to recruitment, research nurses and the field research coordinator visited

all sites to meet and inform relevant staff about the study and ensure necessary on-site equipment was ready for use. A plan of the recruitment schedule, which rotated between study sites, was provided to all directors.

Patient and public involvement

Public stakeholder involvement in study design

Directors of the MFMCs were invited for meetings to discuss the study in October 2018 and in February 2019 (5 months and again 3 weeks prior to the launch of the recruitment of participants, respectively). In these meetings, the purpose and methods of the study were presented. Stakeholder feedback on logistical issues and health priorities in the regions were adapted into the protocol. For example, directors of PHC facilities asked to include data collection on respiratory health since their clinical experience indicated that it was a public health concern with lacking epidemiological evidence in the area. Considering the decentralised system, a signed agreement with all 12 directors of the MFMCs was established for their voluntary participation in the cohort.

Patient involvement in piloting the interview guide

The interview guide was piloted on a convenience sample of nine PHC patients from the MFMC in Obiliq. The questions were adapted according to patient feedback (eg, some questions were repetitive or not culturally appropriate, therefore removed). The first follow-up questionnaire was piloted on 42 cohort participants and the questionnaire was again modified based on feedback.

Variables and data collection

Interviews

The interview guide of the cohort addressed many objectives and was therefore lengthy. To reduce the risk of participant fatigue, the interview guide was divided into two parts, spaced by an interval of approximately 6 months. Part 1 of the interview was conducted in-person at the MFMC by a trained research nurse (approximately 30 min duration) and part 2 of the interview was conducted by telephone (approximately 20 min duration). Refer to table 1 for an overview of variables measured in each of the two parts of baseline data collection which are grouped by theme, and table 2 for a description of validated instruments used.

Data collection was divided into two parts: in-person interviews with health examination (part 1) and telephone interviews (part 2). Variables assessed are grouped by theme, and inclusion in part 1 and/or 2 is indicated with an 'x' or with comments.

Table 1 Overview of variables measured in participant interviews and health examinations

Theme	Variables	Part 1: in-person interview	Part 2: telephone interview
Sociodemographic factors	Age, gender, marital status, residence, ethnicity, education level, occupation, household composition, income level, pension, health insurance	x	
Social and environmental factors	Social support, proximity to health services	x	
Health factors, block I	Health literacy, current diagnoses, family history, comorbidities, symptoms, self-care/health related self-efficacy, disability, sleep, medications, complications of CVDs	x	Repeat only: comorbidities, symptoms, complications of CVDs
Health factors, block II	Somatic symptoms		x
Health system factors	Provider adherence to treatment protocol, healthcare utilisation, patient satisfaction with services	x	Repeat only: provider adherence to protocol, healthcare utilisation
Lifestyle behaviour, block I	Smoking, alcohol consumption, diet, physical activity	x	x
Lifestyle behaviours, block II	Health behaviours and stages of change, Health specific self-efficacy		x
Psychological factors, block I	Depression, anxiety, stress, resilience, post-traumatic stress disorder, quality of life	x	Repeat only: depression, anxiety, stress, quality of life. Add: previous diagnosis of mental illness
Psychological factors, block II	General self-esteem		x
Health examination	Blood pressure, height, weight, waist/hip/neck circumferences, HbA1c, peak expiratory flow	x	

CVD, cardiovascular diseases.

Table 2 Overview of validated instruments used in interviews

Theme	Questionnaire	Description
Sociodemographic factors	None	
Social and environmental factors	Modified Medical Outcome Survey Social Support Scale (mMOS-SSS)	The mMOS-SSS is an 8-item measure of the availability of different kinds of social support scored on a 5-point Likert scale ranging from: 1 (none of the time) to 5 (all of the time). The higher the total score, the more perceived support.[55]
Health factors, part I	Self-report generated Charlson Comorbidity Index (SRG-CCI)	The SRG-CCI is an index consisting of 10 comorbidity categories and have associated weights ranging from 1 to 6 based on risk of mortality or resource use.[56] The sum of all the weights results in a single comorbidity score for a patient. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.
	Rose Angina Questionnaire (RAQ)	RAQ was developed to detect ischaemic heart pain (angina pectoris and myocardial infarction) for epidemiological field surveys.[57] Angina pectoris is indicated by responses to seven questions and possible myocardial infarction is indicated by response to a single question. Five items have binary response options and three items are categorical.
	European Community Respiratory Health Survey II (ECRHS II) Main Questionnaire	A selection of 14 items from the ECRHS II Main questionnaire was included to assess respiratory symptoms. Items assess the presence of wheezing, tightness in chest, shortness of breath, cough and phlegm with binary responses.[58]
	Medical Research Council (MRC) Dyspnea Scale	The MRC Dyspnea Scale was developed to categorise the level of disability in chronic obstructive pulmonary disease.[59] The scale has one item with five levels which range from 'not troubled by breathlessness except on strenuous exercise' to 'too breathless to leave the house, or breathless when dressing/undressing'.
Health factors, part II	Patient Health Questionnaire (PHQ15)	PHQ15 is a 15-item somatic symptom scale which measures the severity of somatisation in patients[60]. Items relate to 15 physical symptoms experienced in the past 4 weeks, with responses rated on a 3-point Likert scale 0 ('not bothered at all') to 2 ('bothered a lot'). The summary score ranges 0–30 and classified as minimal (0–4); mild (5–9); moderate (10–14) and high (15–30) severity of somatic symptoms.
Health system factors	European Task Force on Patient Evaluations of General Practice Care (EUROPEP)	Europep is a 23-item questionnaire which measures patient satisfaction with primary healthcare services such as doctor–patient relationship; medical care; information and support; continuity and cooperation, and accessibility[61]. All items are aggregated into two dimensions: clinical behaviour (items 1–16) and organisation of care (items 17–23). Responses are rated on a 5-point Likert scale 1 (poor) to 5 (excellent).
Lifestyle behaviour, part I	None	

Continued

Table 2 Continued

Theme	Questionnaire	Description
Lifestyle behaviours, part II	Stages of Change Survey	The Stages of Change Survey assesses the stage of lifestyle change based on the stages of change model and has one item with five statements for each type of lifestyle behaviour (smoking, alcohol consumption, nutritional consultation, physical activity) which represent different stages of change. Participants must choose from the list of statements which most closely matches what they currently do.[62]
	Smoking Abstinence Self-Efficacy Questionnaire (SASEQ)	SASEQ has six items with statements of various situations where one might be tempted to smoke and asks for the participant's confidence level that they will not smoke.[63] Response options are on a 5-point Likert scale ranging from certainly (4) to certainly not (0).
	Health-Specific Self-Efficacy Scales (HSSES)	The HSSES assesses a person's optimistic self-belief about being capable to resist temptations and to adopt a healthy lifestyle[64]. The question 'How certain are you that you could overcome the following barriers?' is followed by a list of barriers for each of the following lifestyle behaviours: nutrition (five items), physical exercise (five items) and alcohol consumption (three items). Response options range on a 4-point Likert scale from (1) very uncertain to (4) very certain.
	RAND-12 Health Status Inventory (RAND-12 HSI)	The RAND-12 HSI is a 12-item version of the RAND-36 HSI, which measures health-related quality of life.[65] The RAND-12 HSI provides estimated scores on Physical Health, Mental Health and Global Health composites of the 36-item instrument. The RAND-12 HSI uses the item response theory (IRT) and oblique (correlated) factor rotations to generate the physical and mental health summaries.[65] The composite scores range from 0 to 100, where a 0 score indicates the lowest level of health and 100 indicates the highest level of health.
Psychological factors, part I	Depression, Anxiety, Stress Scale (DASS-21)	Depression, anxiety and stress were measured using the DASS-21,[45 66] a 21-item questionnaire consisting of three subscales, each containing seven items scored on a 4-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much), and multiplied by 2. The scores are classified as depression 0–9 (normal), 10–13 (mild), 14–20 (moderate), 21–27 (severe), ≥28 (very severe); anxiety 0–7 (normal), 8–9 (mild), 10–14 (moderate), 15–19 (severe) ≥20 (very severe); stress 0–14 (normal); 15–18 (mild), 19–25 (moderate), 26–33 (severe), ≥34 (very severe).
	Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)	PC-PTSD-5 is a 5-item screen designed for primary care settings. The first item assesses whether the respondent has had any exposure to traumatic events. If a respondent denies exposure, the PC-PTSD-5 is complete with a score of 0. However, if a respondent indicates that they have experienced a traumatic event over the course of their life, five additional items are asked regarding how that trauma exposure has affected them over the past month. Each item receives a binary score: 0 (no) or 1 (yes). The scores are classified as: ≤2 (improbable PTSD) and ≥3 (probably PTSD).[67]
	Resilience Scale (RS-14)	RS-14 is a 14-item questionnaire that assesses individual resilience in a general population.[68] Items are scored on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). Scores are categorised into very low (14–56), low (57–64), on the low end (65–73), moderate (74–81), moderately high (82–90) and high (91–98).
Psychological factors, part II	Self-esteem (SE)	SE is a 1-item scale developed as an alternative to the Rosenberg self-esteem scale[69]. It is measured on a 7-point Likert scale from 1 (not true of me) to 7 (very true of me).
Health examination	Not applicable	

PTSD, post-traumatic stress disorder.

Validated instruments used in each of the interview themes are described in the table. Questions developed by the study team and questions from non-validated questionnaires are not included in the table.

Physical examination

Immediately following the in-person interview, the research nurse performed a brief health examination of about 10 min.

- *Height (cm) and weight (kg)* were measured using stadiometers and scales which were available at the MFMCs (various brands). The precision of scales was assessed regularly with a weight of 10 kg. Circumferences of the waist, hip and neck were measured using the SECA 201 measuring tape (Seca GmbH & Co. KG., Switzerland).
- *Peak expiratory flow* (PEF) (L/min) was measured 3 times with 30 s pause between attempts, using the OMRON Peak Flow Meter PFM20 (Omron Healthcare, Switzerland). PEF predicted (%) was calculated as follows: estimated (measured) PEF/expected PEF. The expected PEF values were derived based on age, gender and height using the regression equation developed by Hankinson *et al*.[50]
- *Systolic and diastolic blood pressure (in mm Hg)* were measured three times, at least 3 min apart, after sitting quietly for about 10 min, using an M3 model Omron blood pressure monitor (Omron Healthcare, Switzerland). The research nurses placed the blood pressure cuff 2 cm above the elbow on the bare left upper arm (in the case of arteriovenous fistula, radiotherapy or removal of lymph nodes in the armpit of the left arm, the right arm was used) of the seated participant and elevated the arm on the table to the level of the fourth intercostal space.
- Towards the end of the battery of tests, the research nurse accompanied participants to the laboratory of the MFMC for a finger-prick (non-invasive) *glycated haemoglobin test (HbA1c, %)*. The HbA1c test was performed by an MFMC staffed laboratory technician who received training by the supplier on how to use the SUPER ID clinchem device (Dr. Müller Gerätebau GmbH, Germany).
- Participants were given a 'self-care passport' at baseline, which was developed by local experts in collaboration with the AQH project. The research nurses transcribed the participants' health examination results in the passport which also had additional space for participants to write blood pressure or blood glucose measurements taken at home. Participants were instructed that they will be recontacted in 6 months for a telephone interview.

Definitions of main variables by objective

Objective 1

- *Depression* was defined as self-reported depression diagnosis by a healthcare professional and/or prescribed antidepressant medications and/or a DASS depression score of >13 (moderate to very severe depressive symptoms). *Uncontrolled depression* was defined as being diagnosed with depression and/or taking antidepressant medication yet having a DASS depression score of >13. *Undiagnosed depression* was defined as not being diagnosed with depression nor taking antidepressant medication yet having a DASS depression score of >13
- *Hypertension* was defined as a self-reported hypertension diagnosis by a healthcare professional and/or prescribed antihypertensive medications and/or a blood pressure measurement ≥140/90 mm Hg. *Uncontrolled hypertension* was defined as being diagnosed with hypertension and/or taking antihypertensive medication yet having a blood pressure measurement ≥140/90 mm Hg. *Undiagnosed hypertension* was defined as not being diagnosed with hypertension nor taking antihypertensive medication yet having a blood pressure measurement ≥140/90 mm Hg.
- *Diabetes* was defined as a self-reported diabetes diagnosis by a healthcare professional and/or prescribed antidiabetic medications and/or an HbA1c measurement ≥6.5%. *Uncontrolled diabetes* was defined as being diagnosed with diabetes and/or taking antidiabetic medication yet having an HbA1c measurement ≥6.5%. *Undiagnosed diabetes* was defined as not being diagnosed with diabetes nor taking antidiabetic medication yet having an HbA1c measurement ≥6.5%.
- *COPD* was defined as a self-reported COPD diagnosis by a healthcare professional and/or a PEF <80% predicted with breathlessness and/or cough symptoms for greater than 6 months. *Uncontrolled COPD* was defined as being diagnosed with COPD yet having a PEF <80% predicted. *Undiagnosed COPD* was defined as not being diagnosed with COPD yet having a PEF <80% predicted with breathlessness and/or cough symptoms for greater than 6 months. A PEF <80% predicted with respiratory symptoms (breathlessness or cough for greater than 6 months) was found to be an appropriate cut-off to detect COPD in the absence of spirometry.[51]
- *Lifestyle factors included:* smoking (current smoker, ex-smoker, never smoker), meeting WHO recommendations for physical activity (at least 150 min of moderate-intensity physical activity throughout the week, or at least 75 min of vigorous-intensity physical activity throughout the week, or an equivalent combination of moderate-intensity and vigorous-intensity activity[52]), meeting WHO recommendations for fruit and vegetable intake (at least five portions (400 g) of fruits and vegetables per day[53]), binge drinking (consumption of ≥60 g of pure alcohol (six or more standard drinks) on at least one single occasion at least once in a month[54]), and BMI: weight (kg)/height (m^2).

Objective 2

- *Motivational counselling sessions*: are a non-experimental community intervention, where all patients being treated at a MFMC, FMC or FMA aged 40 or older with diabetes, hypertension or at risk for developing diabetes and/or hypertension are eligible to be referred by a doctor or nurse to the nearest health resource centre. There, the nurse provides one-on-one motivational counselling sessions on lifestyle changes based on the patient's needs. Prior to rolling out this intervention, several preparatory steps were undertaken by the AQH project. First, health resource centres were established within MFMCs as a new location for nurses to provide motivational counselling sessions and other preventive services for management of NCDs. Furthermore, nurses from MFMCs completed several training sessions on motivational counselling. At the time of baseline, motivational counselling was offered in 5 of the 12 study sites (Fushë Kosovë, Gjakovë, Malishevë, Mitrovicë and Vushtrri), and a staggered introduction of the intervention to other study sites is anticipated. Attending a motivational counselling session was the main exposure, a dichotomous variable where participants answered yes or no to the question: 'Have you ever participated in a motivational counselling session/health education session with a nurse in a health resource centre?'
- *Lifestyle factors* were among the main outcomes, described under 'objective 1'.
- *Clinical measurements* were among the main outcomes, which were continuous variables that included blood pressure, BMI and HbA1c described under 'physical examination'.
- *Stage of behavioural change* was one of the main outcomes, an ordinal variable assessed using the Stages of Change Survey. For each lifestyle (smoking, nutrition, physical activity and alcohol consumption), participants were categorised into one of the following stages of change based on their responses: maintenance, action, preparation, contemplation and precontemplation.
- *Patient satisfaction* and *quality of care* were predictors included in the secondary analysis. *Patient satisfaction* was a binary variable defined as an average EUROPEP score per item of ≥4. *Quality of care* was a continuous variable defined as the number of patient-reported healthcare provider actions completed from the list of recommendations in the PEN protocol during the participant's last visit in a PHC centre.

Objective 3

- *Depression* was the main exposure, a dichotomous variable defined under 'objective 1'.
- *Change in blood pressure* was the main outcome, which was the blood pressure (described under 'physical examination') from baseline subtracted from blood pressure at follow-up.
- *Hypertension incidence, uncontrolled hypertension and underdiagnosed hypertension* are secondary binary outcomes described under 'objective 1'.

Non-participants

Non-participants (patients approached who declined to participate or who did not meet inclusion criteria) were asked nine optional questions with the purpose to understand if participants differ from non-participants. The optional questions provided information on sex, age, education level, diagnosis of diabetes, lung disease, CVD, smoking status, weight, level of satisfaction with PHC services and reason for non-participation.

Data management

Data from in-person and telephone interviews were collected using Open Data Kit (ODK) software. Results from health examinations were also entered into ODK. Data quality was assured through (1) formulation of SOPs for all aspects of the study, (2) extensive and careful training of the study team according to the SOPs, (3) onsite supervision of field activities ensuring adherence to protocol and (4) regular monitoring and internal evaluation of data entry during the field visits. The ODK and STATA programmes kept track of all changes made to the data. All data were merged into a single database at the end of data entry using STATA V.15.1 (STATA Corporation).

Power calculation

Power calculation without local effects

The following is a power calculation for the longitudinal study of the association of change in blood pressure with depression in the case of a single homogenous population with the prevalence of depression d=40%. We denote the relative effect of the depression at baseline on the change of blood pressure at follow-up as *tau*. For a small effect *tau*=0.25, which under the normal distribution assumption corresponds to the shift from the median to the 60 percentile, and assuming a 20% loss to follow-up, we arrive at the minimal cohort size of 883 people for 90% power. The control for confounding variables will lead to a reduction of power, as will the discretisation of the blood pressure measurement to study hypertension as a binary outcome, and so we aim to recruit a total of 1000 patients into the cohort. The number of participants to be recruited by each MFMC was proportional to their mean number of medical visits in the months of June 2018 and October 2018.

Power in the presence of clustering

To take into account the potential local variation in the effect of depression on blood pressure, we performed explicit simulations to make sure that the study has sufficient power under a range of plausible scenarios. Specifically, we posited that the mean blood pressure can vary between the 12 municipalities (random effect with variance *sigma*^2), and also that the effect of depression on blood pressure can be different in each municipality

Table 3 Simulation of statistical power

	Tau=0.25	Tau=0.30	Tau=0.35	Tau=0.4	Tau=0.45	Tau=0.5
Rho=0.1	80%	91%	97%	99%	99%	99%
Rho=0.2	66%	80%	91%	96%	98%	99%
Rho=0.3	49%	65%	77%	87%	93%	97%

(random effect with variance *rho*^2). The magnitudes *sigma* and *rho* of these local effects were tunable parameters of the simulation, as was the overall effect size *tau*. Preliminary analyses showed that the power of the study is driven by the relationship of *tau* and *rho*, and is not sensitive to *sigma*; this is because the municipality-level effect affects depressed and non-depressed people equally. Thus, we fixed *sigma=tau* in what follows.

For 18 combinations of plausible values of *tau* and *rho*, we simulated normal data on 800 participants (ie, the target cohort size minus 20% loss to follow-up) 10 000 times and computed the fraction of instances when the mixed regression model fitted on this synthetic data reported depression as a significant factor. This fraction can be interpreted as the statistical power of the study for the given *tau* and *rho*. The results of the simulations are reported in table 3 (rounded down to the nearest percent). We found that the study retains sufficient power for as long as the overall effect of depression dominates the local variation in that effect (that is *tau* is much greater than *rho*), which is likely. This requirement is progressively relaxed as the overall effect size grows.

The simulations did not take into account the loss of power due to adjustment for confounders.

Statistical analysis plan

Figure 1 provides an overview of associations of interest for the cohort. Statistical methods are presented by objective.

Objective 1

The descriptive statistics of depression, hypertension, diabetes, COPD as well as the control and underdiagnoses of these diseases will be presented as follows: categorical variables will be presented as numbers and percentages. Normally distributed quantitative variables will be presented as mean and SD. Other quantitative variables will be presented as medians and IQRs. χ^2 tests, t-tests and Wilcoxon rank-sum tests will be used for bivariate analysis where appropriate, such as to assess differences by age, gender or socioeconomic status (SES).

Objective 2

The main exposure of interest was attendance in motivational counselling sessions (non-experimental PHC intervention). In light of the absence of pure controls for this non-experimental intervention, comparisons will be made between those who chose to participate in the invention and those who did not within the same centre. The first outcome variable was stage of behaviour change, which was ordinal (maintenance, action, preparation, contemplation and precontemplation). Two approaches will be used: initially, the analysis will be done using ordinal regression, then the outcome variable will be split into two categories: (1) high motivation (maintenance, action, preparation) and (b) low motivation (contemplation and precontemplation) and logistic regression will be applied. The second outcome was adherence to the following aspects of healthy lifestyles: nutrition, physical activity, alcohol consumption and smoking. Logistic regression analysis will be conducted for each lifestyle. For the third outcome (clinical measurements), a mixed linear regression model will be constructed for each outcome of interest: blood pressure, BMI and HbA1c. Comorbidities, physical ability, SES, living status and employment status are potential confounders and will be controlled for during data analysis. The intrinsic municipality and participant effects will be modelled with random effects. Potential effect modifiers include sex, age and social support. Self-efficacy will be considered as a potential mediator. Secondary analyses with predictors of patient satisfaction and quality of care will be conducted with logistic regression models.

Objective 3

The main outcome for this objective was change in blood pressure. Secondary outcomes included hypertension incidence, control and underdiagnosis. We will use an explanatory model with a focus on depression among predictor variables. Covariates systematically considered as confounders as well as effect modifiers in all models will be sex, age, urban/rural, ethnicity, education level and employment status. Additional covariates considered in some models include: smoking, alcohol, physical activity, obesity, family history, anxiety, stress, PTSD, resilience, social support, self-esteem, health literacy, healthcare seeking, patient satisfaction, comorbidity, sleep quality and duration, and medication. Antidepressant use and lifestyle factors will be assessed as a potential mediators.

Two approaches will be explored to assess the longitudinal association between depression and change in blood pressure.

1. Predictive perspective: a regression model will be constructed with the outcome of change in blood pressure from baseline (continuous). Baseline blood pressure will be adjusted for by including it as a covariate in the model. This model will allow predicting the future course of blood pressure, based on a set of variables observed at baseline. This model is of value for a provider

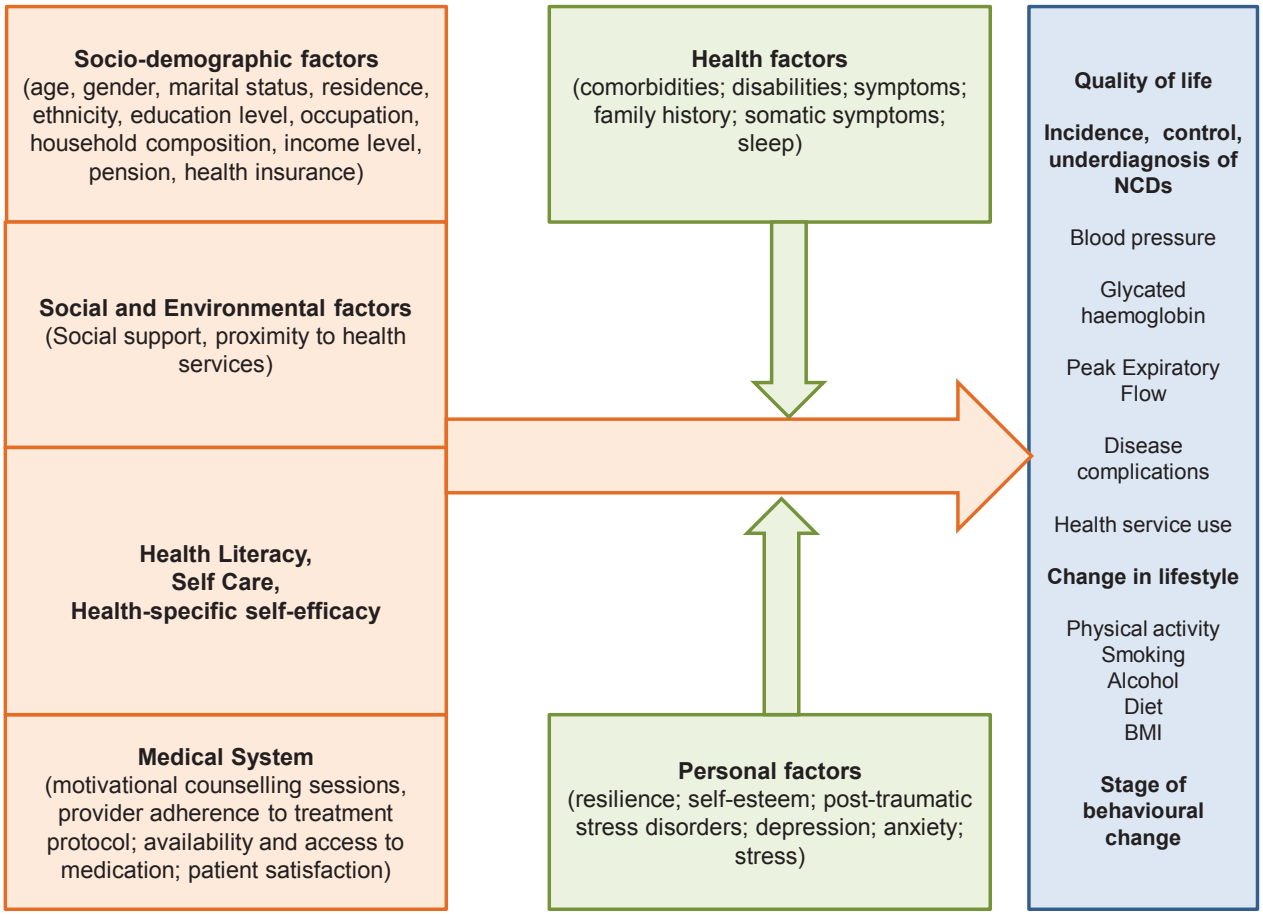

Figure 1 Hypothesised associations between variables under study. The hypothesised associations between outcome variables on the right, predictor variables on the left and mediating variables in the middle are represented in the figure. Sociodemographic factors, social and environmental factors, health literacy and self-care, as well as health system factors are thought to impact the outcome of quality of life, the incidence and control of chronic diseases and lifestyle change, and mediated by personal and health factors. BMI, body mass index; NCD, non-communicable disease.

perspective: based on what the provider observes at a specific point in time, what is the predicted course of blood pressure?

2. Change perspective: the effect of change in depression (predictor) on change in blood pressure (outcome) will be assessed with a repeated measures model. This model will allow assessing the parallel change in depression and blood pressure and in that sense takes cross-sectional short-term associations at baseline and follow-up into consideration.

Analyses with secondary outcomes of hypertension incidence, control and underdiagnosis will be conducted with logistic regression models. The secondary outcomes are relevant for primary and secondary prevention in PHC. Anxiety and stress will also be included as focal predictor variables in secondary analyses.

Strengths and limitations

Given the limited evidence on NCDs in Kosovo, the cohort is of great benefit for healthcare decision-makers which rely on health data. Results from this cohort study will provide an overall insight into the relationship between NCDs and their determinants through study objective 1. Considering that this study is assessing the longitudinal association of PHC interventions (such as delivery of motivational counselling sessions for behaviour change) in study objective 2, the scientific findings of this study can be applied in designing *targeted behaviour change interventions*. Behaviours affect morbidity, and extremely unhealthy behaviours may lead to mortality, therefore understanding what causes patients to do certain behaviours and what motivates them to change, provides information which could be useful for populations with similar characteristics.[14] Further, understanding potential mutual influences between depression and hypertension could indicate the need for integrated mental health services in PHC for more effective control of both conditions,[46] and will be addressed through objective 3.

Having embedded this cohort in an existing local implementation project, namely AQH which builds on strong partnerships with local stakeholders, greatly increased the ease of implementation and acceptability of this study. For example, the study population lives in mostly rural areas, with high levels of poverty and low levels of education which meant that there was little awareness of research and their benefits. Being embedded within the AQH project, which had established trust with municipalities, helped in the recruitment process. Further, given that the healthcare system is decentralised, getting directors of MFMCs from multiple municipalities on board to participate in the cohort study would normally be a long and complicated process, but was simplified since the directors had a longstanding relationship with the AQH project.

A pilot of the questionnaire with 9 PHC users aged 40 years and above conducted in March 2019 and in the MFMC of Obiliq and again in October 2019 with 42 cohort participants from various municipalities served to identify the understanding and flow of questions. Some questions were identified as inappropriate or irrelevant in the cultural context and were omitted. For example, the original PC-PTSD-5 questionnaire listed sexual abuse as an example of a traumatic event and this was considered offensive by one person in the pilot survey. Thus, the example was removed. One question asked if the participant had ever been diagnosed with a mental disorder by a physician. Local research nurses unanimously stated that this question was not culturally acceptable since it was not perceived well by the participants; therefore, it was removed from part 1 of the baseline data collection (initial contact with participants) and moved to part 2 to allow participants time to grow trust with research nurses. The PHQ asks questions about menstruation pain during intercourse, which were also culturally unacceptable and considered unpleasant to ask in an interview and a disclaimer statement was added before the items to preface the question. A question in the EUROPEP which assesses satisfaction with 'getting through to the practice on telephone' was removed as it is not common practice in Kosovo. Given that the average level of education in Kosovo's older population is of primary school or lower, some instruments' questions were abstract and difficult to understand by participants. In particular, respondents of the pilot survey noted that multiple questions in the RS-14 were difficult to understand, such as 'I am friends with myself' which was considered a Western ideal and 'I keep interested in things' often yielded participant questions like 'what things?' A debriefing with research nurses ensured that these questions were clarified with participants in a uniform way. It was confirmed through the pilot that the questionnaire was too lengthy, demonstrated by participants asking to end the interview before the end. It was decided to separate questions into two parts, asked with an interval of 6 months.

During the preparation period which involved site visits before the launch of recruitment, the first author learnt that lab hours were shorter than anticipated, which limited the amount of hours of recruitment (from 7:00 to 13:00). This meant that the original estimated recruitment timeline was extended from 3 months to 8 months. Further, participation rates were low, which extended recruitment time.

Due to the recruitment scheme in PHC facilities, the study is not population based. Thus, the study is limited in its generalisability as well as it may overestimate the prevalence of health conditions. However, patients visit MFMCs for an array of conditions as well as for general check-ups; thus, healthy persons are also included in the study. Providing participants incentives with free health consultations may bias towards participation of persons with chronic conditions, and thus may also overestimate the prevalence of NCDs and their determinants. The relevance of the study, in the absence of being entirely representative for Kosovo as a whole, lies in the longitudinal design; furthermore, it evaluates care and its perception and utilisation in a large number of relevant health service infrastructures. The findings will therefore be relevant and guiding for other similar structures in the country.

The non-randomised nature of PHC interventions mentioned in this study is a limitation in the interpretation of results regarding the effectiveness of interventions. But randomisation of interventions was not possible: centres offering the interventions were selected based on feasibility and interest of the MFMC staff to increase success of the pilot health centres, and the intervention is offered to all patients; therefore, exposure is self-selected.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

Ethical approvals for the study were obtained from Ethics Committee Northwest and Central Switzerland (reference number 2018-00994) on 11 December 2018 and the Kosovo Doctors Chamber (reference number 11/2019) obtained on 30 January 2019 and expiring on 31 December 2023. Before any data were collected, participants were asked for their verbal and written consent. To obtain consent, participants were informed that (1) their participation was voluntary, (2) they could withdraw from participation at any time and (3) non-participation would not have any negative effects. The participants were asked for additional consent whether, in the case a previously unrecognised medical problem was detected, they approve that qualified staff or the research team would inform them of the results and provide advice on what the participant should do next. SOP developed by the study team and approved by MFMC directors (who are physicians), were provided to research nurses to guide them in referring participants to appropriate care. Severe findings (systolic blood pressure ≥180 mm Hg and diastolic blood pressure ≥110) were referred immediately to emergency services in the MFMC. Participants were informed how the data will be used and that confidentiality is ensured as their

data are coded. Potential risks and benefits of participation were also discussed with participants, and ample time was given to ask questions. Once consent was obtained, the research nurse proceeded to data collection.

Data protection

Data entry was done using a tablet (Samsung Galaxy Tab A, Samsung Group, Switzerland), where data were sent to a server and erased from tablets daily. Only participant identifiers, but not names of the participants were included in electronic health databases. HbA1c results were recorded in laboratories as per facility protocol with participant name, but not participant ID. Consent forms were kept in a locked file cabinet in Pristina, with restricted access to project personnel. Each participant has a code which is linked to their personal identifying data (PID) and a code linked to the study data (DID). The participant identifying information with PID is kept in one document stored by the Deputy Team Leader of the AQH project in Pristina, Kosovo. The DID, study data and key which links PID and DID are kept in a password-protected document with the principal investigator (NPH) in Basel, Switzerland.

Collaboration

The overall coordination of the cohort activities is the joint responsibility of the Board of Collaboration, which consists of two representatives from the University of Prishtina, two representatives of Swiss TPH and two representatives from National Institute of Public Health. Focus, content and protocols for follow-up assessments of the KOSCO study are approved by the Board of Collaboration.

Research questions assessed using cohort data will be published in scientific journals.

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Contributors KAO: codeveloped and implemented the study protocol, coordinated and supervised data collection, will analyse and interpret data. NJ contributed to study objectives related to non-communicable diseases in Kosovo. SS contributed to study objectives related to mental health in Kosovo. MK conducted statistical power calculations and will supervise data analysis. MZ, QR, AB-K and JG contributed to the study objectives related to the evaluation of health service provision and to the integration of the study protocol within the AQH framework. NP-H developed the KOSCO cohort concept, study objectives and protocol, directed the implementation, data analysis and result interpretation. All authors read and approved the final protocol.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Correction: *Study protocol: a prospective cohort on non-communicable diseases among primary healthcare users living in Kosovo (KOSCO)*

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This article was previously published with errors. The authors noticed below errors:

On page 9, table 2 under Questionnaire column, 4th row "Short Form Health Survey version 1 (SF12v1)" has been corrected to "RAND-12 Health Status Inventory (RAND-12 HSI)".

On page 9, table 2 under Description column, fourth row "The SF12v1 is a 12-item questionnaire which measures health-related quality of life.65 Item 1 has a 5-point Likert scale from 1 (excellent) to 5 (poor); items 2 and 3 have a 3-point Likert scale from 1 (Yes, limited a lot) to 3 (No, not limited at all); Items four through seven have response choices of yes (1) and no (2). Item 8 has a 5-point Likert scale from 1 (not at all) to 5 (extremely). Items 9–12 has a 6-point Likert scale from 1 (all of the time) to 6 (none of the time). Items are divided to make physical (items 1–5, 8) and mental health (items 6–7, 9–12) composite scores using a norm-based method and transformed to each have a mean of 50. The total score ranges from 0 to 100, where a 0 score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health." has been corrected to "The RAND-12 HSI is a 12-item version of the RAND-36 HSI, which measures health-related quality of life.65 The RAND-12 HSI provides estimated scores on Physical Health, Mental Health and Global Health composites of the 36-item instrument. The RAND-12 HSI uses the item response theory (IRT) and oblique (correlated) factor rotations to generate the physical and mental health summaries.65 The composite scores range from 0 to 100, where a 0 score indicates the lowest level of health and 100 indicates the highest level of health.".

Reference 65 "Ware J, Kosinski M, Keller SD. A 12-Item short-form health survey: construction of scales and preliminary tests of eliability and validity. Med Care 1996;34:220–33." was incorrect. The correct reference is:

Hays RD, Prince-Embury S, Chen H. Rand-36 health status inventory. San Antonio, TX: The Psychological Corporation; 1998.

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CHAPTER 4 – ARTICLE 2

Strengthening primary healthcare in Kosovo requires tailoring primary, secondary and tertiary prevention interventions and consideration of mental health

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Strengthening Primary Healthcare in Kosovo Requires Tailoring Primary, Secondary and Tertiary Prevention Interventions and Consideration of Mental Health

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Objectives: Kosovo has the lowest life expectancy in the Balkans. Primary healthcare (PHC) plays an essential role in non-communicable disease (NCD) prevention. We described primary, secondary and tertiary prevention indicators in Kosovo and assessed their association with depressive symptoms.

Methods: PHC users (n = 977) from the Kosovo NCD cohort baseline study were included. Depressive symptoms were assessed using the Depressive Anxiety Stress Scale-21. Cross-sectional associations between depressive symptoms and prevention indicators were quantified with mixed logistic regression models.

Results: Poor nutrition (85%), physical inactivity (70%), obesity (53%), and smoking (21%) were common NCD risk factors. Many cases of hypertension (19%), diabetes (16%) and Chronic Obstructive Pulmonary Disease (COPD) (45%) remained undetected by a PHC professional. Uncontrolled hypertension (28%), diabetes (79%), and COPD (76%) were also common. Depressive symptoms were positively associated with physical inactivity (OR 1.02; 95% CI 1.00–1.05 per 1-point increase in DASS-21) and undetected COPD (OR 1.07; 95% CI 1.00–1.15), but inversely with undetected diabetes (OR 0.95; 95% CI 0.91–1.00).

Conclusions: Continued attention and tailored modifications to primary, secondary and tertiary prevention in Kosovo are needed to narrow the Balkan health gap.

Keywords: depressive symptoms, hypertension, diabetes, COPD, prevention, public health

INTRODUCTION

Over the last 30 years, there has been a discernible shift toward a greater proportion of the global disease burden (GBD) caused by non-communicable diseases (NCDs) (1). In 2019, NCDs accounted for 1,620,165,811 Disability Adjusted Life-Years (DALYs) or 64% of all DALYs globally, up from 43% in 1990 (2). Although the NCD burden in Kosovo is not well documented in part due

to a health information system that is not yet fully functional (3), a heavy disease burden is evident from the considerably lower life expectancy (72.5 years) compared to neighboring countries such as Albania (78.6 years), Montenegro (76.9 years), North Macedonia (75.5 years), and Serbia (75.7 years) (4).

NCD management interventions are essential for achieving the SDG target of a one-third reduction in premature deaths from NCDs by 2030. The World Health Organization supports efforts toward achieving the 2030 Sustainable Development Goal 3 aimed at reducing NCD-related premature deaths by one-third by 2030. In fact, a Global Action Plan for the Prevention and Control of NCDs (5) was developed to help states reduce the burden of NCDs. Primary healthcare (PHC) plays an important role in NCD prevention and control (6). The Accessible Quality Healthcare (AQH) is a prominent project in Kosovo which is funded by the Swiss Agency for Development and Cooperation (SDC) and has been working with local stakeholders since 2016 to improve the quality of PHC in the public sector through a health system strengthening approach and with a focus on NCDs.

PHC has interventions at each stage of disease: Primary prevention aims to prevent the onset of disease through health promotion, secondary prevention aims to detect diseases early in an asymptomatic stage so that treatment can delay or block the occurrence of symptoms, and tertiary prevention attempts to deter adverse consequences of existing clinical disease (7, 8).

A rapid assessment of the PHC system in Kosovo conducted by the World Health Organisation (WHO) in 2019 (9) found that hospitalizations related to hypertension and diabetes decreased rapidly between 2012 and 2016, indicating major improvements in disease management in general (tertiary prevention). However, the life expectancy gap between Kosovo and its neighbors still exists in 2021. Equivalent data for chronic respiratory disease, and especially chronic obstructive pulmonary disease (COPD) is lacking. Identifying areas for improvement along the chain of care for common NCDs, i.e., in primary, secondary and tertiary prevention, can facilitate evidence-informed policymaking for PHC stakeholders in Kosovo and AQH project interventions.

A potentially important barrier to NCD prevention and control in Kosovo is poor mental health. as a post-conflict outcome. Depressive symptoms among PHC users were reported to be about 10% worldwide (10), while the prevalence of depressive symptoms reported in Kosovo far exceeds this, ranging from 30 to 67% (11–15). Depression has been linked to unhealthy behaviors such as smoking, physical inactivity, poor nutrition and alcohol consumption (16, 17). Depression has also been linked with uncontrolled hypertension (18–20) and poor glycemic control among diabetics (21) in other settings. Given the high prevalence of depressive symptoms reported in Kosovo, it is important to investigate its role in NCD management in the specific context.

Figure 1 depicts the study's conceptual framework. Primary care participants represent different stages of a disease continuum, from a healthy person to disease onset, to disease progression. Primary healthcare aims to prevent people from moving forward along the continuum. Primary, secondary and tertiary prevention strategies target people at different stages of the disease continuum. Our study assessed the distribution of negative cross-sectional indicators to identify gaps at the different prevention stages which may hinder NCD control in the Kosovo primary health care system. Specifically, it describes the prevalence of NCD risk factors (targets of primary prevention), as well as the prevalence of undetected hypertension, diabetes and chronic obstructive pulmonary disease (COPD) (targets of secondary prevention) and uncontrolled hypertension, diabetes and COPD (targets of tertiary prevention) among Kosovo public PHC users. It further assesses the association between depressive symptoms and these indicators to evaluate whether depressive symptoms act as a barrier to disease prevention and control.

MATERIALS AND METHODS

Study Design

The current cross-sectional study uses baseline data of the KOSovo NCD COhort (KOSCO), which began in March 2019. Details of the study protocol are described elsewhere (22). In brief, the overarching goal of the KOSCO study was to contribute epidemiological evidence to the prevention and control of NCDs in the Kosovo public primary health care system as the basis for policy and decision-making. Initially, 1,011 consecutive PHC users aged 40 years and above were recruited from 12 PHC facilities in Kosovo. The data collected through interviews and health examinations included: socio-demographic characteristics, social and environmental factors, comorbidities, health system, lifestyle, psychological factors, and clinical attributes (blood pressure, height, weight, waist/hip/neck circumferences, peak expiratory flow and HbA1c measurements). Cohort data were collected annually in two phases, approximately 6 months apart, with an projected total follow-up time of 5 years. The current study is based on cross-sectional data from the baseline assessment.

Setting

The study was conducted in Kosovo, which is situated in the middle of the Western Balkans and has a population of ∼1.8 million. In Kosovo, the public PHC system is divided into three tiers: each municipality has one main family medicine centre (MFMC), several family medicine centres (FMC) and several family medicine ambulantas (FMA). MFMCs are the largest facilities at the highest level of PHC, which offer more services, employ more staff and have more medical equipment and therefore have a higher patient flow compared with the second-level FMCs and third-level FMAs. There is also the private PHC sector with only one tier consisting of private clinics.

Study sites include the MFMCs from the following 12 municipalities: Gračanica, Drenas, Skënderaj, Malishevë, Rahovec, Gjakovë, Junik, Fushë Kosovë, Vushtrri, Mitrovicë, Lipjan, and Obiliq.

Participants

Recruitment and baesline data collection were conducted between March and November 2019. A total of 1,011 consecutive and consenting PHC users were included in the cohort. Ethical approvals were obtained from the Ethics Committee Northwest

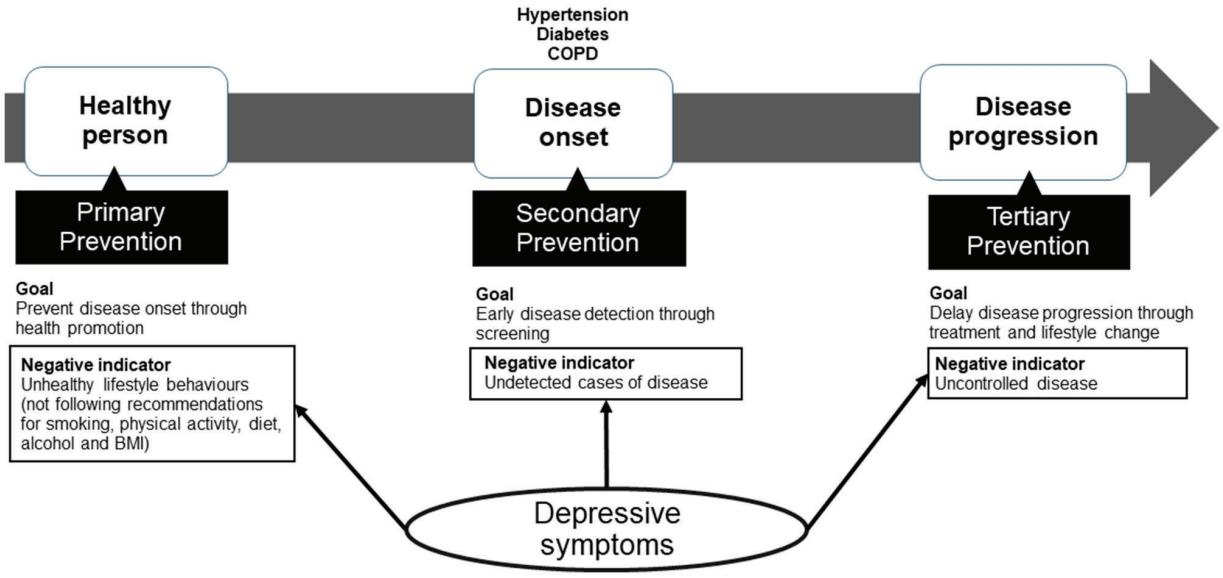

FIGURE 1 | Conceptual framework. Primary care participants exist on a disease continuum, from a healthy person to disease onset, to disease progression. Primary healthcare aims to prevent people from moving forward along the continuum. Primary, secondary and tertiary prevention strategies target people at different stages of the disease continuum. To evaluate gaps in primary, secondary and tertiary prevention in Kosovo's PHC system, our study assesses negative indicators of each stage of prevention. Specifically, it describes the prevalence of lifestyle risk factors (targets if primary prevention), as well as undetected hypertension, diabetes and chronic obstructive pulmonary disease (COPD) (targets of secondary prevention) and uncontrolled hypertension, diabetes and COPD (targets of tertiary prevention) among Kosovo PHC users. It further assesses the association between depressive symptoms and these indicators to evaluate whether depressive symptoms act as a barrier to disease prevention.

and Central Switzerland (Ref. 2018-00994) and the Kosovo Doctors Chamber (Ref. 11/2019).

Participants were included in the cohort if they were aged 40 years or older and consulted healthcare services irrespective of the reason on the day of recruitment. Participants were excluded from the cohort if they had a terminal illness, were not able to understand or respond to screening questions, did not live in one of the 12 study municipalities, or lived abroad for more than 6 months of the year.

Baselien participants who had complete data on confounders (age, sex, work status, highest level of education achieved, living in a rural or urban setting, and ethnicity), smoking status, physical activity, nutrition, alcohol, height, weight, blood pressure, glycated hemoglobin (HbA1c), peak expiratory flow (PEF), depressive symptoms score, and status of hypertension, diabetes and COPD diagnoses were included in the current study ($n = 977$). We excluded 34 participants due to incomplete data.

Variables and Data Sources

NCD Risk Factors

Participants answered questions during an in-person interview with a trained study nurse regarding lifestyle and mental health symptoms. Height (in meters) and weight (in kilograms) were measured, body mass index (BMI) was derived (weight/height^2). The following indicator variables for NCD risk factors were defined as follows:

- smoking status (current smoker).
- physical inactivity (<150 min of moderate-intensity physical activity per week, <75 min of vigorous-intensity physical activity per week, and less than an equivalent combination of moderate-intensity and vigorous-intensity activity).
- Poor nutrition (<5 fruit and/or vegetable portions per day).
- Alcohol consumption (any alcohol consumed in the last 30 days).
- Obesity (BMI $\geq$ 30).

A lifestyle index was equally derived by taking the sum of the indicators above, where one point was given for each criterion met.

Undetected and Uncontrolled Disease

Participants answered questions about physician-diagnosed hypertension, diabetes and COPD. Blood pressure, HbA1c and PEF were measured at the end of the interview. Systolic and diastolic blood pressures (in mmHg) were measured three times, at least 3 min apart, after sitting quietly for about 10 min, using an M3 model Omron blood pressure monitor (Omron Healthcare, Switzerland). The research nurses placed the blood pressure cuff 2 cm above the elbow on the bare left upper arm (in the case of arteriovenous fistula, radiotherapy or removal of lymph nodes in the armpit of the left arm, the right arm was used) of the seated participant and elevated the arm on the table to the level of the fourth intercostal space. The non-invasive (finger-prick blood sample) HbA1c test was performed by the MFMC staffed laboratory technician who received training from the

supplier on how to use the SUPER ID clinchem device (Dr. Müller Gerätebau GmbH, Germany). In the absence of sufficient funds for the conduct of spirometry to assess irreversible obstruction to air flow for COPD assessment, PEF (L/min) was measured 3 times with a 30-second pause between attempts, using the OMRON Peak Flow Meter PFM20 (Omron Healthcare, Switzerland). PEF predicted (%) was calculated as the ratio of the estimated (measured) PEF to the expected PEF. The expected PEF values were derived based on age, gender and height using the regression equation developed by Hankinson et al. (23). From these data sources, indicator variables of undetected and uncontrolled hypertension, diabetes and COPD variables were defined as follows:

- Undetected hypertension: no self-reported physician diagnosis of hypertension as well as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
- Undetected diabetes: no self-reported physician diagnosis of diabetes and HbA1c ≥ 6.5%.
- Undetected COPD: no self-reported physician diagnosis of COPD as well as PEF <80% Predicted (24) with breathlessness for 6 months or longer or cough for at least 3 months.
- Uncontrolled hypertension: self-reported physician diagnosis of hypertension as well as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
- Uncontrolled diabetes: self-reported physician diagnosis of diabetes and HbA1c ≥ 6.5%.
- Uncontrolled COPD: self-reported physician diagnosis of COPD and PEF <80% Predicted.

Undetected and uncontrolled diseases were further stratified by stage of the disease:

- Hypertension: Stage 1 is systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and stage 2 is systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100, according to the international society of hypertension (25).
- Diabetes: Level 1 is an HbA1c 6.5–7.4%, level 2 is an HbA1c 7.5–9.0%, level 3 is an HbA1c 9.1–11%, and level 4 is an HbA1c > 11% (26).
- COPD: level 1 is a PEF 50–79% Predicted, level 2 is a PEF < 50% predicted.

Depressive Symptoms

Depressive symptoms were measured using the Depressive Anxiety Stress Scale (DASS-21) (27), a 21-item questionnaire consisting of subscales for depressive, anxiety and stress symptoms, each containing seven items scored on a 4-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much). The sum of scores from the depressive symptoms subscale was then multiplied by 2. The depressive symptoms scores range from 0 to 42.

Statistical Analyses

Sociodemographic factors among PHC users were presented as frequency and percentages for categorical variables and as the median and interquartile range for non-normal distributed continuous variables.

The prevalence of NCD risk factors (smoking, physical inactivity, poor nutrition, alcohol consumption, obesity and lifestyle index) among PHC users were described as frequencies and percentages for the total study population and were stratified by sex (male, female) and highest education level attained (primary school, secondary school, university). The prevalences of undetected and uncontrolled hypertension, diabetes and COPD among PHC users were presented as frequency and percentages of the relevant subsample, and also stratified by sex and highest education level attained. For the outcome of undetected disease, participants were included in the subsample if they had either a diagnosis for the disease or pathological clinical findings for that disease (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg for hypertension; HbA1c ≥ 6.5% for diabetes; PEF < 80% Predicted with breathlessness for 6 months or longer or cough for at least 3 months for COPD). For the outcome of uncontrolled disease, only those with a self-reported doctor's diagnosis of the disease were included in the subsample.

The adjusted cross-sectional associations between depressive symptoms as a continuous predictor variable and outcomes of smoking, physical inactivity, alcohol consumption, poor nutrition, and obesity, undetected hypertension, diabetes and COPD as well with uncontrolled hypertension and diabetes were quantified using mixed logistic regression models, while mixed ordinal logistic regression was used for the association between depressive symptoms and lifestyle index. Municipality (Gračanica, Drenas, Skënderaj, Malishevë, Rahovec, Gjakovë, Junik, Fushë Kosovë, Vushtrri, Mitrovicë, Lipjan, and Obiliq) was included as a random effect in all models. We selected potential confounders for inclusion in these models based on prior knowledge: age (years), sex (male, female), work status (currently working, house person, retired or disabled, unemployed), highest level of education achieved (primary school, secondary school, university), living in a rural or urban setting (rural, urban), and ethnicity (Albanian, Serbian, Roma or Ashkali or Egyptian or Other). Due to few observed cases of alcohol consumption in the last 30 days, the model of the association between depressive symptoms and alcohol was reduced to include only age, sex and ethnicity as confounders. Due to even fewer cases of uncontrolled COPD, a regression model for the association between depression and uncontrolled COPD was not interpretable. The same subsamples of undetected and uncontrolled disease apply to the regression models as the descriptive outcomes. The same methods were applied with depressive symptoms as a binary predictor variable and are available (moderate to very severe depressive symptoms equate to a DASS-21 depressive symptoms score ≥14) in the supplementary data (**Supplementary Table 1**).

Analyses were performed with Stata statistical software, release 16.

RESULTS

Sociodemographic Characteristics

We included 977 participants from KOSCO in this study. The participant characteristics are described in **Table 1**. There were more women than men in the study, and most had attained

TABLE 1 | Participant characteristics (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

Sociodemographic factors	All participants ($n = 977$)
Age, median (IQR)	60 (53–67)
Sex, frequency (%)	
Male	402 (41.2)
Female	575 (58.8)
Education, frequency (%)	
Primary school or less	618 (63.3)
Secondary school	300 (30.7)
University/College	59 (6.0)
Work status, frequency (%)	
Currently working	162 (16.6)
House person	467 (47.8)
Retired or disabled	314 (32.1)
Unemployed	34 (3.5)
Residence, frequency (%)	
Rural	549 (56.2)
Urban	428 (43.8)
Municipality, frequency (%)	
Drenas	96 (9.8)
Fushe Kosova	109 (11.2)
Gjakova	72 (7.4)
Gracanica	52 (5.3)
Junik	21 (2.2)
Lipjan	171 (17.5)
Malisheva	77 (7.9)
Mitrovica	81 (8.3)
Obiliq	70 (7.2)
Rahovec	77 (7.9)
Skenderaj	93 (9.5)
Vushtrri	58 (5.9)
Ethnicity, frequency (%)	
Albanian	890 (91.1)
Serbian	48 (4.9)
Roma, Ashkali, Egyptian, Other	39 (4.0)
Clinical measurements	
Blood pressure (mmHg),	
Systolic, median (IQR)	133 (123–146)
Diastolic, median (IQR)	86 (80–93)
HbA1c (%), median (IQR)	6.5 (5.7–7.7)
PEF (L/min), median (IQR)	260 (187–350)
BMI, median (IQR)	30.3 (27.4–34.1)
Disease	
Diagnosed hypertension, freq (%)	605 (61.9)
Diagnosed Diabetes, freq (%)	506 (51.8)
Diagnosed COPD, freq (%)	59 (6.0)
Depressive symptoms score (median, IQR)	2 (0–6)
Depressive symptoms severity (freq, %)	
Normal (DASS depression score 0–9)	792 (81.1)
Mild (DASS depression score 10–13)	66 (6.8)
Moderate (DASS depression score 14–20)	84 (8.6)
Severe (DASS depression score 21–27)	17 (1.7)
Very severe (DASS depression score 28–42)	18 (1.8)

IQR, Interquartile range; mmHg, millimeters of mercury; HbA1c, glycated hemoglobin; PEF, Peak Expiratory Flow; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DASS, Depression Anxiety Stress Scale.

primary school education or less. Most participants were not working. The majority of participants identified as ethnic-Albanian and living in rural settings.

Primary Prevention

Table 2 describes the prevalence of NCD risk factors in the PHC users. More than 40% of participants reported 3 or more unhealthy lifestyle factors. Prevalence was highest for poor nutrition, with 85.1% reporting insufficient fruit and vegetable consumption, followed by 70.3% reporting physical inactivity, and 52.7% being obese. There existed important gender differences for smoking, alcohol consumption and obesity. Obesity and multiple unhealthy lifestyles were common among participants of low socioeconomic status, while higher socioeconomic status privileged smoking.

Secondary and Tertiary Prevention

Table 3 describes the prevalence of undetected (secondary prevention) and uncontrolled (tertiary prevention) diseases. Many cases of hypertension (19%), diabetes (16%) and COPD (45%) remained undetected by a healthcare professional in PHC facilities. Uncontrolled disease was also very common in diabetes patients (79%) and COPD patients (76%). Most undetected cases of hypertension and diabetes were within the lower stages of the disease, but at higher stages of disease for uncontrolled hypertension and diabetes. There were important sex differences in the detection and control of COPD. Highly educated people tended to have higher undetected hypertension and people with less education had a higher prevalence of uncontrolled COPD.

Association Between Depressive Symptoms Score and Primary, Secondary and Tertiary Prevention Indicators

Figure 2 shows the adjusted associations between depressive symptoms score and NCD risk factors (smoking, physical, inactivity, poor nutrition, alcohol consumption, obesity, and unhealthy lifestyle index), undetected and uncontrolled hypertension, diabetes and COPD. Per one-point increase in depressive symptoms, we found the following trends: increase in odds of physical inactivity (OR 1.02; 95% CI 1.00–1.05), a decrease in odds for undetected diabetes (OR 0.95; 95% CI 0.91–1.00), and an increase in odds for undetected COPD (OR 1.07; 95% CI 1.00–1.15). The coefficients represented in **Figure 2**

TABLE 2 | Prevalence of non-communicable disease risk factors, stratified by sex and highest level of education attained (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

Risk factor	All participants (*n* = 977)	Sex			Highest level of education attained			
		Male (*n* = 402)	Female (*n* = 575)	*p*-value	Primary (*n* = 618)	Secondary (*n* = 300)	University (*n* = 59)	*p*-value
Current smoker	201 (20.6)	110 (27.4)	91 (15.8)	<0.001*[a]	106 (17.2)	77 (25.7)	18 (30.5)	0.002*[a]
Physical inactivity	687 (70.3)	250 (62.2)	437 (76.0)	<0.001*[a]	482 (78.0)	165 (55.0)	40 (67.8)	<0.001*[a]
Poor nutrition	831 (85.1)	340 (84.6)	491 (85.4)	0.725 [a]	537 (86.9)	246 (82.0)	48 (81.4)	0.106[a]
Alcohol consumption	44 (4.5)	43 (10.7)	1 (0.2)	<0.001*[a]	14 (2.3)	26 (8.7)	4 (6.8)	<0.001*[a]
Obesity	515 (52.7)	151 (37.6)	364 (63.3)	<0.001*[a]	381 (61.7)	111 (37.0)	23 (39.0)	<0.001*[a]
Lifestyle index [b]				<0.001*[c]				<0.001*[c]
0	16 (1.6)	13 (3.2)	3 (0.5)		2 (0.3)	11 (3.7)	3 (5.1)	
1	155 (15.9)	81 (20.2)	74 (12.9)		69 (11.2)	77 (25.7)	9 (15.3)	
2	379 (38.8)	156 (38.8)	223 (38.8)		240 (38.8)	115 (38.3)	24 (40.7)	
3	348 (35.6)	112 (27.9)	236 (41.0)		259 (41.9)	72 (24.0)	17 (28.8)	
4	74 (7.6)	35 (8.7)	39 (6.8)		46 (7.4)	23 (7.7)	5 (8.5)	
5	5 (0.5)	5 (1.2)	0 (0.0)		2 (0.3)	2 (0.7)	1 (1.7)	

*[a]Chi² test. [b]Lifesyle index is the sum of indicators for current smoker, physical inactivity, poor nutrition, alcohol consumption and obesity. [c]Kruskal-Wallis test. *p < 0.05.*

TABLE 3 | Prevalence of undetected and uncontrolled hypertension, diabetes and COPD, also disaggregated by disease severity and stratified by sex and educational level (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

Category	All participants of subsample	Sex			Highest level of education attained			
		Male	Female	*P*-value[a]	Primary	Secondary	University	*P*-value[a]
Undetected hypertension (*n* = 743)	138 (18.6)	70 (24.0)	68 (15.1)	0.002*	75 (15.3)	51 (23.6)	12 (31.6)	0.004*
SBP 140–159 or DBP 90–99	111 (14.9)							
SBP ≥ 160 or DBP ≥ 100	27 (3.6)							
Undetected diabetes (*n* = 601)	95 (15.8)	36 (14.7)	59 (16.7)	0.478	62 (16.3)	27 (14.5)	6 (17.7)	0.826
Hba1c 6.5–7.4%	67 (11.2)							
Hba1c 7.5–9.0%	22 (3.7)							
Hba1c 9.1–11.0%	4 (0.7)							
Hba1c >11.0%	2 (0.3)							
Undetected COPD (*n* = 108)	49 (45.4)	13 (36.1)	36 (50.0)	0.172	35 (46.7)	13 (43.3)	1 (33.3)	0.870
PEF predicted 50–70%	25 (23.2)							
PEF predicted <50%	24 (22.2)							
Uncontrolled hypertension (*n* = 605)	171 (28.3)	74 (33.3)	97 (25.3)	0.350	114 (27.5)	49 (29.7)	8 (30.8)	0.837
SBP 140–159 or DBP 90-99	73 (12.1)							
SBP ≥160 or DBP ≥100	98 (16.2)							
Uncontrolled diabetes (*n* = 506)	400 (79.1)	170 (80.6)	230 (78.0)	0.478	258 (80.9)	121 (76.1)	21 (75.0)	0.416
Hba1c 6.5–7.4%	150 (29.6)							
Hba1c 7.5–9.0%	146 (28.9)							
Hba1c 9.1–11.0%	86 (17.0)							
Hba1c >11.0%	18 (3.6)							
Uncontrolled COPD (*n* = 59)	45 (76.3)	15 (65.2)	30 (83.3)	0.111	32 (80.0)	12 (70.6)	1 (50.0)	0.503
PEF predicted 50–70%	29 (49.2)							
PEF predicted < 50%	16 (27.1)							

*[a]Chi² test, *p < 0.05. SBP, systolic blood pressure in mmHg; DBP, diastolic blood pressure in mmHg; HbA1c, glycated hemoglobin; PEF, peak expiratory flow; COPD, chronic obstructive pulmonary disease. Subsamples for undetected hypertension, diabetes and COPD included all participants with a self-reported physician diagnosis or pathological findings for the given disease (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg for hypertension; HbA1c ≥ 6.5% for diabetes; PEF < 80% Predicted with breathlessness for 6 months or longer or cough for at least 3 months for COPD). Subsamples for uncontrolled disease included all participants with a self-reported physician diagnosis for the given disease. The vertical red line indicates the limit of the odds ratio of one. *p < 0.05.*

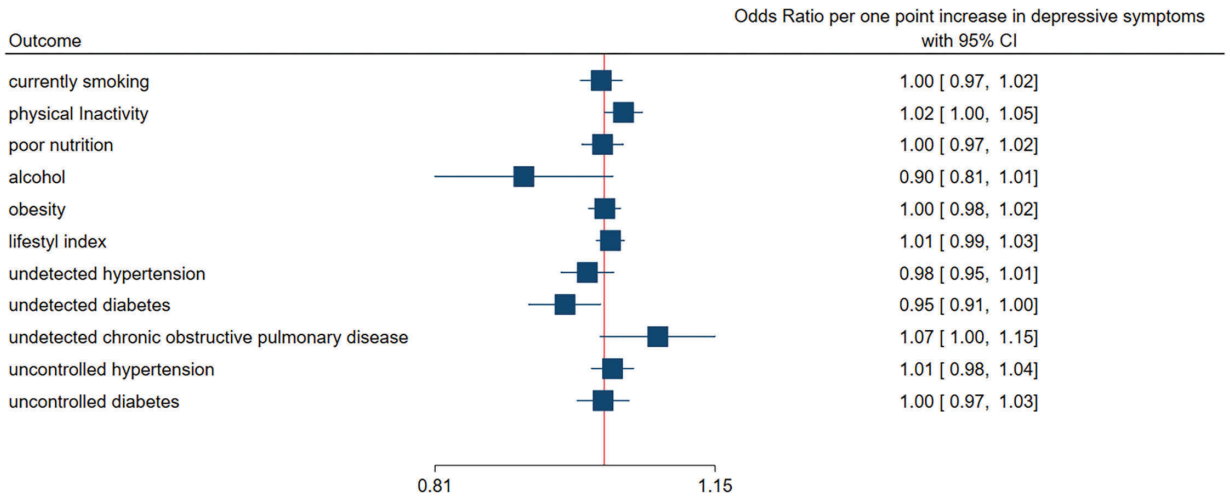

FIGURE 2 | Association between depressive symptoms (continuous score) and primary, secondary and tertiary prevention negative indicators. Squares indicate the odds ratio per one-point increase in depressive symptoms. Lines indicate the 95% confidence interval. Depressive symptoms were assessed using the Depression, Anxiety, Stress Scale-21. Mixed ordinal logistic regression models quantified the association between depressive symptoms and lifestyle index. The associations between depressive symptoms and all other outcomes were quantified with mixed logistic regression models. All models included municipality as a random effect and were adjusted for age, sex, work status, education level, living in a rural or urban setting, and ethnicity with exception of alcohol, which was reduced to adjustment for only age, sex and ethnicity.

are also available in table format available in the supplementary data (**Supplementary Table 2**).

DISCUSSION

The results of this study in Kosovo indicate that the need for improving NCD prevention and control in PHC remains high along the chain of care for disease prevention. NCD risk factors were common among PHC users. Many cases of hypertension, diabetes and possibly COPD remained undetected and also poorly controlled after their diagnosis. Depressive symptoms occurring at a high prevalence and being associated in particular with low levels of physical activity are an important control target and a potential barrier to the control or other NCDs.

Primary Prevention

Smoking

In a national STEPS population-based survey (n = 6,117) conducted in 2010, it was found that 28.4% were smokers, where the prevalence was nearly double among men compared to women. The age group with the highest prevalence was between 35 and 44 years (28). We found a lower prevalence of smokers in our sample of PHC users aged 40 years and older in 2019. The finding that smoking was more prevalent among those with higher education level was surprising, but may indicate socioeconomic mechanisms, as a symbol of status. Our findings may point toward success in smoking cessation among adult smokers, but they may also reflect the generally lower smoking rates in older persons. Given the increasing concern about smoking among younger people in Kosovo (29) and a general concerning increase in popularity of electronic cigarettes (vaping) among adolescents worldwide (30), careful planning of interventions to prevent the onset of smoking at an early age must continue to avoid a future health burden due to tobacco in the coming decades.

Physical Inactivity

Our findings point toward very low adherence to WHO recommended guidelines for physical activity. A study comparing elderly populations in European countries found that Kosovo performed the worst among 28 countries (31). One national survey in Kosovo conducted in 2015 (32) among people aged 65 and older found that only 14.3% were practicing regular physical activity, where males (20.2%) reported regular physical activity more often than women (9.2%). Our study indicates that nearly 30% of PHC users aged 40 years and older are physically active. Although our sample is younger than the 2015 survey, it is still promising that progress is being made toward improving physical activity. Nevertheless, 70% of PHC users are still physically inactive and thus interventions promoting regular exercise should remain in the focus of PHC interventions. Furthermore, additional research needs to identify personal and structural barriers to physical acitivity in the specific context of Kosovo.

Depression has been associated with physical inactivity (16) and our study supports these findings in the Kosovo setting. This relationship suggests that depression may play a role as a barrier to interventions aimed at physical activity. Therefore, adequately treating depressive symptoms may improve physical activity interventions in itself and thereby propagating a positive feedback loop as physical activity interventions have a beneficial effect on depressive symptoms (33).

Poor Nutrition

We found that poor nutrition was very common (85%), meaning that most participants did not consume at least 5 servings of fruit and/or vegetables per day. There were no differences between sex and education level.

Alcohol Consumption

We found a very low prevalence of alcohol consumers in the last 30 days. These findings were unsurprising given that our sample includes older adults who may be more inclined toward traditional practices in a country that has a Muslim majority. Yet, the fact that both, alcohol consumption and smoking were more prevalent among more educated participants suggests that adults in Kosovo are adopting a Western European lifestyle. A shift toward unhealthy lifestyles that parallels the economic development of the country should be prevented at all costs.

Obesity

Over 50% of PHC users were obese and the prevalence was higher among people with lower levels of education. More women were obese compared to men. A previous small study ($n = 423$) conducted in two Kosovar communities in 2010 had only 30% obesity (34). Interventions in PHC targeting obesity should pay special attention to tailor to women and those of lower socioeconomic status.

Lifestyle Index

Women and those with lower education levels tended to have more unhealthy lifestyles overall compared to men and higher education levels respectively. There was no association between depressive symptoms and the number of unhealthy lifestyle factors after adjusting for confounders. This was unexpected given that depression has been associated with a cluster of unhealthy lifestyles (16). The results of this study point to physical inactivity as a central aspect of an unhealthy lifestyle in persons with signs of depression.

Secondary Prevention

We found that nearly one in five PHC users with hypertension were unaware of it, nearly one in six with diabetes were not aware of it and nearly half with potential COPD were not aware of it. The diagnostic gap is scarcely studied in Kosovo. One study conducted in 2006 in adults 18 years and older ($n = 423$) found that over 1 in 3 people with pathological fasting glucose were not diagnosed with diabetes (34).

All of our participants received medical care for various reasons on the day of baseline data collection. Since 2019, the AQH project supports PHC with the implementation of WHO Package of Essential Non-Communicable Disease (PEN) Protocols (35) in five municipalities of Kosovo (Fushe Kosovo, Mitrovica, Malisheva, Gjakova and Vushtrri). The PEN protocol is used for the assessment and management of cardiovascular risk using hypertension, diabetes mellitus and tobacco use as entry points. It outlines screening recommendations for hypertension and diabetes in target groups through blood pressure and blood glucose measurement, which include people aged 40 years and over. Our findings highlight the importance of continuing and adapting the AQH efforts in implementing the PEN protocol and support its expansion to other municipalities and scaling up.

We found a high prevalence of potentially undetected COPD. In the absence of post-bronchodilation spirometry, though, the differentiation between COPD and/or asthma remains imperfect. But the results point to the importance of airflow obstruction. Although PEN protocols are available from the WHO for COPD, they were not yet implemented in Kosovo by AQH at the time of writing this paper. The MFMC directors requested that the study protocol include lung function testing for assessing respiratory disease. The stakeholder's clinical observations indicated that respiratory disease was a concern in their communities, and this study supports these observations. Further research on COPD with spirometric testing and considering also environmental factors is warranted. In Kosovo, Coal remains a common method to heat homes in the winter at a lower cost (36). The indoor air pollution from coal may be an important contributor to exacerbated respiratory disease.

Depressive symptoms were associated with lower odds of undetected diabetes in our adjusted models. This can be explained through increased healthcare utilization among people with depression (37). Underlying diabetes may be more likely to be diagnosed in people with depression since they are assessed and screened more often by a healthcare professional. A longitudinal study assessing healthcare utilization as a mediator of the association is warranted.

Tertiary Prevention

Uncontrolled disease was very common among PHC users. Over a quarter of people with diagnosed hypertension still had high blood pressure. Even more troubling was that the majority, over three in every four PHC users with diagnosed diabetes or what we considered as potential COPD, had their disease uncontrolled. Men had more difficulty controlling their blood pressure and women had more trouble controlling their lung function, while no marked differences in sex were observed for diabetes control. There were no marked differences for control of hypertension and diabetes by education level, but less-educated participants were more likely to have uncontrolled COPD, possibly due to a combination of less access to care and poorer indoor environments, favoring disease progression.

Strengths and Limitations

Our study comprehensively assesses the chain of care in the PHC system to identify specific areas for improvement. Given the current limited epidemiological data situation in the country, our findings provide evidence for stakeholders and decision-makers. Our study sample of PHC patients aged 40 years or more is not representative of the general population of Kosovo. However, the alarming prevalences of unhealthy lifestyle behaviors and poor detection and control of NCDs in our sample suggest that the current society-wide NCD prevention strategies are in urgent need of strengthening. While the prevalence estimates for unhealthy lifestyles might be an overestimation of the prevalence in the general population, given that we assessed PHC users, the fact that even in PHC users we observe a high rate of underdiagnosis and poor disease control could point to even

higher rates in the general population with groups of people having very poor access to care.

Our findings brought to light the urgent need for further research on respiratory disease in Kosovo. We found that nearly half of people with problematic lung function were never diagnosed with COPD. Yet, peak flow measurements have limitations concerning detecting irreversible obstruction to airflow and cannot differentiate between COPD and asthma with high accuracy. It is foreseen for future cohort follow-ups to include pre- and post-bronchodilation spirometry as part of the health examinations.

Our study may be subject to response bias for the topics of alcohol and depression. In Kosovo, it is not generally well viewed to drink alcohol, especially among older adults and therefore participants may not have answered truthfully about alcohol intake. As most areas in the world, mental health is still a stigmatized topic in the country and similarly, participants may not have responded truthfully about their depressive symptoms. The prevalence of depression may therefore be an underestimation, which is particulary worrisome in the light of the recent COVID-19 pandemic, which may have increased the prevalence further. Although questions on alcohol were worded as per the WHO STEPS survey and we did not feel they needed to be changed, we decided to preface DASS questions with an introductory statement to frame the questions about wellbeing, which is a more socially acceptable topic.

The study is cross-sectional in nature and does not allow differentiating cause and effect in the association between depression and NCD control. The follow-up of the cohort will provide an opportunity in the future to address these associations longitudinally.

CONCLUSION

An unhealthy lifestyle, undetected and uncontrolled hypertension, diabetes and possibly COPD are common in Kosovo, contributing to the heavy disease burden in the country. Disease prevention in Kosovo is improving, but still needs continued attention and tailored modifications to primary, secondary and tertiary prevention to narrow the health gap between Kosovo and other Balkan countries.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request.

ETHICS STATEMENT

The study involving human participants were reviewed and approved by Ethics Committee Northwest and Central Switzerland (Ref. 2018-00994) and Kosovo Doctors Chamber (Ref. 11/2019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KO co-developed and implemented the study protocol, coordinated and supervised data collection, carried out the data analysis, interpreted results, and wrote the manuscript. NJ contributed to study objectives related to non-communicable diseases in Kosovo. SS contributed to study objectives related to mental health in Kosovo. MK supervised data analysis. MZ, QR, AB-K, and JG contributed to the study objectives related to the evaluation of health service provision and to the integration of the study protocol within the AQH framework. NP-H developed the KOSCO cohort concept, study objectives and protocol, directed the implementation, data analysis, and result interpretation. All authors have read and approved the final protocol.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.794309/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CHAPTER 5 – ARTICLE 3

Depression and cardiovascular disease are not linked by high blood pressure: Findings from the SAPALDIA cohort

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Depression and cardiovascular disease are not linked by high blood pressure: findings from the SAPALDIA cohort

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Depression and cardiovascular disease (CVD) are main contributors to the global disease burden and are linked. Pathophysiological pathways through increased blood pressure (BP) are a common focus in studies aiming to explain the relationship. However, studies to date have not differentiated between the predictive effect of depression on the course of BP versus hypertension diagnosis. Hence, we aimed to elucidate this relationship by incorporating these novel aspects in the context of a cohort study. We included initially normotensive participants (n = 3214) from the second (2001–2003), third (2009–2011), and fourth (2016–2018) waves of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA). We defined depression based on physician diagnosis, depression treatment and/or SF-36 Mental Health score < 50. The prospective association between depression and BP change was quantified using multivariable censored regression models, and logistic regression for the association between depression and incident hypertension diagnosis. All models used clustered robust standard errors to account for repeat measurements. The age-related increase in systolic BP was slightly lower among people with depression at baseline (β = − 2.08 mmHg/10 years, 95% CI − 4.09 to − 0.07) compared to non-depressed. A similar trend was observed with diastolic BP (β = − 0.88 mmHg/10 years, 95% CI − 2.15 to 0.39), albeit weaker and not statistically significant. Depression predicted the incidence of hypertension diagnosis (OR 1.86, 95% CI 1.33 to 2.60). Our findings do not support the hypothesis that depression leads to CVD by increasing BP. Future research on the role of depression in the pathway to hypertension and CVD is warranted in larger cohorts, taking into account healthcare utilization as well as medication for depression and hypertension.

Depression is a leading cause of disability worldwide affecting more than 264 million people[1]. Depression is also an independent risk factor for cardiovascular disease (CVD)[2,3], which continues to cause the greatest disease burden worldwide[4]. The mechanisms underlying the relationship between depression and CVD are not yet elucidated. Pathophysiological pathways involving increased blood pressure (BP) have been the focus of proposed explanations linking depression and CVD[5–8]. Given the heavy burden these conditions cause globally, it is of great public health relevance to investigate the potential causal role of depression in the course of BP to provide greater insight into the potential of depression control in reducing CVD risk and the global disease burden.

Several studies propose mechanisms mediating the relationship between depression and CVD[5–8], and focus on shared pathways with high BP. Firstly, depression and BP are linked by lifestyle. Depression is associated with an increased risk for unhealthy behaviours such as smoking, physical inactivity, increased alcohol consumption, poor nutrition, and poor sleep[9–11], all of which are known risk factors for raised BP. Secondly, biological mechanisms such as autonomic nervous system dysfunction are associated with depression, resulting in decreased heart rate variability and increased heart rate[12], which in turn lead to an increase in BP. Thirdly, there is evidence that antidepressant treatments themselves may independently increase BP[13,14].

The evidence on the prospective associations between depression and BP is currently mixed. Longitudinal studies have concentrated on the predictive association between depression and incident hypertension[13,15–17]. A

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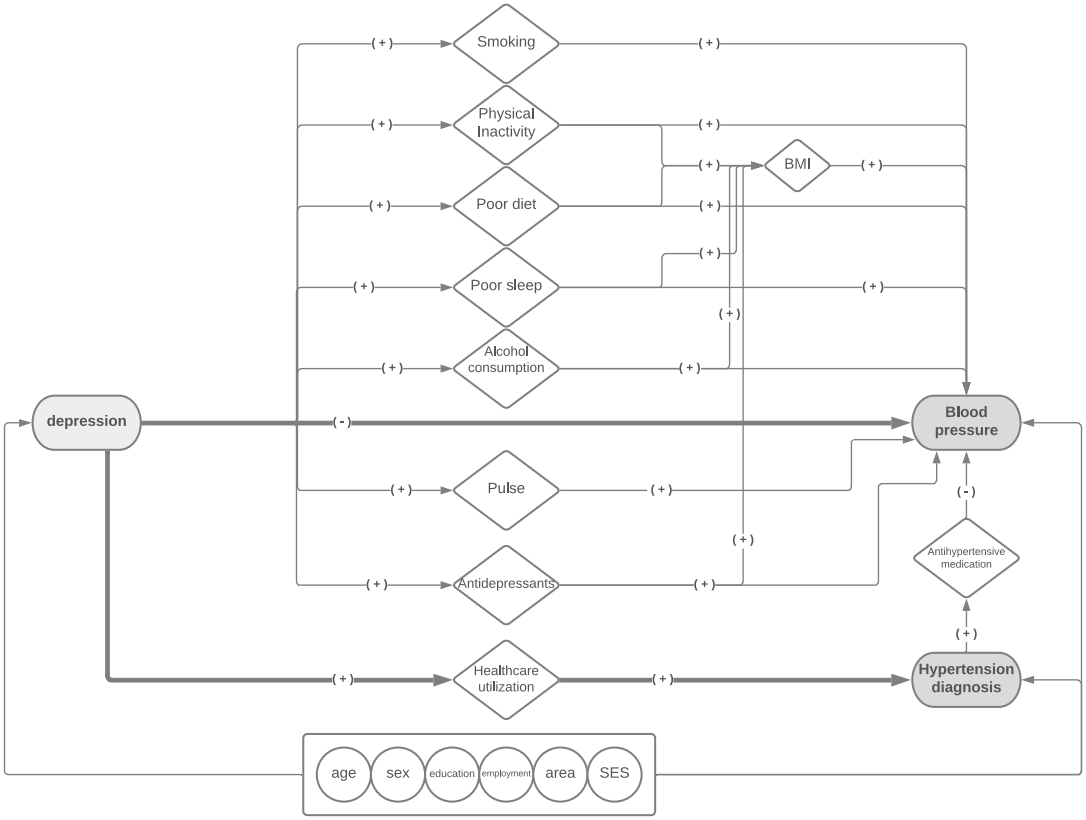

Figure 1. Conceptual Framework. The figure depicts the conceptual framework of the study's main associations of interest (bold lines) between depression and (**a**) change in blood pressure and (**b**) incident hypertension diagnosis, including the confounders (circles) and mediators (rhombus), based on prior knowledge. A (+) indicates a positive association and (−) indicates a negative association. SES: socioeconomic status. BMI: body mass index.

meta-analysis[18] of 9 prospective studies revealed that depression increased the risk of incident hypertension (RR 1.42, 95% CI 1.09 to 1.86). Although some studies detected hypertension with BP measurements alone[19,20] or in combination with hypertension diagnosis or antihypertensive medication use[13,15,17,21–24], several others relied solely on physician-diagnosed hypertension and the use of antihypertension medication to assess the presence of hypertension[16,25–27]. However, many people remain unaware that they have high BP, especially if they do not experience symptoms and fail to get a diagnosis. Depression is associated with higher healthcare utilization[28], thus people living with depression might be more likely to have underlying hypertension diagnosed than those without depression.

Taking direct BP measurement into consideration is important in studies on depression and hypertension. Yet, few longitudinal studies have assessed the association between depression and BP as a continuous variable. One population-based study[29] and a study among people with hypertension[30] provided evidence that baseline depression predicted lower BP[29,30]. Other population-based studies reported that BP increased with increasing[31] or consistently high[17] depressive symptoms. In summary, the little evidence that exists on the effect of depression on BP is mixed. A deeper understanding of how depression affects BP among normotensive people would be particularly valuable from a prevention perspective.

The goal of this study was to elucidate the relationship between depression and the course of BP among normotensive people. We therefore assessed separately the prospective association between depression and the following BP-related outcomes: (a) change in systolic and diastolic BP and, (b) incident hypertension diagnosis. Figure 1 depicts the hypothesized relationships between depression, BP and hypertension based on prior knowledge.

Methods

Participants. We used longitudinal data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) which began in 1991 (SAPALDIA1) with 9651 randomly selected participants aged 18 to 60 from eight representative Swiss areas. SAPALDIA1 focused on air pollution and respiratory health and expanded into cardio-metabolic outcomes and wellbeing thereafter (SAPALDIA2 (2001–2003), SAPALDIA3 (2009–2011), SAPALDIA4 (2016–2018)). The current study used data collected from SAPALDIA2, SAPALDIA3 and SAPALDIA4 for longitudinal analyses. At each of these follow-ups, participants completed a

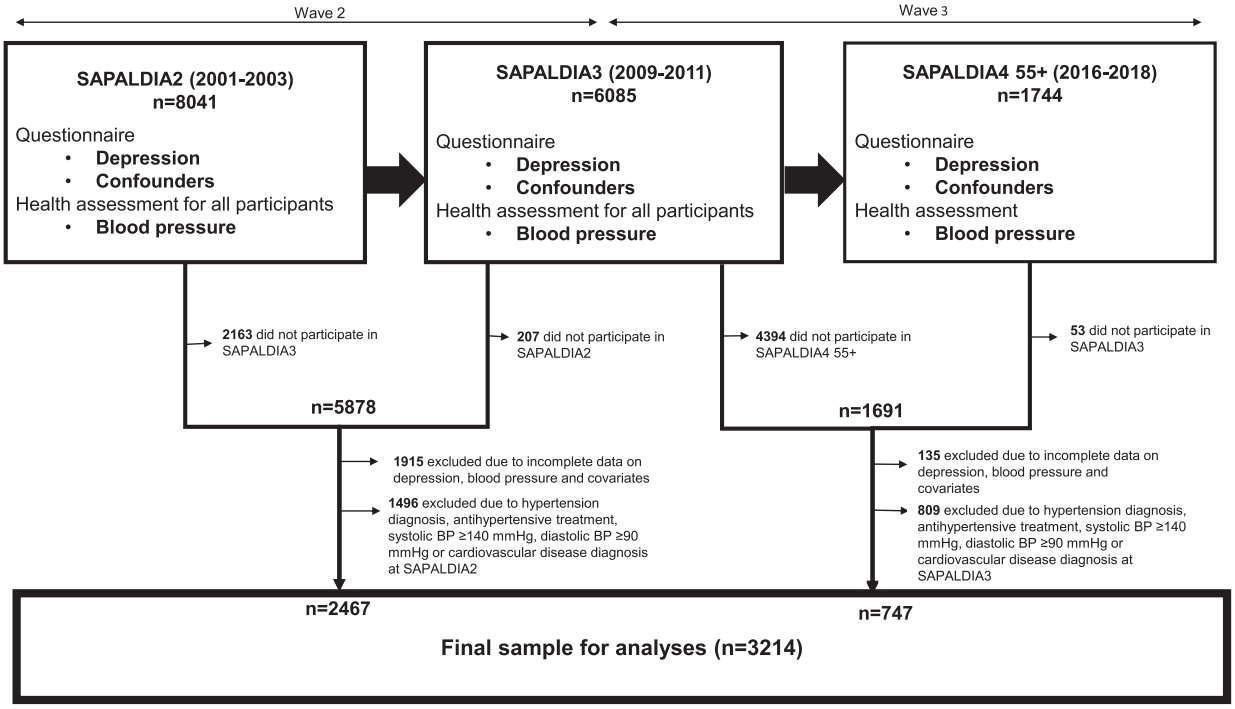

Figure 2. Flow diagram for the inclusion of study participants. The figure summarizes the sources of variables included in the present study as well as the flow diagram for the inclusion of study participants in the repeat measurements analyses. Participants from SAPALDIA2, SAPALDIA3 and SAPALDIA4 55+ were included in the study if within a wave (either SAPALDIA2 to SAPALDIA3 or SAPALDIA3 to SAPALDIA4 55+) they had complete data on systolic and diastolic blood pressure at baseline and follow-up, complete baseline data on depression, potential mediators and confounders, and excluded if at baseline they reported a physician diagnosis of hypertension or cardiovascular disease, antihypertension treatment, or measured high blood pressure (≥ 140/90 mmHg).

health examination and questionnaire covering their lifestyle and health status including information on physician diagnosis, and medication use for depression and hypertension. While all participants at SAPALDIA2 and SAPALDIA3 were subjected to a health assessment, the health examination in SAPALDIA4 was restricted to participants aged 55 years and older at the time (SAPALDIA4 55+). Details of the SAPALDIA study protocols are provided elsewhere[32–34]. The overall participation rate at SAPALDIA1 (n = 9651) was 59.3% of the sample frame[34], with a retention rate of 83% from SAPALDIA1 to SAPALDIA2 (n = 8047), 76% from SAPALDIA2 to SAPALDIA3 (n = 6088), and 85% from SAPALDIA3 to SAPALDIA4 (n = 5149). Of the 5149 SAPALDIA4 participants, 2179 were eligible for the 55+ health exam of whom 1746 underwent it[33]. For our longitudinal analyses, we pooled data from two waves, SAPALDIA2 to SAPALDIA3 (wave 2) and SAPALDIA3 to SAPALDIA4 55+ (wave 3). Participants were included if they met the following criteria within a wave: (1) had complete data on systolic and diastolic BP at first (termed: "baseline") and second time point (termed "follow-up") of each wave; (2) had complete baseline data on depression, potential confounders and mediators, (3) did not report a physician diagnosis of hypertension or CVD at baseline, (4) had no history of antihypertension treatment at baseline, and (5) were normotensive (systolic BP < 140 mmHg and diastolic BP < 90 mmHg) at baseline (n = 3214). A flow diagram for the inclusion of study participants is depicted in Fig. 2. The number of participants meeting these criteria was n = 2467 for wave 2 only, n = 171 for wave 3 only, and n = 576 for both waves. Data use from wave 1 was impeded due to the lack of BP data at the SAPALDIA1 survey.

Ethical approvals for the SAPALDIA studies were obtained from Ethics committees of North-West Switzerland, and the Swiss Academy of Medical Sciences. SAPALDIA complies with the Declaration of Helsinki. All participants provided informed written consent before participating in any aspect of the SAPALDIA studies.

Depression. The presence or absence of depression at baseline (first time point of each wave) was deduced from the following information provided by the participants: First, participants responded to questions about having physician-diagnosed depression and provided a medication list from which antidepressant medication use was derived. Second, participants completed the Medical Outcomes Study Short Form 36 questionnaire (version 1)[35]. The Mental Health domain (SF-36 MH) scores ranged from 0 to 100 and a score below 50 was found to be an appropriate cut-off to screen for depressive disorders[36]. We therefore defined depression as self-reported physician-diagnosed depression or a history of antidepressant use (ATC codes starting with N06A) or an SF-36 MH score < 50. We considered also depression disaggregated by any antidepressant use, and by antidepressant class (N06AA—Non-selective monoamine reuptake inhibitors; N06AB—Selective serotonin reuptake inhibi-

tors; N06AX/combination—other antidepressants and/or using a combination of antidepressants) to assess whether the associations of interest were modified by antidepressants.

Change in blood pressure and incident diagnosis of hypertension. At each health assessment of SAPALDIA2, SAPALDIA3 and SAPALDIA4 55+ surveys, BP was measured twice by trained field workers using an automatic device (705CP and M6, OMRON, Tokyo, Japan) with a cuff of appropriate size (after having measured arm circumference) and using the Riva-Rocci method, in the sitting position after minimum 10 min rest, on the left arm, with 3 min between measurements. The first and second BP measurements were averaged. To obtain the change in BP from SAPALDIA2 to SAPALDIA3 and SAPAPALDIA3 to SAPALDIA4 55+, we subtracted the baseline BP from the follow-up BP within a wave. The coefficients of the censored regression models are interpretable as the difference between depressed and non-depressed participants in age-related increase in BP over 10 years in mmHg. A positive coefficient for the depression variable represented a larger age-related increase in BP among depressed compared to non-depressed people, while a negative coefficient represented a smaller age-related increase in BP among depressed compared to non-depressed people over the wave. Because the length of time between follow-ups varied between 5.6 and 9.7 years among participants, we expressed the observed changes as a per-decade rate, by dividing them by the individual durations of follow-up and multiplying by 10.

Incident hypertension diagnosis was deduced from participants' data on physician diagnoses and medication intake. Participants were identified as having incident diagnosis of hypertension if they had physician-diagnosed hypertension or used antihypertensive medication, regardless of the BP level at corresponding health examination. Participants with high BP level (> 140/90 mmHg) at examination but who reported neither physician-diagnosed hypertension nor antihypertensive medication intake were considered as not having incident diagnosis of hypertension.

Covariates. We selected potential confounders for inclusion in our models based on prior knowledge. These included the participants' age (years), sex (male, female), education (primary school (≤ 9 years), secondary school (> 9– ≤ 12 years), technical college or university (≥ 12 years)), employment status (employed, house person, in training/military service, not working, pensioner), study area (Basel, Wald, Davos, Lugano, Montana, Payerne, Aarau, Geneva), and Swiss socioeconomic position (SSEP) which is a neighborhood socioeconomic status index based on the 2000 census data covering education and occupation of households members as well as room occupancy and rents of households in a neighborhood[37].

In the analysis of the association between depression and change in BP, we considered sex and antidepressant use as potential effect modifiers. We also considered the following as potential mediators: smoking status (never, former, smoker), moderate to vigorous physical activity as per World Health Organization recommendations (less versus more than 150 min per week)[38], alcohol consumption (≤ 1/ > 1 glass per day), vegetable and fruit consumption (not daily/daily), daytime sleepiness (mean item score from the 8-item Epworth's Sleepiness Scale)[39], body mass index (kilograms/meter^2), and pulse (beats per minute).

Statistical analysis. *Depression and change in blood pressure.* Many study participants who were normotensive at baseline developed hypertension and were prescribed antihypertensive medication prior to their follow-up health assessments. Correctly accounting for this treatment is of paramount importance in statistical analyses of BP. Several analytical strategies have been evaluated in a simulation study[40], which recommended the use of censored normal regression. Our own ad-hoc simulations (not reported) corroborated this assessment. In this approach, the BP change for all participants diagnosed or treated for hypertension during a wave was right-censored at the measured value. This is equivalent to assuming that had these participants not received the diagnosis, their BP at the follow-up assessment would have been equal or greater than the value that was actually measured. The coefficients fitted by censored regression have the same familiar interpretation as those from ordinary linear regression.

We fitted separate censored normal models for change in systolic and diastolic BP. We termed models that were adjusted only for the confounders listed above "minimally adjusted", and models further controlled for the suspected mediators "fully adjusted". To account for the sex-specific nonlinear dependency of BP on age, we evaluated a set of nine candidate models with different age and sex adjustments using the Akaike Information Criterion (AIC). The best-fitting model contained linear, quadratic and cubic terms of age, each interacting with sex. No other model selection was performed. Effect modification by sex was assessed by introducing the appropriate interaction term. We did not adjust our models for baseline BP, to guard against bias due to the potential fluctuations of measurements[41]. Effect estimates from otherwise identical models with baseline adjustment are reported in the Supplementary Information.

Depression and incident hypertension diagnosis. The prospective association between baseline depression and incident hypertension diagnosis was assessed with a logistic regression model. We included the same set of covariates as the fully adjusted models for change in BP, and additionally the baseline systolic and diastolic BP, and the follow-up duration of the wave. Effect modification by sex was assessed by introducing the appropriate interaction term.

All analyses used clustered robust standard errors to account for repeat measurements of participants. Analyses were performed with Stata statistical software, release 16.

Results

Participant characteristics. Table 1 displays the baseline participant characteristics by wave. A total of 3214 observations were included in our analyses. About 11% of participants at SAPALDIA2 and 14% at SAPALDIA3 had depression. Depression was slightly less frequent among those who met our inclusion criteria compared to those who did not (12.4% at wave 2 and 15.3% at wave 3). An age-related increase in systolic BP was observed from SAPALDIA2 and SAPALDIA3. There was 12% and 10% incident hypertension diagnosis in wave 2 and wave 3 respectively.

Association between depression and change in blood pressure. Table 2 shows the coefficients of the censored regression models for the association between depression and change in systolic and diastolic BP among people who were normotensive at baseline. Depression was also disaggregated first by antidepressant use, then further by antidepressant class. We found that non-disaggregated depression was associated with age-related systolic BP increase both in our minimally adjusted model ($\beta = -1.99$, 95% CI −4.02 to 0.04) and the model adjusted further for suspected mediators ($\beta = -2.08$, 95% CI −4.09 to −0.07), although the former result did not meet the conventional statistical significance threshold of $p < 0.05$. The direction of the association with diastolic BP was the same, but did not reach statistical significance in either model: $\beta = -0.82$, 95% CI −2.10 to 0.45; and $\beta = -0.88$, 95% CI −2.15 to 0.39, respectively.

Effect modification and mediation of the association of depression with change in blood pressure. We found no evidence that the association of depression with age-related increase in systolic or diastolic BP differed by sex ($P_{interaction} = 0.45$ and 0.54, respectively), nor by antidepressant use ($P_{interaction} = 0.48$ and 0.44, respectively).

The direction of effect modification with antidepressant use and antidepressant classes may be of biological interest and is therefore presented as input for future, larger studies. The association of depression with lower age-related increase in systolic BP tended to be weaker in persons without a history of antidepressant use ($\beta = -1.59$, 95% CI −4.01 to 0.83), but stronger among persons with a history of antidepressant use ($\beta = -3.03$, 95% CI −6.35 to 0.29) in the fully adjusted models,. Similar but also statistically non-significant patterns were observed for diastolic BP where associations weakened in depressed persons without antidepressant use ($\beta = -0.55$, 95% CI −2.12 to 1.01) and were stronger in the case of antidepressant use ($\beta = -1.52$, 95% CI −3.50 to 0.46).

We also observed suggestive differences between antidepressant classes, although the confidence intervals of all findings also crossed zero. Depressed persons using non-selective monoamine reuptake inhibitors (NO6AA) had the largest lowering in age-related increase of systolic BP ($\beta = -5.70$, 95% CI −12.22 to 0.82) among antidepressant classes, although age-related increase in systolic BP was also lowered in all other classes but with even less confidence. Equivalent patterns were observed for diastolic BP.

We found that controlling the minimally adjusted model further for covariates related to lifestyle (smoking, physical activity, alcohol, sleepiness, fruit consumption, vegetable consumption) and autonomic nervous system (pulse) had little impact on the estimates of the effect of depression, which is consistent with no or little mediation by these factors).

Association between depression and incident hypertension diagnosis. Table 3 shows the odds ratios of incident hypertension diagnosis at follow-up. There were a total of 286 events of hypertension diagnosis (11.6%) in wave 2, and 71 events (9.5%) in wave 3. There was a clear increase in odds for depressed persons to receive a diagnosis of hypertension at follow-up (OR 1.86, 95% CI 1.33 to 2.60). This increase was larger and statistically significant for the participants without a history of antidepressant use (OR 2.23, 95% CI 1.53 to 3.27), but weaker and not statistically significant for those with antidepressant use (OR 1.21, 95% CI 0.66 to 2.24). We found no evidence that the effect of depression on incident hypertension diagnosis differs by sex ($P_{interaction} = 0.77$).

Discussion

We found that in normotensive people, the age-related increase in systolic BP was lower by about 2 mmHg among depressed compared to non-depressed participants over 10 years of follow-up. However the presence of depression at baseline increased the odds of having hypertension diagnosed if it developed.

Predictive association between baseline depression and change in blood pressure. *Main effect.* To the best of our knowledge, our study is the first to report the predictive association between depression and change in BP as a continuous variable among normotensive people and incident hypertension diagnosis in the same study sample. While BP tends to increase with age, we found that systolic BP increased less among people with depression compared to those without depression at baseline. This association did not vary by sex in our study, although there is evidence of effect modification by sex in another study[31] which included people with hypertension. Our observations suggest that systolic BP is not a relevant mediator in the causal effect of depression on CVD as it was recently confirmed in the context of a bi-directional Mendelian Randomization (MR) study[42]. In the MR study, a slight attenuation of the causal effect of depression on CVD was observed after adjustment for BP, but neither was a mediation analysis conducted, nor was the sample restricted to normotensive persons.

Few other longitudinal studies have assessed depression and BP as a continuous variable. Our findings are consistent with one general population-based study (age 40 ± 10.6) which included both normotensive and hypertensive people and found that a higher depression symptoms score (continuous) was predictive of attenuated BP after 11 years of follow-up[29], as was depression as a binary exposure, albeit with less confidence. A second study,

	Wave 2 (SAPALDIA2 to SAPALDIA3) (n = 2467)	Depressed at wave 2 (criteria iv) (n = 262)	Wave 3 (SAPALDIA3 to SAPALDIA4 55+) (n = 747)	Depressed at wave 3 (criteria iv) (n = 101)
Depression, frequency (%)				
i. Depression diagnosis	113 (4.6)		73 (9.8)	
ii. Depressive symptoms (SF-36 MH < 50)	149 (6.0)		31 (4.2)	
iii. History of antidepressant use	83 (3.4)		38 (5.1)	
iv. Presence of depression[b] (any of i, ii, or ii)	262 (10.6)		101 (13.5)	
Age, mean (SD)	48.0 (10.5)	49.1 (11.0)	58.7 (7.4)	58.5 (7.3)
Sex, frequency (%)				
Male	1103 (44.7)	85 (32.4)	311 (41.6)	30 (29.7)
Female	1364 (55.3)	177 (67.6)	436 (58.4)	71 (70.3)
Education level, freq (%)				
Primary school	87 (3.5)	21 (8.0)	20 (2.7)	7 (6.9)
Secondary school	1556 (63.1)	165 (63.0)	456 (61.0)	61 (60.4)
Technical College or University	824 (33.4)	76 (29.0)	271 (36.3)	33 (32.7)
Employment, frequency (%)				
Employed	1968 (79.8)	187 (71.4)	501 (67.1)	60 (59.4)
House person	302 (12.2)	45 (17.2)	52 (7.0)	11 (10.9)
In training/military service	31 (1.3)	4 (1.5)	5 (0.7)	0 (0)
Not working	25 (1.0)	13 (5.0)	5 (0.7)	3 (3.0)
Pensioner	141 (5.7)	13 (5.0)	184 (24.6)	27 (26.7)
Area, frequency (%)				
Basel	299 (12.1)	25 (9.5)	93 (12.5)	10 (9.9)
Wald	494 (20.0)	33 (12.6)	105 (14.1)	12 (11.9)
Davos	196 (7.9)	13 (5.0)	80 (10.7)	6 (6.0)
Lugano	265 (10.7)	29 (11.1)	106 (14.2)	11 (10.9)
Montana	287 (11.6)	47 (17.9)	79 (10.6)	21 (20.8)
Payerne	289 (11.7)	43 (16.4)	96 (12.9)	17 (16.8)
Aarau	406 (16.5)	38 (14.5)	103 (13.8)	10 (9.9)
Geneva	231 (9.4)	34 (13.0)	85 (11.4)	14 (13.9)
Swiss Socioeconomic Position, mean (SD)	64.4 (9.6)	62.5 (9.8)	65.0 (9.2)	63.5 (9.4)
Smoking status, frequency (%)				
Never	1211 (49.1)	115 (43.9)	387 (51.8)	50 (49.5)
Former	660 (26.8)	59 (22.5)	235 (31.5)	31 (30.7)
Smoker	596 (24.2)	88 (33.6)	125 (16.7)	20 (19.8)
Physical activity, frequency (%)				
Insufficiently active[c]	615 (24.9)	76 (29.0)	151 (20.2)	26 (25.7)
Sufficiently active[d]	1852 (75.1)	186 (71.0)	596 (79.8)	75 (74.3)
Vegetable consumption, frequency (%)				
Not daily	1913 (77.5)	196 (74.8)	552 (73.9)	73 (72.3)
Daily	554 (22.5)	66 (25.2)	195 (26.1)	28 (27.7)
Fruit consumption, frequency (%)				
Not daily	2212 (85.6)	224 (85.5)	638 (85.4)	73 (72.3)
Daily	355 (14.4)	38 (14.5)	109 (14.6)	28 (27.7)
Alcohol				
Less than several times a week	1587 (64.3)	168 (64.1)	444 (59.4)	69 (68.3)
Several times per week	880 (35.7)	94 (35.9)	303 (40.6)	32 (31.7)
Sleepiness[e], mean (SD)	1.8 (0.4)	1.8 (0.5)	1.8 (0.5)	1.8 (0.5)
Body mass index (kg/m^2), mean (SD)	24.6 (3.6)	24.4 (3.8)	24.6 (3.7)	24.6 (4.0)
Pulse (beats per minute), mean (SD)	69.4 (9.8)	69.5 (10.3)	67.8 (9.5)	69.9 (10.0)
Systolic BP (mmHg), mean (SD)	116.6 (12.4)	115.0 (12.5)	121.5 (10.2)	119.6 (9.4)
Continued				

	Wave 2 (SAPALDIA2 to SAPALDIA3) (n = 2467)	Depressed at wave 2 (criteria iv) (n = 262)	Wave 3 (SAPALDIA3 to SAPALDIA4 55+) (n = 747)	Depressed at wave 3 (criteria iv) (n = 101)
Diastolic BP (mmHg), mean (SD)	74.8 (7.7)	73.4 (7.9)	74.2 (7.1)	74.2 (6.0)
Incident hypertension diagnosis	286 (11.6)	46 (17.6)	71 (9.5)	12 (11.9)

Table 1. Baseline[a] participant characteristics (total n = 3214) by wave for the analysis of the prospective association between depression and change in blood pressure as well as incident hypertension diagnosis. [a]First time point of each wave is defined as baseline. [b]The primary exposure for this study. [c]Insufficiently active (< 150 min of moderate physical activity and < 75 min of vigorous physical activity per week). [d]Sufficiently active (> 150 min of moderate physical activity or > 75 min of vigorous physical activity per week). [e]Sleepiness—mean score per item of the Epworth Sleepiness Scale.

	Change in systolic blood pressure over 10 years				Change in diastolic blood pressure over 10 years			
	Minimally adjusted [b]		Fully Adjusted [c]		Minimally adjusted [b]		Fully Adjusted [c]	
	Coef	95% CI	Coef	95% CI	Coef	95% CI	Coef	95% CI
Presence of depression								
Not depressed (n = 2851)	(Reference)		(Reference)		(Reference)		(Reference)	
Depressed (n = 363)	− 1.99	(− 4.02, 0.04)	− 2.08	(− 4.09, − 0.07)	− 0.82	(− 2.10, 0.45)	− 0.88	(− 2.15, 0.39)
Depression, disaggregated by antidepressant medication use								
Not depressed (n = 2851)	(Reference)		(Reference)		(Reference)		(Reference)	
Depressed, not medicated (n = 242)	− 1.59	(− 4.03, 0.85)	− 1.59	(− 4.01, 0.83)	− 0.58	(− 2.15, 0.99)	− 0.55	(− 2.12, 1.01)
Depressed, medicated (n = 121)	− 2.80	(− 6.15, 0.56)	− 3.03	(− 6.35, 0.29)	− 1.30	(− 3.31, 0.72)	− 1.52	(− 3.50, 0.46)
Depression, disaggregated by type of antidepressant								
Not depressed (n = 2851)	(Reference)		(Reference)		(Reference)		(Reference)	
Depression, not medicated (n = 242)	− 1.60	(− 4.04, 0.83)	− 1.60	(− 4.02, 0.82)	− 0.59	(− 2.16, 0.98)	− 0.56	(− 2.12, 1.01)
Depressed, on N06AA[d] (n = 16)	− 5.75	(− 12.58, 1.08)	− 5.70	(− 12.22, 0.82)	− 5.27	(− 9.74, − 0.81)	− 5.47	(− 9.61, − 1.33)
Depressed, on N06AB[e] (n = 55)	− 4.24	(− 9.00, 0.52)	− 4.39	(− 9.16, 0.37)	− 1.17	(− 4.02, 1.67)	− 1.12	(− 3.92, 1.67)
Depressed, on other or multiple antidepressants (n = 46)	0.09	(− 5.67, 5.85)	− 0.35	(− 6.01, 5.31)	− 0.04	(− 3.57, 3.49)	− 0.63	(− 4.10, 2.84)

Table 2. Prospective association between baseline[a] depression (binary, and disaggregated by antidepressant use and antidepressant class) and age-related increase in systolic and diastolic blood pressure over 10 years among normotensives at baseline [a] (n = 3214). [a]First time point of each wave is defined as baseline. [b]Censored normal regression models "minimally adjusted" included age, quadratic age term, cubic age term, sex, age and sex interactions, education, employment, SSEP, study area, and wave. [c]Fully adjusted models included all of the above and BMI, pulse, sleepiness, physical activity, fruit consumption, vegetable consumption, alcohol, and smoking. [d]N06AA—Non-selective monoamine reuptake inhibitors. [e]N06AB—Selective serotonin reuptake inhibitor.

which was restricted to persons with hypertension, did not find that depression at case-level was predictive of change in BP (β = − 1.3, 95% CI − 5.3 to 2.7)[30]); however when they stratified depression by severity, they found that moderate major depressive disorder (but not mild or severe) predicted lower BP (systolic BP (β = − 7.5, 95% CI − 13.2 to − 1.9) and diastolic BP (β = − 4.5, 95% CI − 7.8 to − 1.3))[30]. Studies with contrasting evidence to our findings did not assess BP change over time[31] or were restricted to women[17].

There are two main hypotheses which need to be discussed in the context of our finding that depression attenuates age-related BP increase. Firstly, it has been hypothesized before that lower BP among depressed persons may be due to a higher use of antihypertensive drugs[14]. Our analyses provide no support for this hypothesis, since the effect was observed even though we removed baseline antihypertensive drug users from the sample and controlled for initiation mid-wave with censored regression. However, as our medication data is self-reported, the possibility of differential misclassification remains. The second hypothesis argues for a shared biology between depression and low BP, and therefore not a causal pathway between the two. The monoamine theory of depression[43] suggests that the underlying pathogenesis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system. Monoamines also play a central role in raising BP and therefore low BP is observed when there is a depletion of these monoamines. Thus when there is a depletion of monoamines, both depressive symptoms and low BP could be observed.

The effect size of the lower age-related increase in systolic BP (depressed people had about 2 mmHg smaller increase in systolic BP than non-depressed over 10 years) may not be of clinical significance at the individual level. However at the level of the population it will decrease substantially the number of individuals becoming hypertensive due to the slight shift in the distribution of BP towards lower values. This preventive effect is not

	Incident hypertension diagnosis	
	Odds ratio	95% CI
Depression		
No depression (n = 2851)	(Reference)	
Depressed (n = 363)	1.86	(1.33, 2.60)
Depression		
No depression (n = 2851)	(Reference)	
Depression, not medicated (n = 242)	2.23	(1.53, 3.27)
Depression, medicated (n = 121)	1.21	(0.66, 2.24)
Depression		
No depression (n = 2851)	(Reference)	
Depression, not medicated (n = 242)	2.22	(1.52, 3.26)
Depressed, on N06AA[b] (n = 16)	0.55	(0.06, 4.93)
Depressed, on N06AB[c] (n = 55)	0.85	(0.32, 2.25)
Depressed, on other or multiple antidepressants (n = 46)	2.02	(0.88, 4.64)

Table 3. Prospective association between baseline[a] depression (binary, disaggregated by antidepressant use, and disaggregated by antidepressant class) and incident hypertension diagnosis (self-reported physician diagnosis or antihypertensive treatment use at follow-up) among normotensives at baseline[a] (n = 3214). A total of 357 incidences of hypertension diagnosis (11.1%) were observed. Logistic regression models with adjustment for age, sex, education, employment, Swiss SEP, area, wave, BMI, pulse, daytime sleepiness, physical activity, fruit consumption, vegetable consumption, alcohol, smoking, baseline systolic and diastolic BP, and years of follow-up. [a]First time point of each wave is defined as baseline. [b]N06AA—Non-selective monoamine reuptake inhibitors. [c]N06AB—Selective serotonin reuptake inhibitor.

irrelevant given the high prevalence of both depression and hypertension. Furthermore, our findings have important implications on cardiovascular epidemiology. Hypertension as a potential mechanism linking depression and CVD is in the literature spotlight. However, our findings suggest that the association between depression and CVD is not mediated through hypertension. Therefore epidemiological studies investigating other potential mechanisms are warranted.

Effect modification antidepressant use. In addition to assessing depression as a binary exposure, we also stratified depression by antidepressant use. When compared to persons without depression, we observed that participants reporting depression with a history of antidepressant treatment may have a greater attenuation in systolic and diastolic BP change than did participants reporting depression without a history of antidepressant treatment. This statistically non-significant finding was unexpected in light of the fact that antidepressants increase monoamines in the brain to improve depressive symptoms. Also other researchers did not find effect modification by general antidepressant use in longitudinal studies, however they were not restricted to normotensive persons[29,30]. We further conducted an analysis disaggregating depression by antidepressant class and found suggestive, but not statistically significant, evidence that attenuation of BP course may be strongest for N06AA class of antidepressants. This is in contrast to one cross-sectional study which found that certain subclasses of antidepressants (tricyclic antidepressants as well as noradrenergic and serotonergic acting antidepressants) increased BP[14]. In addition, a meta-analysis of Randomized Controlled Trials found that although the N06AB class of antidepressants did not change BP, N06AA led to a modest increase in systolic and diastolic BP when compared to N06AB[44]. The reporting of these suggestive results arising from a small study sample is meant to stimulate further investigation in the context of larger cohorts.

There are two potentially opposite effects of antidepressants to be considered to explain the trends in our findings. The first is the short-term action, whereby the antidepressant increases monoamines in the brain and therefore neurotransmitters which are responsible for signaling vasoconstriction and increased BP. The second is in the long term action consistent with our findings. Antidepressant therapy aims to alleviate depressive symptoms, thereby potentially removing the effect of depression on BP attenuation. A history of antidepressant use may however be a proxy for longer exposure and/or more severe depression, given that there are clearer benefits of antidepressant treatment for more severe and longstanding depression[45]. Given that the N06AB antidepressant class is currently the recommended first-line antidepressant treatment, the apparent strongest effect in N06AA users observed in our study might be an indication of longer-standing and/or treatment-resistant depression.

Effect mediation. We saw no meaningful attenuation in any effect estimate between the corresponding minimally and fully adjusted models (Table 2). This might indicate weak or no mediation by the factors that we considered. Depression however is a complex disease that has different clinical presentations, for example increase versus decrease in appetite and sleep, masking the mediating effect of such factors in single depression category analyses. For this reason, some studies differentiate subtypes of depression[46,47], which could not be assessed in the present study. The biggest limitation of our approach to mediation was that depression and the hypothesized

mediators were measured at the same time. Future studies seeking to elucidate the mechanisms linking depression and BP should ideally be based on longitudinal designs with more frequent follow-ups.

Predictive association between baseline depression and incident hypertension diagnosis. Baseline depression was associated with higher odds of incident hypertension diagnosis at follow-up compared to no depression. Our findings are consistent with the large body of evidence on the association between depression and the incidence of hypertension, which often includes hypertension diagnosis solely or as part of its definition[15,16,18,48,49]. We interpret our findings as an indication that people with depression are more likely to have underlying hypertension diagnosed, likely mediated by increased healthcare-seeking behaviour[28]. We could not adjust for healthcare utilization in our study because data collection on health-seeking behaviours began in SAPALDIA4.

Our analyses indicate that depression increases the likelihood of being diagnosed and treated for hypertension through mechanisms that might not involve increasing BP. This finding has an important methodological implication for future studies of the depression-BP relationship. Because depression and increased BP modify the likelihood of hypertension treatment independently, adjusting analyses for treatment introduces collider bias[50]. The effects of depression and antihypertensive medication can be disentangled more easily in longitudinal studies with multiple and more frequent follow-ups.

Strengths and limitations. This study points to the importance of disentangling the mixed evidence on the predictive association between depression and the course of BP by assessing in the same sample of normotensive persons the prospective association of depression with BP course and with obtaining a new diagnosis of hypertension. The longitudinal design allowed for a temporal sequence of exposure and outcome. The inclusion of SF-36 MH score to identify potential cases of undiagnosed depression minimized exposure misclassification in our study and allowed for identifying persons with depressive symptoms in the absence of treatment. The association remained when we removed the SF-36 MH criteria from the exposure definition in a sensitivity analysis. The association between diagnosed depression and age-related increase in systolic BP in the fully adjusted model was − 2.65 (95-CI − 4.95 to − 0.35) and − 1.54 (95 CI − 2.86 to − 0.21) for diastolic BP.

One limitation of our study was that we did not measure the duration of exposure and severity of depressive symptoms. Observing a dose–response effect would increase the evidence for a causal relationship for shared biological pathways, as was done in another study[29]. We did not consider persistent depression in order to maintain the prediction perspective and to avoid reverse causation bias in the light of only three follow-up time points. An important limitation of the study is the fact that BP was only measured at three time points several years apart. Therefore, the calculated changes in BP between these points may incorporate intra-individual fluctuations of BP over short time intervals. A limitation of any cohort is the loss of participants to follow-up. In light of the restriction of the study sample to normotensive persons, it is very difficult to judge bias due to loss of follow-up. We observed that depression was slightly less prevalent in the study sample. We may have underestimated the effect of depression in the course of BP in case participants lost to follow-up in this cohort had more depression and at the same time more hypertension.

The relatively small sample size may be a limitation to our study. However, only one similar study[29] had a larger sample size (n = 17 410), while others were significantly smaller (n < 2100)[17,20,30,31]. The results of this study can guide research approaches in mega-cohorts established more recently and currently being followed up in various countries.

Conclusion

In normotensive participants without a history of hypertension or antihypertensive treatment, depression goes along with an attenuation of the age-related increase in systolic BP, possibly rooted in a central monoamine deficiency underlying both depression and low BP. The effect is unlikely to be clinically relevant at the level of the individual, but shifts the distribution of BP towards lower values at the population level. At the same time, the presence of depression or depression symptoms at baseline was predictive of a higher likelihood for obtaining a hypertension diagnosis during follow-up, possibly the result of increased healthcare-seeking behaviour among depressed people. Further disentangling the inconsistencies in the literature and understanding the pathways from depression to high BP, hypertension and CVD is of public health relevance given the contribution of these phenotypes to disease burden worldwide.

Data availability

The datasets analysed during the current study are not publicly available due to the protection of non-anonymized data in the context of cohort data, but are available from the corresponding author on reasonable request.

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Author contributions
K.A.O. and M.K. contributed to the concept of the study, to the analysis of the results and to the writing of the manuscript. E.S. prepared the data for analysis. E.S., U.E.L., D.S., I.C.E. and M.I. aided in interpreting the results, M.I. lead the data collection and data management of SAPALDIA, N.P.-H. is the Primary Investigator of the SAPALDIA study, developed the study concept, contributed to the writing of the manuscript and supervised the analysis. All authors discussed the results and commented on the manuscript.

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CHAPTER 6 – ARTICLE 4

Prospective association between depressive symptoms and blood-pressure related outcomes in Kosovo

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PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Prospective association between depressive symptoms and blood-pressure related outcomes in Kosovo

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Abstract

Kosovo has the lowest life expectancy in the Western Balkans, where cardiovascular disease (CVD) accounts for over half of all deaths. Depression also contributes to disability in the country, with a prevalence of moderate to severe symptoms reported as high as 42% in the general population. Although the mechanisms are not yet well understood, evidence suggests that depression is an independent risk factor for CVD. Our study assessed the prospective association between depressive symptoms and blood pressure (BP)-related outcomes among primary healthcare users in Kosovo to understand the role of BP in the relationship between depression and CVD. We included 648 primary healthcare users from the KOSCO study. The presence of depressive symptoms was defined as moderate to very severe depressive symptoms (DASS-21 depressive symptoms score $\geq$14). Multivariable censored regression models assessed prospective associations between baseline depressive symptoms and changes in systolic and diastolic BP while taking hypertension treatment into consideration. Multivariable logistic regression models assessed prospective associations between baseline depressive symptoms and hypertension diagnosis among normotensive patients (n = 226) as well as uncontrolled hypertension in hypertensive patients (n = 422) at follow-up. Depressive symptoms were associated with attenuated diastolic BP (β = -2.84, 95%-CI -4.64 to -1.05, p = 0.002) over a year of follow-up in our fully adjusted model, although the association with systolic BP (β = -1.98, 95%-CI -5.48 to 1.28, p = 0.23) did not meet statistical significance. We found no statistically significant association of depressive symptoms with hypertension diagnosis among initially normotensive people (OR = 1.68, 95%-CI 0.41 to 6.98, p = 0.48), nor with hypertension control among initially hypertensive people (OR = 0.69, 95%-CI 0.34 to 1.41, p = 0.31). Our findings are not consistent with increased BP as an underlying mechanism between depression and elevated CVD risk and contribute valuable evidence to cardiovascular epidemiology, where the mechanisms between depression, hypertension and CVD are yet to be elucidated.

data in the context of cohort data but are available on reasonable request. The Ethics Committee imposing restrictions is Ethikkommission Nordwest- und Zentralschweiz (Ref. 2018-00994). Data access requests can be sent to: 1. Prof. Dr. Nicole Probst-Hensch Head of Department, Epidemiology and Public Health PI of KOSCO study Swiss Tropical and Public Health Institute nicole.probst@swisstph.ch Direct +41 61 284 83 78 Mobile +41 79 280 34 14 2. Dr. Malin Ziehmer-Wenz Chief Information Security and Data Privacy Officer Swiss Tropical and Public Health Institute malin.ziehmer-wenz@swisstph.ch Direct +41 61 284 87 98.

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Abbreviations: AQH, Accessible Quality Healthcare Project; BMI, Body Mass Index; CI, Confidence interval; COVID-19, Coronavirus disease; CVD, Cardiovascular disease; DASS-21, 21-item Depression Anxiety Stress Scale; HSCL, Hopkins Symptoms Checklist; IQR, Interquartile range; KOSCO, Kosovo Non-Communicable Disease Cohort; MDD, Major Depressive Disorder; MFMC, Main Family Medicine Centre; mmHg, Millimetres of mercury; OR, Odds ratio; PHC, Primary Healthcare; SD, Standard deviation.

1 Introduction

Kosovo has the lowest life expectancy in the Western Balkans [1], and cardiovascular disease is the main contributor to poor health in the country. In 2019, over half (51.1%) of deaths in Kosovo were cardiovascular-related, with women (54.2%) affected more than men (48.5%) [2]. Well-known causes of cardiovascular disease (CVD) include modifiable risk factors such as physical inactivity, smoking, poor diet, alcohol, hypertension and diabetes, as well as genetic predisposition. Baseline findings from the Kosovo non-communicable disease cohort (KOSCO, n = 977) found that poor nutrition (85%), physical inactivity (70%), obesity (53%), and smoking (21%) were common [3].

There is growing evidence that depression is also an independent risk factor for various CVDs. One meta-analysis (n = 80,000, 3–37 years follow-up) found a pooled relative risk of 1.46 (95%-CI 1.37–1.55) [4] for various CVDs, while a more recent meta-analysis (n = 893,850, 2–37 years follow-up) found a pooled relative risk of 1.30 (95%-CI 1.22–1.40) specifically for coronary heart disease and 1.30 (95%-CI, 1.18–1.44) for myocardial infarction [5].

Depression is a leading cause of disability in the world [6]. Understanding the role depression plays in the development and progression of CVD in the Kosovo context is of particular public health relevance given the high prevalence of depression in the country. One 2009 nationally representative study (n = 1161) of persons aged 15 years or older found that 41.7% had moderate to severe depressive symptoms measured by the Hopkins Symptoms Checklist (HSCL) [7]. Another recent study (n = 155) reported 35.6% moderate to severe depressive symptoms during the COVID pandemic in Kosovo [8]. This is well above the mean found in Southeast Asia (16%) [9] but still below the mean found in Africa (45%) [10].

Identifying the underlying mechanisms between depression and CVD is of great value for cardiovascular epidemiology and for integrating mental health and cardiovascular health care, in particular in primary healthcare (PHC). Although the underlying mechanisms are not yet elucidated, the literature has focused on pathways through high blood pressure. Hypertension is a natural target for investigation, given it is the most important risk factor for CVD [11]. Further, when ranked as risk-attributable DALYs, high systolic blood pressure was the leading risk factor globally, accounting for 10.4 million (95%-CI 9.39–11.5) deaths and 218 million (95-%CI 198–237) Disability Adjusted Life-Years [12]. A meta-analysis concluded that depression increases hypertension incidence [13] however the authors cautioned that the limited number of longitudinal studies available may have impacted conclusions. The way hypertension is defined is also an important limitation of the existing literature. Although some studies on the association between depression and hypertension focused on blood pressure measurements alone [14,15], or in combination with hypertension diagnosis or antihypertensive medication use [16–22], several others relied solely on physician-diagnosed hypertension and the use of antihypertension medication to assess the presence of hypertension [23–26]. However, many people remain unaware that they have high blood pressure, especially if they do not experience symptoms and fail to get a diagnosis. Therefore it is important to include blood pressure measurements when defining outcomes related to hypertension.

Looking at changes in blood pressure may improve sensitivity in detecting the effect of depression on increased blood pressure given that some people may fall short of clinical cut-offs of hypertension despite having significant increases in blood pressure over time. The prospective evidence on the effect of depression on the outcome of change in blood pressure is mixed: studies concluded that depression lowered blood pressure [27,28], increased blood pressure [14], or had no effect on blood pressure [16,29]. Further, including change in blood pressure and hypertension diagnosis together in an outcome definition is subject to bias, given that higher primary healthcare utilization unrelated to mental health among people with

depressive symptomology [30] has been observed. Therefore hypertension diagnosis may be a proxy for increased healthcare utilization since healthcare-seeking leads to better detection rather than providing an unbiased assessment of high blood pressure in the population.

In previous work from the authors of this study [31], the prospective association between depression and blood pressure-related outcomes of change in blood pressure and hypertension diagnosis were investigated separately due to the aforementioned limitation. The findings of that study suggest that depressive symptoms among normotensive people both attenuate blood pressure over time yet also increase the likelihood of hypertension diagnosis. The authors, therefore, propose that depression biologically attenuates blood pressure increase over time while increased healthcare utilization among people with depressive symptoms might mediate the association between depression and hypertension diagnosis, however this would need further investigation. This hypothesis however might help explain the conflicting evidence on the association between depression, blood pressure and hypertension, but needs replication.

Our study aims to assess the prospective association between depression and blood pressure related outcomes such as changes in systolic and diastolic blood pressure as well as hypertension diagnosis among normotensive patients and hypertension control among hypertensive patients in Kosovo. The study aims at replicating a previous study conducted in Switzerland [31].

2 Methods

2.1 Ethics statement

Ethical approvals were obtained from the Ethics Committee Northwest and Central Switzerland (Ref. 2018–00994) and the Kosovo Doctors Chamber (Ref. 11/2019). KOSCO complies with the Declaration of Helsinki. All participants provided informed written consent before participating in any aspect of the KOSCO study.

2.2 Study design

We conducted longitudinal analyses using observational data from the Kosovo Non-Communicable Disease Cohort (KOSCO). The KOSCO study is a PHC patient cohort. The main reason for a patient cohort was to enable the evaluation of PHC services given that the KOSCO study is embedded in the Accessible Quality Healthcare Project (AQH), which is devoted to working with local stakeholders to improve the quality of PHC services in Kosovo through health system strengthening strategies.

Data collection occurred approximately every 6 months, starting in 2019 when the cohort was implemented, alternating between in-person interviews and telephone interviews. Due to coronavirus restrictions, the in-person interview planned for follow-up 2 was changed to telephone and the in-person interview was delayed to follow-up 3. At the time of writing, follow-up 4 was completed and follow-up 5 data collection was ongoing. The current study therefore makes use of data from baseline and follow-up 3. The timeline is shown in Table 1. Further details of the KOSCO study are detailed in the study protocol [32].

2.3 Setting

The study was conducted in Kosovo, located in the Western Balkans, with 1.8 million inhabitants throughout 38 municipalities over a surface area of nearly 11 000 km^2. In Kosovo, the PHC system is divided into three tiers: Each municipality has one Main Family Medicine Center (MFMC), several Family Medicine Centers (FMC) and several Family Medicine Ambulantas (FMA). MFMCs are the largest facilities at the highest level of PHC, which offer more

Table 1. Timeline of data collection for the Kosovo Non-Communicable Disease Cohort from baseline to follow-up 3.

	2020				2020				2021			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Baseline		P	P	P								
Follow-up 1				T	T							
Follow-up 2						T	T					
Follow-up 3								P	P			

Q1 –January to March; Q2 –April to June; Q3 –July to September; Q4 –October to December

P–In-person interviews with health assessment; T–Telephone interviews.

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services, staff, and medical equipment and therefore have a higher patient flow compared to the second-level FMCs and third-level FMAs. Study sites included MFMCs from the following 12 participating municipalities: Gjakovë, Drenas, Gračanica, Mitrovicë, Junik, Lipjan, Malishevë, Obiliq, Fushe Kosovë, Rahovec, Skenderaj, Vushtrri. MFMCs are PHC facilities, which currently do not offer mental health services. Given that the KOSCO study is embedded within the AQH project, study municipalities were selected based on their partnership with the AQH project.

PHC practices in Kosovo are not yet standardized. One of the AQH interventions for the improvement of PHC services is the implementation of service packages (SPs). An important aspect of the SPs is improving the quality of care by setting standards that should be provided at PHC facilities, based on the WHO PEN Protocols [33] which have been adapted to the Kosovo context by national experts. The SPs ensure a continuum of care with the family physician in a gatekeeper role, where patients who are at risk of developing diabetes or hypertension, or those who have already been diagnosed are referred to a health educator for one-to-one motivational counselling sessions to facilitate behaviour change.

There are only 2.68 psychiatrists and 0.49 psychologists per 100,000 inhabitants [34] compared to Switzerland, which has 30 psychiatrists per 100,000 inhabitants [35]. There are eight Community-Based Mental Health Centres in Kosovo, each covering approximately 250,000 inhabitants. The implementation of new community mental health services in Kosovo is still characterized by considerable shortages, including financial and human resources, capacity building, stakeholder involvement and service availability [36]. Additionally, the psychiatry clinic of the University Clinical Centre of Kosovo in Pristina provides the majority of psychiatric inpatient capacities of Kosovo (88 beds), and regional psychiatric wards are equipped with 10–25 beds on average, for a total of 166 psychiatric beds excluding Prishtina [34]. This is a psychiatric bed rate (8.3 per 100,000 population) which is roughly 10 times less than in Central European or Scandinavian countries. There are no specialized psychiatric hospitals in Kosovo.

2.4 Participants

KOSCO participants were recruited consecutively irrespective of the reason for the PHC visit by trained study nurses as they exited MFMCs. This recruitment method was chosen due to the absence of patient registries which would have enabled randomization. Inclusion criteria for the KOSCO study included: 1) aged 40 years or older, 2) consulted PCH services at the MFMC on the day of recruitment, 3) residence in one of 12 participating municipalities, 4) ability to respond to questions in Albanian or Serbian, 5) no terminal illness such as stage 4 cancer, stage 4 COPD, stage 4 congestive heart failure, and stage 5 chronic kidney disease (CKD) or severe dementia, and 6) living in Kosovo for at least 6 months of the year. Further

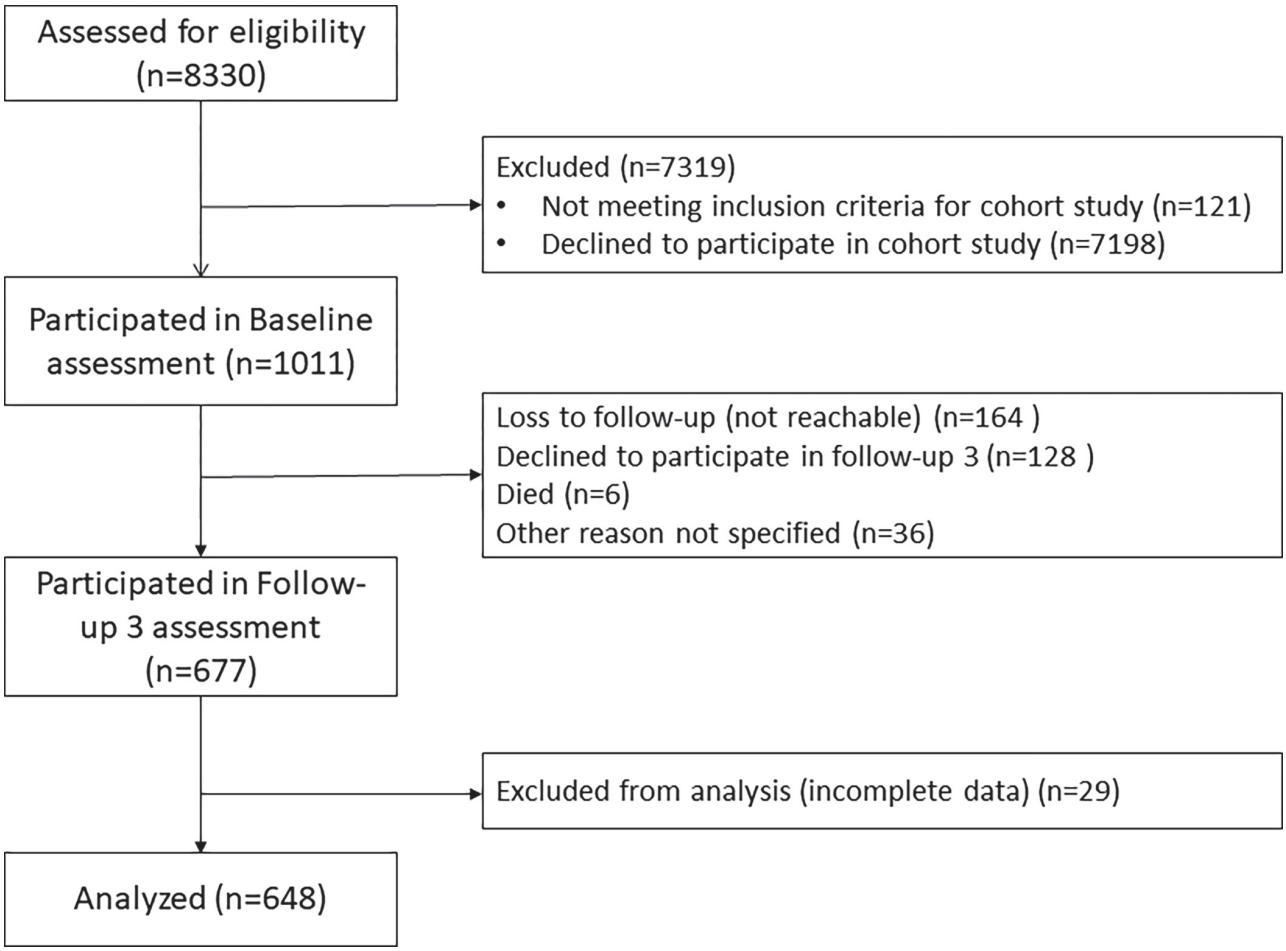

Fig 1. Flow diagram for inclusion of participants in the current study.

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details of the KOSCO recruitment method and study implementation are described in the study protocol [32].

Participants for the current study met additional criteria: (a) had blood pressure measurement data at baseline (March to November 2019) and follow-up 3 (September 2020 to February 2021), (b) had complete baseline data on depression and confounders, and (c) had complete data on hypertension diagnosis and antihypertensive treatment at baseline and follow-up 3. There were 648 participants from the KOSCO study that met inclusion criteria. **Fig 1** depicts the flow of participants for inclusion in the current study and **Table 2** describes the baseline characteristics of participants included in the current study.

The loss-to-follow-up in the KOSCO study was particularly evident following the outbreak of COVID-19. Retention of over 90% of participants was observed at the first follow-up (October 2019-February 2020) but was reduced to approximately 65% by follow-up 3 (September 2020 to February 2021). The fear of exposure to COVID during study visits, especially before the rolling out of vaccines, was a concern voiced by participants thus affecting the retention of participants and reducing the power of the analyses. However, baseline characteristics were comparable between participants and those who dropped out of the study (refer to **S1 Table**).

Table 2. Baseline participant characteristics also disaggregated by depressive symptoms status.

Sociodemographic factors	All participants (n = 648)	Moderate to very severe depressive symptoms (n = 73)	Normal to mild depressive symptoms (n = 575)	
	n (%)	n (%)	n (%)	p-value
Age, mean (Mean±SD)	59.4 ±8.9	59.4±9.0	59.4±8.9	0.966[a]
Sex, frequency				<0.001[b]
Male	273 (42.1)	15 (20.6)	258 (44.9)	
Female	375 (57.9)	258 (44.9)	317 (55.1)	
Education, frequency				0.002 [b]
Primary school or less	399 (61.6)	59 (80.8)	340 (59.1)	
Secondary school	204 (31.5)	12 (16.4)	192 (33.4)	
University/College	45 (6.9)	2 (2.7)	43 (7.5)	
Work status, frequency				0.117 [b]
Currently working	119 (18.4)	6 (8.2)	113 (19.7)	
House person	303 (46.8)	37 (50.7)	266 (46.3)	
Retired or disabled	208 (32.0)	28 (38.4)	180 (31.3)	
Unemployed	18 (2.8)	2 (2.7)	16 (2.8)	
Residence, frequency				0.025 [b]
Rural	372 (57.4)	33 (45.2)	339 (59.0)	
Urban	276 (42.6)	40 (54.8)	236 (41.0)	
Municipality, frequency				*
Drenas	63 (9.7)	17 (23.3)	46 (8.0)	
Fushe Kosova	64 (9.9)	12 (16.4)	52 (9.0)	
Gjakova	51 (7.9)	5 (6.9)	46 (8.0)	
Gračanica	36 (5.6)	3 (4.1)	33 (5.7)	
Junik	11 (1.7)	0 (0.0)	11 (1.9)	
Lipjan	106 (16.4)	4 (5.5)	102 (17.7)	
Malisheva	51 (7.9)	0 (0.0)	51 (8.9)	
Mitrovica	65 (10.0)	13 (17.8)	52 (9.0)	
Obiliq	37 (5.7)	2 (2.7)	35 (6.1)	
Rahovec	53 (8.2)	1 (1.4)	52 (9.0)	
Skenderaj	69 (10.7)	12 (16.4)	57 (9.9)	
Vushtrri	42 (6.5)	4 (5.5)	38 (6.6)	
Ethnicity, frequency				<0.001 [b]
Albanian	589 (90.9)	63 (86.3)	526 (91.5)	
Serbian	34 (5.2)	1 (1.4)	33 (5.7)	
Roma, Ashkali, Egyptian, Other	25 (3.9)	9 (12.3)	16 (2.8)	
Main Family Medicine Center visits in the last 6 months, median (IQR)	3 (2-6)	6 (3-10)	3 (2-6)	0.007 [a]
Smoking, frequency				0.022 [b]
Never or ex-smoker	521 (80.4)	66 (90.4)	455 (79.1)	
Current smoker	127 (19.6)	7 (9.6)	120 (20.9)	
Physical activity, frequency				0.639 [b]
Sufficiently active	211 (32.6)	22 (30.1)	189 (32.9)	
Insufficiently active	437 (67.4)	51 (69.9)	386 (67.1)	
Alcohol, frequency				0.039 [b]
No alcohol in past 30 days	616 (95.1)	73 (100.0)	543 (94.4)	
Consumed alcohol in past 30 days	32 (4.9)	0 (0.0)	32 (5.6)	

(*Continued*)

Table 2. (Continued)

Sociodemographic factors	All participants (n = 648)	Moderate to very severe depressive symptoms (n = 73)	Normal to mild depressive symptoms (n = 575)	
	n (%)	n (%)	n (%)	p-value
Nutrition, frequency				0.039 [b]
Adequate nutrition	98 (15.1)	17 (23.3)	81 (14.1)	
Poor nutrition	550 (84.9)	56 (76.7)	494 (85.9)	
Sleep, frequency				<0.001 [c]
Very good	175 (27.0)	7 (9.6)	168 (29.2)	
Fairly good	236 (36.4)	19 (26.0)	217 (37.7)	
Fairly bad	173 (26.7)	25 (34.3)	148 (25.7)	
Very bad	64 (9.9)	22 (30.1)	42 (7.3)	
Obesity, frequency				0.040 [b]
BMI <30	286 (44.1)	24 (32.9)	262 (45.6)	
BMI ≥ 30	362 (55.9)	49 (67.1)	313 (54.4)	
Systolic blood pressure (mmHg), mean (Mean±SD)	135.7±17.9	137.4±20.1	135.4±17.7	0.383 [a]
Change in systolic blood pressure, mean (Mean±SD)	2.2±14.0	0.5±17.3	2.5±13.5	0.270 [a]
Diastolic blood pressure (mmHg), mean (Mean±SD)	86.4±9.9	88.8±10.8	86.1±9.8	0.029 [a]
Change in diastolic blood pressure, mean (Mean±SD)	0.4±7.8	-2.6±9.0	0.7±7.6	<0.001 [a]
Hypertension, frequency				0.048 [b]
Never diagnosed	246 (38.0)	20 (27.4)	226 (39.3)	
Diagnosed	402 (62.0)	53 (72.6)	349 (60.7)	
Antihypertensive treatment, frequency				0.107 [b]
Not taking	359 (55.4)	34 (46.6)	325 (56.5)	
Taking	289 (44.6)	39 (53.4)	250 (43.5)	
Depressive symptoms at baseline, frequency				N/A
Normal-mild (DASS <14)	575 (88.7)	0 (0.0)	575 (100.0)	
Moderate to very severe (DASS≥14)	73 (11.3)	73 (100.0)	0 (0.0)	

mmHg: millimetres of mercury, DASS: Depression Anxiety Stress Scale, BMI: body mass index, SD: standard deviation, IQR: interquartile range. Normal to mild depressive symptoms if depression subscale of 21-item Depression Anxiety Stress Scale score was <14. Moderate to very severe depressive symptoms if depression subscale of 21-item Depression Anxiety Stress Scale score was ≥14. a t-test; b Chi-square test; cKruskall-Wallis test; *Fisher's exact test not possible due to high number of categories

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2.5 Variables

2.5.1 Change in systolic and diastolic blood pressure. Because clinically significant increases in blood pressure may fall short of specified cut-off criteria for hypertension, we calculated changes in blood pressure and used the change scores as a continuous outcome variable for systolic and diastolic blood pressure.

Systolic and diastolic blood pressure (in mmHg) was measured three times, at least three minutes apart, after sitting quietly for about 10 minutes, using an M3 model Omron blood pressure monitor (Omron Healthcare, Switzerland). The research nurses placed the blood pressure cuff two centimetres above the elbow on the bare left upper arm (in the case of arteriovenous fistula, radiotherapy or removal of lymph nodes in the armpit of the left arm, the right arm was used) of the seated participant and elevated the arm on the table to the level of the fourth intercostal space. Participants provided additional written consent that they would like to be informed by the study nurse in case high blood pressure was detected throughout the study.

Changes in systolic and diastolic blood pressure were calculated by subtracting blood pressure at baseline from blood pressure at follow-up 3. Because follow-up time varied from 0.9 to 1.9 years between participants, we standardized the change in blood pressure as a unit of change over 1 year by dividing it by the follow-up time in years. A positive censored regression coefficient for moderate to very severe depressive symptoms indicates a larger increase in blood pressure over time compared to the reference group, while a negative coefficient represents a smaller increase in blood pressure over time compared to the reference group. A negative coefficient should not be interpreted as a decrease in blood pressure over time.

2.5.2 Incident hypertension diagnosis. Incident hypertension diagnosis was considered as newly self-reported physician-diagnosed hypertension or hypertension treatment at follow-up 3, which were determined from interview questions about medication and disease diagnoses. Incident hypertension diagnosis occurred when a participant had no self-reported diagnosis nor treatment for hypertension at baseline (regardless of the blood pressure measurement), and hypertension diagnosis or treatment at follow-up 3.

2.5.3 Uncontrolled hypertension. Keeping blood pressure within normal limits after the diagnosis of hypertension through lifestyle changes and medication is important to avoid disease progression. Uncontrolled hypertension was considered as systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg at follow-up 3 among people previously diagnosed with hypertension at baseline.

2.5.4 Depressive symptoms. The 21-item Depression Anxiety Stress Scale (DASS-21) was designed to measure current levels of depressive symptomology and should be used as a screening tool rather than a diagnostic tool for Major Depressive Disorder (MDD). Depressive symptoms were measured by interview using the DASS-21 [37,38] questionnaire which includes a subscale for depressive symptoms containing seven items scored on a 4-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much), and multiplied by 2. The presence of depressive symptoms was defined as moderate to very severe depressive symptoms (DASS-21 depressive symptoms score of $\geq$14). The severity of depressive symptoms is categorized as follows: DASS-21 score 0–9 (normal), 10–13 (mild), 14–20 (moderate), 21–27 (severe), and over 28 (very severe).

2.5.5 Statistical methods. *2.5.5.1 Depression and change in blood pressure*. Many study participants who were normotensive at baseline developed hypertension and were prescribed antihypertensive medication before their follow-up health assessments. Other participants who took antihypertensive medication at baseline stopped treatment by follow-up 3 for various reasons. Accounting for the effect of this treatment on the measured blood pressure is of vital importance in statistical analyses of blood pressure. Several analytical strategies have been evaluated in a simulation study [39], which recommended the use of censored normal regression. In this approach, the blood pressure change for all participants newly diagnosed or treated for hypertension at follow-up 3 was right-censored at the measured value. This is equivalent to assuming that had these participants not received the diagnosis and/or treatment, their blood pressure at the follow-up assessment would have been equal to or greater than the measured value. The blood pressure change for all participants who were taking antihypertensive treatment at baseline but stopped treatment at follow-up 3 was left-censored at the measured value. The coefficients fitted by censored regression have the same familiar interpretation as those from ordinary linear regression.

We fitted separate mixed censored regression models for change in systolic and diastolic blood pressure. We termed models that were adjusted only for the confounders "minimally adjusted", and models further controlled for the suspected mediators "fully adjusted". Effect modification by sex was assessed by introducing the appropriate interaction term. We adjusted our models for baseline blood pressure, because of evidence of severe regression to the mean.

As this adjustment may introduce bias due to the potential fluctuations of measurements [40], we report also effect estimates from otherwise identical models without baseline adjustment in the **S2 Table**.

We considered the following confounders based on prior knowledge in all models: age (in years), sex (male, female), highest level of education completed (primary school or less, secondary school, university/college or more), work (working, home-person, retired/disabled, unemployed), urban-rural classification (rural, urban), and municipality as a random effect (Gjakovë, Drenas, Graçanicë, Mitrovicë, Junik, Lipjan, Malishevë, Obiliq, Fushe Kosovë, Rahovec, Skenderaj, Vushtrri), and ethnicity (Albanian, Serbian, Roma/Ashkali/Egyptian/Other).

We considered the following factors as potential mediators of the association between depression and change in blood pressure based on previous evidence [41–44]: *smoking status* (current smoker), *physical inactivity* (<150 min of moderate-intensity physical activity per week, or <75 min of vigorous-intensity physical activity per week, or less than an equivalent combination of moderate-intensity and vigorous-intensity activity); *poor nutrition* (<5 fruits and/or vegetables per day), *alcohol consumption* (any alcohol in the last 30 days), *obesity* (BMI≥30), *heart rate* (beats per minute, and the *number of visits to an MFMC in the last 6 months)*. Each of these mediators was also assessed individually for mediating effect by introducing each variable one at a time in the minimally adjusted model. These results are provided in **S3 Table**.

2.5.5.2 Depression and incident hypertension diagnosis as well as uncontrolled hypertension. The prospective associations between baseline depression and the outcomes of incident hypertension diagnosis and uncontrolled hypertension were assessed with mixed multivariable logistic regression models. We included the same set of covariates as the fully adjusted models for change in blood pressure and additional adjustment for time of follow-up. Effect modification by sex was assessed by introducing the appropriate interaction term (see **S4 Table**).

Analyses were performed with Stata statistical software, release 16.

3 Results

3.1 Baseline depression and change in systolic and diastolic blood pressure

Table 3 shows the findings of the minimally and fully adjusted models on the prospective association between depressive symptoms (binary, severity category) and change in systolic and diastolic blood pressure over one year of follow-up. Depressive symptoms as a binary predictor were associated with attenuated diastolic blood pressure increase (β = -2.84, 95%-CI -4.64 to -1.05, p = 0.002) over a year of follow-up in our fully adjusted models, while the attenuation of systolic blood pressure increase (β = -1.98, 95%-CI -5.25 to 1.28, p = 0.233) was not statistically significant. When considering the severity of depressive symptoms as categories defined by Lovibond and Lovibond [37], we found that only moderate levels of depressive symptoms were predictive of attenuation of diastolic blood pressure increase in the minimally and fully adjusted models. No other findings were statistically significant. No effect modification by sex was observed (see **S4 Table**) and no evidence of mediation by lifestyle risk factors was found.

3.2 Baseline depression and incidence of hypertension diagnosis as well as uncontrolled hypertension

Table 4 shows the findings of the minimally and fully adjusted models of the prospective association between depressive symptoms and incident hypertension diagnosis among normotensive patients as well as uncontrolled hypertension among hypertensive patients. Although no

Table 3. Prospective association between depression and change in systolic and diastolic blood pressure per year.

	Change in systolic blood pressure						Change in diastolic blood pressure					
	Minimally [a] adjusted			Fully [b] adjusted			Minimally [a] adjusted			Fully [b] adjusted		
	Coef	95%-CI	p-value	Coef	95%-CI	p-value	Coef	95%-CI	p-value	Coef	95%-CI	p-value
Depression												
Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)			(Ref)			(Ref)		
Moderate to very severe depressive symptoms (DASS ≥14)	-2.31	(-5.48 to 0.87)	0.155	-1.98	(-5.25 to 1.28)	0.233	-2.93	(-4.68 to -1.18)	0.001	-2.84	(-4.64 to -1.05)	0.002
Depression severity (categorical)												
Normal (DASS-21 score 0-9)	(Ref)			(Ref)			(Ref)			(Ref)		
Mild (DASS-21 score 10-13)	1.08	(-2.65 to 4.80)	0.571	1.64	(-2.11 to 5.40)	0.391	1.41	(-0.64 to 3.46)	0.178	1.86	(-0.19 to 3.92)	0.075
Moderate (DASS-21 score 14-20)	-3.41	(-7.16 to 0.35)	0.075	-3.14	(-6.96 to 0.67)	0.107	-3.43	(-5.50 to -1.35)	0.001	-3.41	(-5.51 to -1.32)	0.001
Severe (DASS-21 score 21-27)	-1.15	(-8.47 to 6.18)	0.759	-0.23	(-7.56 to 7.10)	0.951	-2.67	(-6.72 to 1.38)	0.196	-2.29	(-6.32 to 1.73)	0.265
Very severe (DASS-21 score ≥ 28)	2.24	(-5.25 to 9.73)	0.557	2.91	(-4.66 to 10.49)	0.451	0.20	(-3.92 to 4.31)	0.925	0.92	(-3.21 to 5.05)	0.663

Results from multivariable censored regression models. [a] minimally adjusted: age (in years), sex (male, female), highest level of education completed (primary school or less, secondary school, university/college or more), work (working, home-person, retired/disabled, unemployed), urban-rural classification (rural, urban), ethnicity (Albanian, Serbian, Roma/Ashkali/Egyptian/Other), baseline systolic blood pressure, baseline diastolic blood pressure. [b] fully adjusted: minimally adjusted covariates and additionally, smoking status (current smoker), physical inactivity (<150 min of moderate-intensity physical activity per week, or <75 min of vigorous-intensity physical activity per week, or less than an equivalent combination of moderate-intensity and vigorous-intensity activity; poor nutrition (<5 fruits and/or vegetables per day), alcohol consumption (any alcohol in the last 30 days), obesity (BMI≥30), heart rate (beats per minutes), number of main family medicine center visits in the last 6 months. DASS-21: 21-item Depression Anxiety Stress Scale; Ref: Reference group; mmHg: millimetres of mercury

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finding met statistical significance, depressive symptoms as a binary predictor were associated with a suggestive increase in odds of hypertension diagnosis (OR = 1.68, 95%-CI 0.41, 6.98, p = 0.475) and decrease in odds of uncontrolled hypertension (OR = 0.69, 95%-CI 0.34, 1.40, p = 0.302) in the fully adjusted models.

4 Discussion

4.1 Main findings

This is the first study to the best of our knowledge to investigate the effect of mental health on blood pressure-related outcomes in Kosovo. We purposefully separately assessed the outcomes of blood pressure change, hypertension diagnosis, and uncontrolled hypertension, in contrast to studies which used a mixture of diagnosis, medication or blood pressure measurement cut-off in the outcome definition. We wanted to disentangle outcomes related to biological processes (blood pressure change) versus behavioural factors (hypertension diagnosis and control), which may help elucidate the mixed evidence on the association between depression and blood pressure.

On the one hand, we found suggestive evidence that baseline moderate to very severe depressive symptoms were associated with an attenuation of systolic and diastolic blood pressure increase over a year. Blood pressure tends to increase with age. On the other hand, we also found suggestive evidence that baseline moderate to very severe depressive symptoms were associated with an increase in odds of hypertension diagnosis among initially normotensive people and a decrease in odds of uncontrolled hypertension among initially hypertensive

Table 4. Prospective association between depression and incident hypertension diagnosis as well as uncontrolled hypertension.

	Incident hypertension diagnosis (n = 226)						Uncontrolled hypertension (n = 422)					
	Minimally [a] adjusted			Fully [b] adjusted			Minimally [a] adjusted			Fully [b] adjusted		
	OR	95%-CI	p-value	OR	95%-CI	p-value	OR	95%-CI	p-value	OR	95%-CI	p-value
Depression (binary)												
Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)			(Ref)			(Ref)		
Moderate to very severe depressive symptoms (DASS ≥14)	1.22	(0.37 to 4.01)	0.745	1.68	(0.41 to 6.98)	0.475	0.66	(0.34 to 1.28)	0.219	0.69	(0.34 to 1.41)	0.309
Depression severity (categorical)												
Normal (DASS-21 score 0–9)	(Ref)			(Ref)			(Ref)			(Ref)		
Mild (DASS-21 score 10–13)	5.17	(1.10 to 24.28)	0.037	6.87	(1.32 to 35.68)	0.022	0.74	(0.35 to 1.59)	0.439	0.97	(0.44 to 2.13)	0.940
Moderate (DASS-21 score 14–20)	1.79	(0.49 to 6.52)	0.375	2.50	(0.55 to 11.49)	0.238	0.54	(0.24 to 1.21)	0.138	0.55	(0.24 to 1.28)	0.168
Severe (DASS-21 score 21–27)	1	-	-	1	-	-	0.66	(0.15 to 2.90)	0.579	0.83	(0.17 to 4.09)	0.836
Very severe (DASS-21 score ≥ 28)	0.81	(0.03 to 21.72)	0.900	1.68	(0.05 to 53.36)	0.768	1.14	(0.23 to 5.81)	0.871	1.47	(0.27 to 8.09)	0.658

Results from multivariable logistic regression models. [a] minimally adjusted: age (in years), sex (male, female), highest level of education completed (primary school or less, secondary school, university/college or more), work (working, home-person, retired/disabled, unemployed), urban-rural classification (rural, urban), ethnicity (Albanian, Serbian, Roma/Ashkali/Egyptian/Other), baseline systolic blood pressure, baseline diastolic blood pressure. [b] fully adjusted: minimally adjusted covariates and additionally, smoking status (current smoker), physical inactivity (<150 min of moderate-intensity physical activity per week, or <75 min of vigorous-intensity physical activity per week, or less than an equivalent combination of moderate-intensity and vigorous-intensity activity; poor nutrition (<5 fruits and/or vegetables per day), alcohol consumption (any alcohol in the last 30 days), obesity (BMI≥30), heart rate (beats per minutes), baseline number of main family medicine center visits in the last 6 months, follow-up time (years). DASS-21: 21-item Depression Anxiety Stress Scale, Ref: reference group; mmHg: millimetres of mercury

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people. Only the findings with attenuated diastolic blood pressure met statistical significance. Overall, the direction of the results from this replication study agrees with those from a Swiss cohort with longer-term follow-up [31]. Although the findings taken together appear contradicting, they expose two probable differing effects of depression: depression attenuates blood pressure, which is in line with the monoamine theory of depression, while depression also likely improves the diagnosis and treatment of hypertension related to increased healthcare utilization among depressed people.

4.2 Depression and change in systolic and diastolic blood pressure

The finding that depression is longitudinally associated with attenuated blood pressure increase is supported by one study that also included both normotensive and hypertensive people over an 11-year follow-up [27] and another study with only normotensive people [31]. The attenuation of the increase in blood pressure in people with depressive symptoms could be due to several factors including biological, social, and healthcare factors. First, our findings are consistent with the monoamine theory of depression [45], which suggests that the pathogenesis of depression is a depletion of serotonin, norepinephrine and dopamine, which are important for raising blood pressure. This means that in the instance of depletion of monoamines, both depressive symptoms and lower blood pressure can be observed. However, there exist many other theories of the pathogenesis of depression which would argue more for an effect of an increase in blood pressure. One main theory includes autonomic nervous system dysfunction, resulting in decreased heart rate variability and increased heart rate [46] which in turn lead to an increase in blood pressure. There is a risk that we controlled for this effect by

including heart rate as a mediator, however there were no notable differences in effect when it was accounted for individually as seen in **S3 Table.** Several other theories are discussed elsewhere [41,47–49]. It should also be noted that neurobiological evidence on its effect on blood pressure is mostly theoretical and has not sufficiently been observed in human studies. Secondly, given the limited research in the Kosovo context, we may have inadvertently omitted important confounding sociodemographic factors for this population that may bias the association between depressive symptoms and blood pressure change. Finally, given that care standards are still being developed in the country, it is highly probable that patients are being treated inconsistently. The use of censored regression to account for treatment effects may not have sufficiently accounted for this. The AQH project is supporting the implementation of the World Health Organization WHO package of essential noncommunicable (PEN) disease interventions for primary health care, however the adoption of the PEN protocols is only in its early phases. The evaluation of the effect modification by different care standards was thus beyond the scope of this study.

A further investigation into the severity response of depression on blood pressure change is warranted, given our observation that moderate depressive symptoms saw the largest effect of diastolic blood pressure attenuation with a decreasing attenuation in severe depressive symptoms and even a positive change in blood pressure in very severe depressive symptoms, although only the level of moderate depressive symptoms on diastolic blood pressure was statistically significant.

We accounted for lifestyle risk factors such as smoking, alcohol consumption, poor diet, physical inactivity and obesity in our analyses because they are associated with depression [41,42] and are risk factors for hypertension and cardiovascular disease. There were only minimal discrepancies between our minimally and fully adjusted models, suggesting that they neither confounded nor mediated the observed associations in major ways (see **S2 Table**). This is only true under the assumption that these variables were captured adequately and with little reporting bias. We previously observed gender differences between lifestyle factors of this population [3], but the sample size limitations did not allow for taking these interrelations between covariates into consideration. Our finding of little change in effect size from non-adjusted and adjusted lifestyle models is consistent with a review [41], suggesting that the increased risk for CVD mortality is not simply due to differences in lifestyle risk factors.

4.3 Depression and incident of hypertension diagnosis

We found suggestive evidence that initially normotensive people with depressive symptoms were more likely to be diagnosed with hypertension by a general practitioner in comparison to non-depressed, although our findings did not meet statistical significance. While the direction of these estimates is entirely consistent with the findings of other studies with a similar definition of hypertension diagnosis as in our study [23–26,31], they are also consistent with the null hypothesis of no association. We ascribe this large uncertainty to the small sample sizes and the short follow-up in this current study. As previously mentioned, the outcome of hypertension diagnosis without the consideration of blood pressure measurement (and therefore underdiagnosis) has implications for the interpretations of the findings. It should be interpreted to be a proxy for the act of receiving a diagnosis of hypertension, which is influenced by several factors related to behaviours. One explanation for our findings is related to healthcare-seeking behaviour. A Swiss study [31] hypothesized that the increased risk of hypertension diagnosed among people with depression was potentially related to their higher healthcare-seeking behaviour, but the study could not verify this factor. Higher health service utilization among depressed people was observed in other studies [30,44] as well as in our sample (see

Table 2). As healthcare utilization was included among covariates of our fully-adjusted model, we may have accounted for its mediating effect and this may contribute to non-statistically significant findings. Another explanation for our findings may be related to a higher prevalence of disease comorbidity [50] or lifestyle risk factors related to other chronic diseases [41,42] among people living with depression, leading to increased hypertension screening. Although lifestyle risk factors were accounted for in our study, comorbidity was not. Nevertheless, both minimally and fully adjusted models did not meet statistical significance.

4.4 Depression and uncontrolled hypertension

We also found suggestive evidence that among initially hypertensive subjects, depressive symptoms were associated with a decrease in odds for uncontrolled hypertension, although again these findings did not meet statistical significance. In other words, people with depressive symptoms might be more likely to have their blood pressure under control. This is in contrast to several other studies [51–56]. However, a recent cross-sectional study in the Netherlands (HELIUS study, n = 21 363) found that hypertension control among depressed people differed between ethnic groups [57]. This supports the importance to understand the association in the Kosovo context, especially given that we observed a much higher prevalence of depression among the Roma, Ashkali, and Egyptian ethnic minority group and poorer hypertension control was observed in ethnic minority groups as seen in the United States [58,59] who might have lower access to healthcare. Lower odds of uncontrolled hypertension among the depressed is also in keeping with the hypothesis of higher health-seeking behaviour among people with depression, i.e. as depressed people use more healthcare, they are exposed to treatment that can help reduce blood pressure. However, we accounted for it in our fully adjusted models, possibly explaining findings of no statistically significant findings. Nevertheless, we consider the small sample size and short follow-up time to play an important role (n = 422).

4.5 Implications for clinicians and policymakers

Clinicians should interpret our findings carefully. At first glance, one might be inclined to see our findings as promoting depression as a protective factor against hypertension. However, blood pressure increased over time in both those with and without depressive symptomology. Therefore people with depression can still develop hypertension, especially if their baseline blood pressure is borderline hypertensive.

Currently there is no practice in Kosovo PHC to screen for hypertension among depressed people or vice versa. Given the strong stigma of mental illness still present in the country [60] as in many other countries, caution should be taken in regards to widespread screening of depression because it may deter patients from seeking PHC services. One must also consider the ethical implications of screening for depression. A diagnosis should be followed by adequate treatment. Mental health services, especially at the community level in Kosovo are still in development and need to be strengthened [34,36], which require a considerable amount of human and financial resources. A more pressing recommendation would be for policymakers to invest in contextually-acceptable already-validated inexpensive interventions promoting mental health.

4.6 Strengths and limitations

This is the first study to the best of our knowledge to assess the effect of depression on blood pressure-related outcomes in Kosovo, a context where both depression and CVD are highly prevalent. It contributes valuable findings on chronic disease epidemiology.

The current study is one of the first publications on KOSCO findings, which was implemented in 2019. Therefore the mean follow-up time for the analyses conducted for this study was 1.3 years (min 0.9 years–max 1.9 years), and may not be sufficient follow-up time to assess change in blood pressure at the population level. Follow-up of the KOSCO participants is anticipated for 5 years which would allow greater follow-up time to observe changes in blood pressure.

As our study is a PHC patient-based cohort, the study is limited in its generalizability to the general population. Further, selection bias must be considered when interpreting our findings, given that most patients approached to be included in the study declined (seen in Fig 1).

The relatively small sample size is a limitation of our study. The loss to follow-up is summarized in the methods indicating retention of 67% from baseline to follow-up 3. Nevertheless, an assessment of baseline characteristics between those lost to follow-up and those included in the study indicates no meaningful differences.

Loss to follow-up was larger after the onset of the COVID-19 pandemic which is well known to impact depression symptoms [61]. Differential loss-to-follow-up of hypertensive participants with elevated symptoms of depression may have introduced bias. But no difference in follow-up participation according to either hypertension-related factors or symptoms of depression was observed.

4.7 Conclusion

In Kosovo, depression is associated with an attenuation of diastolic blood pressure increase and we have suggestive evidence of better detection and control of hypertension. Given that the mechanisms between depression, hypertension and CVD are yet to be elucidated, this study contributes valuable evidence towards cardiovascular epidemiology. Larger studies on the prospective association between depression and blood pressure-related outcomes are warranted that attempt to address the full complexity of potentially interacting pathways.

Supporting information

S1 Table. Baseline characteristics disaggregated by participant and non-participant status. mmHg: Millimetres of mercury, DASS: Depression Anxiety Stress Scale, BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range. Normal to mild depressive symptoms if depression subscale of 21-item Depression Anxiety Stress Scale score was <14. Moderate to very severe depressive symptoms if depression subscale of 21-item Depression Anxiety Stress Scale score was ≥14.
(DOCX)

S2 Table. Prospective association between depression and change in systolic and diastolic blood pressure per year, without adjustment for baseline systolic and diastolic blood pressure. Results from multivariable censored regression models. [a] Minimally adjusted: Age (in years), sex (male, female), highest level of education completed (primary school or less, secondary school, university/college or more), work (working, home-person, retired/disabled, unemployed), urban-rural classification (rural, urban), ethnicity (Albanian, Serbian, Roma/Ashkali/Egyptian/Other). [b] Fully adjusted: Minimally adjusted covariates and additionally, smoking status (current smoker), physical inactivity (<150 min of moderate-intensity physical activity per week, or <75 min of vigorous-intensity physical activity per week, or less than an equivalent combination of moderate-intensity. DASS-21: 21-item Depression Anxiety Stress Scale, Ref: Reference group.
(DOCX)

S3 Table. Prospective association between depression and change in systolic and diastolic blood pressure, minimally adjusted model and introduction of potential mediators individually.
(DOCX)

S4 Table. P-values of the interaction term between depression and sex in main fully adjusted models.
(DOCX)

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CHAPTER 7 – DISCUSSION

7.1 Summary of main findings

The overarching aim of this dissertation was to elucidate the prospective association between depression and elevated blood pressure as a potential causal pathway between the well-established association between depression and CVD.

In Chapter 4, the dissertation provides evidence on the burden of CVD risk factors in Kosovo. Poor nutrition (85%), physical inactivity (70%), obesity (53%), and smoking (21%) were common risk factors among PHC users, contributing to the CVD burden in the country. Although mental health in Kosovo appears to have improved since reports from the early 2000s, moderate to very severe depressive symptoms were still highly prevalent (12.1%) in 2019.

The dissertation includes to the best of our knowledge the first reports of the predictive association between depression and two blood pressure-related outcomes in the same sample: the continuous outcome of change in blood pressure and the binary outcome of incident hypertension diagnosis. These analyses were conducted both in Kosovo and in Switzerland for reasons of replication. The dissertation contributes to cardiovascular epidemiology by further elucidating the prospective association between depression and CVD through different pathways involving blood pressure. In Chapter 5 (SAPALDIA study), we found that depression was associated with smaller age-related increases in systolic blood pressure in normotensive adults in Switzerland (β=-2.08 mmHg/10 years, 95% CI -4.09 to -0.07). In the same sample, there was an increase in odds of hypertension diagnosis among the depressed (OR 1.86, 95% CI 1.33 to 2.60). We had similar findings among PHC users in Kosovo in Chapter 6 (KOSCO study): we found that depressive symptoms were associated with smaller age-related increases in diastolic blood pressure among PHC users in Kosovo (β=-2.84 mmHg/year, 95% CI -4.64 to -1.05). There was also an increase in odds of being diagnosed with hypertension among those with depressive symptoms (OR = 1.68, 95%-CI 0.41, 6.98), but the latter did not meet statistical significance potentially related to the smaller sample size and shorter follow-up time compared to SAPALDIA. Taken together, depression was associated with both attenuated age-related blood pressure increase as well as increased odds of hypertension diagnosis. These findings can be explained first by shared biology between depression and lower blood pressure, while higher healthcare utilization among people with depression may explain the observed increase in the risk of having underlying hypertension diagnosed.

In summary, the findings of this dissertation do not support the hypothesis that hypertension is a causal mediator in the association between depression and CVD. The findings of this dissertation help explain the mixed evidence on the prospective association between depression and hypertension. The dissertation also provides evidence that depression and hypertension remain important disease burdens in Kosovo which need improved prevention. This thesis points to the important need for further research into other possible pathways between depression and CVD given their high contribution to disease burden and disability.

7.2 Indicators of primary, secondary and tertiary prevention in Kosovo

7.2.1 The burden of CVD risk factors in Kosovo – primary prevention indicators

The study presented in Chapter 4 provides evidence of CVD risk factors among PHC users in Kosovo. Given the population of this study was PHC users aged 40 years and older, we expected a comparatively unhealthy sample compared to a population-based study. Still, we found that several CVD risk factors were extremely common in Kosovo. Over half (53%) of PHC users were obese, 85% did not consume at least 5 servings of fruits or vegetables each day, 21% smoked and 70% were insufficiently active. This indicates that primary prevention through lifestyle change is currently insufficient among PHC users in Kosovo, and thus a failed opportunity to prevent CVD. Risk factor modification in observational studies was associated with 44% of the decline of CVD in Finland (1) and the USA (2). Therefore risk factor modification can be an effective intervention and should stay in the focus on PHC in Kosovo.

Current efforts for risk factor modification in Kosovo include motivational counselling sessions, which are a non-experimental community intervention implemented by the AQH project, where all patients being treated at an MFMC, FMC or FMA aged 40 or older with diabetes, hypertension or at risk for developing diabetes and/or hypertension are eligible to be referred by a doctor or nurse to the nearest Health Resource Center. There, the nurse provides one-on-one motivational counselling sessions on lifestyle changes based on the patient's needs. The dissertation provides in Chapter 4 evidence that can support tailoring the motivational counselling for improved risk factor modification based on our findings on risk profiles of the PHC population. For example, there existed important gender differences for smoking, alcohol consumption and obesity: women were more affected by obesity, while men were more affected by smoking and alcohol consumption. Obesity and multiple unhealthy lifestyles were common among participants of low socioeconomic status, while higher socioeconomic status privileged smoking.

Although depression is classically associated with CVD risk factors such as physical inactivity, smoking and poor diet (3), people with depressive symptoms in Kosovo were more likely to have some but not all of the CVD risk factors compared to those without depressive symptoms as seen in **Table 2 of Chapter 6 (pages 77-78)**. Specifically, people with depressive symptoms were less likely to be current smokers, more likely to eat at least 5 servings of fruits and vegetables per day, and did not consume alcohol. However, they were more often obese and had poorer sleep quality. These differences were likely linked to sociodemographic factors linked to depression because only physical inactivity was cross-sectionally associated with increasing depressive symptoms after accounting for confounders (**Figure 2 of Chapter 4, page 55**) and there were no meaningful differences between the minimally (confounders) and fully adjusted (lifestyle) models in **Table 3 of Chapter 6 (page 81).**

7.2.2 The burden of undetected hypertension in Kosovo – secondary prevention indicator

Chapter 4 reports prevalences of undetected hypertension for the first time in Kosovo to the best of our knowledge. Hypertension detection is the first step towards preventing CVD initiation and/or progression. If left undetected and subsequently untreated, hypertension can lead to deleterious progression towards CVD. We found that among PHC users aged 40 years and over, nearly 1 in 5 people (18.6%) who were not previously diagnosed with hypertension had a blood pressure measurement over 140/90mmHg, indicating undetected cases of hypertension. Our findings point to the diagnostic gap (health system failure to screen for hypertension) free from the influence of patient health-seeking behaviour, which is present in population-based studies.

Since 2019, the AQH project supports PHC with the implementation of the WHO Package of Essential Non-Communicable Disease (PEN) Protocols (4), described in Chapter 1, section 1.6.4. Given that hypertension screening in risk groups by PHC providers was part of an AQH PHC strengthening intervention in study municipalities, we expected a lower prevalence of undetected hypertension in our PHC user-based study compared to population-based studies. Indeed, the prevalence of undetected hypertension in Kosovo (18.6%, **Table 3 in Chapter 4, page 54)** was about half that found in population-based studies in Switzerland (36%) (5), and Finland (34.5%) (6). However, undetected hypertension in Kosovo was also about half of what was reported in other similar patient-based studies conducted in high-income countries like the United States of American (37.1%) (7) and San Marino (37.7%) (8). This was surprising given that more exhaustive hypertension detection is expected in PHC of higher-income countries. A systematic review indicated that the few available studies on undetected hypertension were too

heterogeneous to conduct a meta-analysis (9). There was no evidence of the cross-sectional association between depression and undetected hypertension (Chapter 4). Despite all participants in the KOSCO study fitting the AQH intervention criteria for high blood pressure screening, still, nearly one in five people left the PHC center unaware that they had high blood pressure. Our findings highlight the success of hypertension screening of the AQH intervention as well as room for refining and scaling up the PEN protocol.

Whitecoat hypertension (WCH), which is elevated clinic blood pressure but normal ambulatory (24-hour) blood pressure, should be discussed in the context of hypertension detection. The methodology in the KOSCO and SAPALDIA studies does not allow to differentiate between true (sustained) hypertension and WCH due to measurements conducted exclusively in the health facility or study centers. Therefore potential WCH was classified as true hypertension. There is an ongoing debate as to whether WCH should be considered as true hypertension. There is growing evidence, however, that WCH is an indicator for future sustained hypertension. For this reason, a review suggests that WCH should be considered at the least as a pre-hypertensive state (10), and should be treated given that people with untreated WCH were at higher risk of CVD events and mortality compared to normotensive people (11). This is further supported by the finding that no differences were observed when normotensives were compared to treated white coat hypertension in the same study. Further, the KOSCO and SAPALDIA studies also could not distinguish between normotensive and masked hypertension (normal clinic blood pressure yet elevated ambulatory blood pressure). For this reason, it will be important to assess ambulatory blood pressure in future studies.

7.2.3 The burden of uncontrolled hypertension in Kosovo – teritary prevention indicator

Chapter 4 additionally reports the prevalence of uncontrolled hypertension for the first time in Kosovo to the best of our knowledge. Over one in four people (28.3%) who were previously diagnosed with hypertension had a blood pressure measurement over 140/90mmHg (**Table 3 in Chapter 4, page 54**). Men had more difficulty controlling their blood pressure, which was also observed in a population-based study in Switzerland (5). In that study, 59% of people with doctor-diagnosed hypertension had blood pressure over 140/90mmHg (5). Although PHC patients in Kosovo were doing relatively well in terms of uncontrolled hypertension (28.3%), uncontrolled diabetes (79%) was much more problematic in this population and maybe a more important contributor to CVD risk than hypertension. Depression was not associated cross-sectionally with uncontrolled hypertension in Chapter 4.

Several possible factors may contribute to uncontrolled hypertension in Kosovo. Firstly, the cost of health services and drugs is not affordable for all patients. Although Kosovo is striving for universal health coverage, about 80% of households in Kosovo still incurred out-of-pocket (OOP) health payments in one study (12). Except for vulnerable population groups that are exempt by law, patients pay user fees for health services provided at primary, secondary, and tertiary levels of care. Essential drugs are provided free of charge (13), and patients must pay OOP for drugs that are not included on the essential drugs list. Only 1% (12 of 1011) of PHC users in the KOSCO study had private health insurance (preliminary KOSCO results not reported in dissertation articles, baseline 2019). Among KOSCO participants who were prescribed medicines, about 60% at baseline in 2019 (414 of 699) and follow-up 2 in 2020 (120 of 196) said that they were worried that they could not always afford the medication (preliminary KOSCO results not reported in dissertation articles).

Despite essential drugs being free of charge, the list is limited. This is evident by the fact that the share of out-of-pocket spending for drugs in 2011 was 85 percent of total OOP spending (14). In addition, the public procurement of medicines in Kosovo is still flawed with bid-rigging (15) which can lead to essential medicines being too expensive for public procurement and thus unavailable to patients who might then be forced to search for these medicines in the private sector. Alarmingly, about 18% of KOSCO respondents taking medication at baseline (129 of 699) and follow-up 2 (35 of 196) said that the medication that they need is generally not available in their pharmacy. This proportion increased to 28% at follow-up 3, after the first wave of the pandemic. Thus, the poor control of NCDs in Kosovo may in large part be due to system-wide factors beyond an individual's control.

In summary, our findings indicate that PHC centers in Kosovo are performing generally well in secondary prevention through hypertension screening and detection. However, CVD prevention through behaviour change in primary prevention needs strengthening. Tertiary prevention is also performing relatively well in Kosovo, but system-wide barriers to treatment adherence should also be evaluated for improved prevention.

7.3 The burden of depression in Kosovo

Moderate to very severe depressive symptoms as per DASS-21 classification among PHC users in Kosovo were present in 12.1% of participants at baseline (**Table 1 in Chapter 4, page 53**). This prevalence is well above the global prevalence of depressive disorders among adults 40 years and older at 5.6% (16). It was also well above the mean of depressive symptoms in the

general population of Europe (6.4%) using the PHQ-8 score of 10 or higher (17), and higher than reported in other studies of primary healthcare patients (5-10%) (18,19). Depression is generally more common among PHC users though because of its association with chronic illness. It should be noted that depression is highly stigmatized in Kosovo, as in many other LMICs. Despite our efforts in minimizing potential feelings of stigmatization of depression in our questionnaire by avoiding direct questions about mental illness and prefacing the DASS-21 questionnaire with our interest in overall well-being, depressive symptoms may be underestimated in the KOSCO study due to response bias in light of the stigmatization of mental illness in Kosovo. In one study (120), 15.8% of those who believed that they needed professional help, actually reported receiving psychological/psychiatric help and stigma was an important barrier. Our findings suggest nonetheless that mental health in Kosovo has drastically improved since the war in 1999. The prevalence of depressive symptoms prevalence was reported at 41.7% in a population-based study 10 years after the end of the war (20) measured by the HSCL-25, much higher than we found 20 years after the war in 2019. No large representative study to our knowledge has reported depressive symptoms in the last decade. Vigilance over depression should be maintained in Kosovo though because those with a history of depression are at higher risk of subsequent episodes of depression (21,22). One online survey of 155 respondents conducted in 2020 assessing depression in Kosovo during the pandemic found that 35.5% had moderate to severe depressive symptoms as per PHQ-9 criteria (23).

There are several potential causes of poor mental health in Kosovo. Kosovo is the poorest country on the European continent, and thus financial worries are common in Kosovo, which can cause a great deal of stress. Over 1 in 5 people (22%) in the second follow-up of the KOSCO study (n=745) rated their financial situation as poor or very poor, and about half of respondents (47%) felt that their financial situation was getting worse (preliminary findings of the KOSCO study not reported in dissertation articles). It would be important to assess how depressive symptoms evolved post-pandemic given that other studies suggest that the hardships of the pandemic lead to a worsening effect on mental health (24,25). The frequent follow-ups pre- and peri- and post-pandemic will allow us to assess changes in depressive symptoms over time.

In summary, depressive symptoms in Kosovo seem to have improved over the last two decades, yet are still highly prevalent. Nonetheless, there remain several factors that contribute to poor mental health in Kosovo including stigmatization and poverty.

7.4 Prospective association between depression and change in blood pressure

7.4.1 The main effect between depression and change in blood pressure

We found consistent findings of the prospective association between depression/depressive symptoms and change in blood pressure in Swiss and Kosovar populations. Depression was associated with a smaller age-related increase in **systolic** blood pressure (β=-2.08 mmHg/10 years, 95% CI -4.09 to -0.07) and, with less confidence, diastolic blood pressure (β=-0.88 mmHg/10 years, 95% CI -2.15 to 0.39) in the SAPALDIA study restricted to initially normotensive adults in the general population of Switzerland (**Table 2 in Chapter 5, page 66**). Similarly, moderate to very severe depressive symptoms were associated with smaller age-related increases in **diastolic** blood pressure (β=-2.84 mmHg/year, 95% CI -4.64 to -1.05) and with less confidence, systolic blood pressure (β=-1.98 mmHg/year, 95% CI -5.25 to 1.28) in normotensive and hypertensive PHC users in Kosovo (**Table 3 in Chapter 6, page 81**).

Few longitudinal studies to date have assessed the prospective association between depression or depressive symptoms and change in blood pressure. However, a handful of studies present findings that are consistent with our own. Two studies found that depressive symptoms as a binary variable are associated with lower age-related increases in systolic and diastolic blood pressure, but the findings were not statistically significant: A population-based Norwegian study (age 40 ±10.6, n=17,410) found that binary exposure (HADS-D ≥8, 3.5% prevalence) was associated with an attenuation of age-related increase in systolic (β=-0.74, p=0.078) and diastolic (β=-0.42, p=0.085) blood pressure (26), and a German study restricted to hypertensive people (n=541, 12 years of follow-up) found that a history of MDD trended with an attenuation of systolic (β =-1.3, p=0.52) and diastolic (β =-1.4, p=0.65) blood pressure (27). However, these studies found statistically significant findings when investigating further the severity of depressive symptoms on blood pressure change. Hildrum and colleagues (2011), found that an increase in depression score (per standard deviation increase) was predictive of attenuated systolic (β=-0.46, p<0.001) and diastolic (β=-0.20, p=0.006) blood pressure increase after 11 years of follow-up. Similarly, Speerforck and colleagues (2018) found that depressive symptoms severity was an important correlate of long-term changes in blood pressure: moderate severity of depressive symptoms (but not mild or severe) had an attenuating effect on systolic (β=-7.5, 95%-CI -13.2, -1.9) and diastolic (β=-4.5, 95%-CI -7.8, -1.3) blood pressure after 12 years of follow-up. In contrast, another study (n=541) restricted to normotensive women found that increasing depressive symptoms over time were associated with small increases in systolic

blood pressure (β=0.03, p<0.003) with 9.3 years of follow-up (28). This study did not assess the association between baseline depression (binary) and change in blood pressure. Due to the operationalization of depression using diagnosis in combination with depressive symptoms using SF36MH in the SAPALDIA study (Chapter 5), we could not assess depression severity as a continuous predictor variable. We did however conduct a secondary analysis by removing the SF36MH (depressive symptoms) in the depression definition, thereby only including previously diagnosed depression which could be considered equivalent to longer-standing or more severe depressive symptoms. In this case, a history of diagnosed depression was associated with a greater attenuation in age-related systolic (β=-2.65 mmHg/10 years, 95% CI -4.95 to -0.35) and diastolic (β=-1.54 mmHg/10 years, 95% CI -2.85 to -0.21) blood pressure increase compared to when SF36MH was included in the predictor definition. In the KOSCO study (Chapter 6), we did not include findings of the association between depressive symptoms severity and change in blood pressure in the article, but preliminary findings indicate that depressive symptoms per point increase in DASS-21 depression score were negatively associated with change in systolic (β=-0.06 mmHg/year, 95% CI -0.24 to 0.12) and diastolic (β=-0.10 mmHg/year, 95% CI -0.20 to -0.00) and blood pressure. As per case-level depression analysis, only the association with diastolic blood pressure was statistically significant. Taken together, the existing evidence of the association between case-level depressive symptoms and change in blood pressure, including that in this dissertation, trends towards attenuated age-related blood pressure increase. There is also some evidence that there may be a dose-response relationship with depressive symptom severity, but the evidence is still limited and mixed. The existing evidence on the prospective association between depression and change in blood pressure is still too few and inconsistent to confidently state in which direction depression affects blood pressure. Future studies should include depression symptoms severity and duration as a predictor of blood pressure change for stronger arguments for causality.

Two main hypotheses need to be discussed in the context of our finding that depression attenuates age-related blood pressure increase. Firstly, it has been hypothesized before that lower blood pressure among depressed people may be due to the higher use of antihypertensive drugs (29). Our analyses provide no support for this hypothesis since the effect was observed even though we removed baseline antihypertensive drug users from the sample in Chapter 5 and controlled for initiation mid-wave with censored regression in Chapters 5 and 6. However, as our medication data is self-reported, the possibility of differential misclassification remains. The second hypothesis argues for shared biology between depression and low blood pressure, and therefore not a causal pathway between the two. The monoamine hypothesis of depression

was first described in the 1960s (30,31). The hypothesis proposes that depression has underlying biological pathogenesis that involves a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system. This theory has been further strengthened with evidence that people with depression have increased levels of monoamine oxidase A (MAO-A) enzyme which metabolizes monoamines (32). On this basis, various classes of antidepressant agents have been developed that act to increase levels of monoamines in the synaptic cleft by inhibiting their degradation or blocking their reuptake. The success of these antidepressants further confirms this theory. Monoamines play a central role in raising blood (33) and therefore low blood pressure is observed when there is a depletion of these monoamines. Thus when there is a depletion of monoamines, both depressive symptoms and low blood pressure could be observed.

Looking at the reverse association, there is also evidence that low blood pressure among initially non-depressed individuals had a higher incidence of depression (34,35) or had no association (36). Further, the findings of a meta-analysis did not support the prospective association between hypertension and subsequent depression (37). The findings of these studies support the hypothesis that depression has shared biology or at least a simultaneous relationship with low blood pressure. One study found however that despite lower blood pressure at baseline among people who had incident depression, they had more significant increases in blood pressure at follow-up (38).

It should be noted that no theory of depression pathophysiology is yet universally accepted. Several authors summarize and discuss the strengths of the various theories (39,40,41), yet the etiology and pathophysiology of depression are still not fully elucidated. One author argues against a "unified hypothesis of depression" and suggests that depression is a clinically and etiologically heterogeneous disorder (39). Among them, theories such as autonomic dysregulation and HPA-axis dysregulation have been used to explain the link between depression and hypertension or CVD (42). More epidemiological studies are needed which assess the prospective association between depressive symptoms and blood pressure as a continuous outcome to conduct a meta-analysis and further elucidate the direction of the association and direct potential confirmatory studies in the laboratory.

7.4.2 Addressing the effect of antihypertension treatment on change in blood pressure

Many study participants who were normotensive at baseline developed hypertension and were prescribed antihypertensive medication before their follow-up health assessments. Other

participants who took antihypertensive medication at baseline stopped treatment by follow-up for various reasons. Accounting for this treatment is of vital importance in statistical analyses of blood pressure. Previous work has either included antihypertensive treatment as a covariate (27) or restricted a sub-analysis to those without treatment (26). Chapters 5 and 6 used censored regression, a novel approach, to address this issue in the association between depression/depressive symptoms and change in blood pressure.

This regression method was chosen because several analytical strategies were evaluated in a simulation study (43), which recommended the use of censored regression. Our own ad-hoc simulations (not reported) corroborated this assessment. In this approach, the blood pressure change for all participants newly diagnosed or treated for hypertension at follow-up were right-censored at the measured value. This is equivalent to assuming that had these participants not received the diagnosis, their blood pressure at the follow-up assessment would have been equal or greater than the value that was actually measured. The blood pressure change for all participants who were taking antihypertensive treatment at baseline but stopped treatment at follow-up was left-censored at the measured value. The coefficients fitted by censored regression have the same familiar interpretation as those from ordinary linear regression.

Addressing the effect of antihypertension treatment in blood pressure analysis in the context of depression in Kosovo is complicated by several other factors. First, depression has been associated with lower adherence to antihypertension treatment (44,45,46), therefore the impact of antihypertension treatment use on its effect on blood pressure may differ between people with and without depressive symptoms. Further, as previously discussed in this chapter, medication is not always affordable nor available to patients. Therefore although participants may report antihypertension medication use, its use may likely be interrupted or inconsistent for these reasons. People with limited funds might feel that spending money on a disease where no symptoms are felt is less important than other priorities and thus may stop taking medication as soon as they feel better. Medication adherence would therefore be an important dimension of antihypertension medication use to account for in future studies on the association between depression and blood pressure change.

7.4.3 Effect modification by sex

There are well-established differences in depression between men and women. Depression is nearly twice as common in women as in men (47,48). Men and women also experience depression differently (48) and are triggered by different adverse life events (49). Therefore sex

was assessed as a potential effect modifier of the association between depression and change in blood pressure. We did not find that sex was an effect modifier of this association in both the general and normotensive Swiss population (Chapter 5) or among PHC users in Kosovo (Chapter 6). Our findings are consistent with the population-based Norwegian study (26) whom also did not find an interaction. One population-based study (n=2087) with 7.8 years of follow-up found that depressive symptoms score was associated with higher average systolic blood pressure in women (β=2.24, p=0.006) but not in men (50), however the outcome was not a measure of change in blood pressure. Although depression affects men and women differently, we did not find evidence that sex was an effect modifier in the association between depressive symptoms and change in blood pressure after accounting for confounders and potential mediators in Chapters 5 and 6.

7.4.4 Effect modification by antidepressant medication

In addition to assessing depression as a binary exposure, depression was stratified by antidepressant use in the SAPALDIA study (Chapter 5). When compared to people without depression, we observed trends that participants reporting depression with a history of antidepressant treatment had a greater attenuation in systolic and diastolic blood pressure change than did participants reporting depression without a history of antidepressant treatment. Yet, the influence of antidepressant use was not statistically significant, possibly as a result of the small sample size. The trend was at first unexpected because antidepressants increase monoamines in the brain to improve depressive symptoms, and monoamines increase blood pressure, aligned with a cross-sectional study which found that tricyclic antidepressants had higher mean systolic and diastolic blood pressures (29).

We further conducted an analysis disaggregating depression by antidepressant class and found suggestive evidence that attenuation of age-related blood pressure increase may be strongest for N06AA class of antidepressants (non-selective monoamine reuptake inhibitors), however, the findings were also not statistically significant. A recent review summarized the literature on the effect of each class of antidepressants on blood pressure (51). Some classes have stronger effects on blood pressure than others. Selective Serotonin Reuptake Inhibitors (SSRIs or ATC code N06AB) were considered the safest class of antidepressants in terms of risk of increasing blood pressure given their limited effects on the autonomic nervous system. Tricyclic antidepressants and dopamine (TCAs or ATC code N06AA) have been associated with both increases in blood pressure and orthostatic hypotension. Serotonin-norepinephrine reuptake

inhibitors (SNRI or ATC code N06AX) have the greatest risk of hypertension, possibly related to greater effects on the sympathetic nervous system. The SAPALDIA study likely had insufficient power to assess differences between classes with statistical significance.

There are two potentially opposite effects of antidepressants to be considered to explain the trends between antidepressant users and non-users. The first is the short-term action, whereby the antidepressant increases monoamines in the brain and therefore neurotransmitters that are responsible for signalling vasoconstriction and increased blood pressure. The second is in the long-term action consistent with our findings. Antidepressant therapy aims to alleviate depressive symptoms, thereby potentially removing the effect of depression on blood pressure attenuation. A history of antidepressant use may however be a proxy for a longer exposure and/or more severe depression, given that there are clearer benefits of antidepressant treatment for more severe and longstanding depression (52). Given that the N06AB antidepressant class is currently the recommended first-line antidepressant treatment, the apparent strongest effect in N06AA users observed in our study might be an indication of longer-standing and/or treatment-resistant depression. However, the findings related to antidepressant use should be interpreted cautiously given that they are not statistically significant.

7.4.5 Effect Mediation by lifestyle factors

We saw no meaningful difference in any effect estimate between the corresponding minimally adjusted (confounders) and fully adjusted (lifestyle factors) models (**Table 2 in Chapter 5, page 66** and **Table 3 in Chapter 6, page 81**). This might indicate weak or no mediation by the factors that we considered. Depression however is a complex disease that has different clinical presentations, for example, increase versus decrease in appetite and sleep, masking the mediating effect of such factors in single depression category analyses. For this reason, some studies differentiate subtypes of depression (53,54), which was not included in the articles of this dissertation but included in a later section (section 7.7.1). The biggest limitation of our approach to mediation was that depression and the hypothesized mediators were measured at the same time. Future studies seeking to elucidate the mechanisms linking depression and blood pressure should ideally be based on longitudinal designs with more frequent follow-ups. This is possible at a later stage of the KOSCO study, as follow-ups are conducted every 6 months and planned to have a total of 5 years of follow-up.

In summary, observations in Chapters 5 and 6 suggest that blood pressure is not a relevant mediator in the causal effect of depression on CVD as depression was associated with an

attenuation of age-related blood pressure increase. This finding was recently confirmed in the context of a bi-directional Mendelian Randomization (MR) study (192). In the MR study, a slight attenuation of the causal effect of depression on CVD was observed after adjustment for blood pressure, but a mediation analysis was not conducted.

7.5 Depression and hypertension diagnosis

In the same sample of participants where depression was associated with an attenuation of age-related blood pressure increase, baseline depression was also associated with an increase in odds of being diagnosed with hypertension at follow-up in initially normotensive adults in Switzerland (OR 1.86, 95% CI 1.33 to 2.60) and with less confidence among PHC users in Kosovo (OR = 1.68, 95%-CI 0.41, 6.98) possibly related to small sample size. Our findings are consistent with the large body of evidence on the association between depression and the incidence of hypertension, which often includes hypertension diagnosis solely or as part of its definition (55,56,57,58,59).

Increased odds of being diagnosed with hypertension for those with depressive symptoms can be partly explained by increased healthcare utilization. For example, depressive symptoms were found to be associated with higher healthcare utilization (60,61) and higher healthcare costs (61), even when mental healthcare visits, count of medical diagnoses and medical severity were accounted for (62). Also, one study found that people with depressive symptoms often consult healthcare services for somatic symptoms of depression rather than psychological symptoms of depression (63). Somatic complaints include changes in appetite and libido, lack of energy, sleep disturbances, dizziness, palpitations, dyspnea, and general aches, and pains such as headache, back and other musculoskeletal pain, and gastrointestinal disturbances. Such seemingly vague symptoms could prompt general practitioners to conduct a general assessment which often includes blood pressure measurement and incidentally identify undiagnosed hypertension.

Higher healthcare utilization among those with depressive symptoms could not be verified in the SAPALDIA study, but was confirmed in the KOSCO study (**Table 2 in Chapter 6, page 77**). Given that the association was not statistically significant in the KOSCO study (Chapter 6) with adjusted for healthcare utilization (number of visits to the MFMC in the last 6 months) compared to statistically significant findings in the SAPALDIA study (Chapter 5) without adjustment for healthcare utilization, this may suggest that mediation through healthcare utilization hypothesis is valid, but the sample size in the KOSCO study still might not be large

enough for sufficient power to detect the association, and so the implications should be taken with caution. Future larger studies on the association between depression and hypertension should include healthcare utilization as an important covariate in their models.

In summary, we interpret our findings as an indication that people with depression are more likely to have underlying hypertension diagnosed, explained at least in part by increased healthcare-seeking behaviour.

Taken together with the findings of the previous section, depression is not likely linked to CVD through increased blood pressure as it predicts smaller increases of blood pressure compared to non-depressed. Nevertheless, depression predicted hypertension diagnosis at follow-up even when adjusted for baseline blood pressure. This suggests that the higher rates of hypertension diagnosed among the depressed may not be an effect of higher blood pressure, but related to higher health-seeking behaviour which enables better hypertension detection when it is present.

7.6 Depression and uncontrolled hypertension

The dissertation includes the first report on the association between depression and uncontrolled hypertension in Kosovo (Chapter 6) to the best of our knowledge. No statistically significant association was found between depressive symptoms and uncontrolled hypertension (OR = 0.69, 95%-CI 0.34 to 1.40) among initially hypertensive people (n=422) in the KOSCO study, although the evidence could suggest there may be a decrease in odds. Another longitudinal 4-year retrospective study found that depression was associated with faster rates of hypertension control (64), whereas a case-control study (65), cross-sectional study (66), and longitudinal study (67) found that depression was associated with uncontrolled hypertension. However, a recent cross-sectional study in the Netherlands (HELIUS study, n=21 363) found that hypertension control among depressed people differed between ethnic groups (68). This supports the importance to understand the association in the Kosovo context. It should also be noted given that we adjusted for healthcare utilization in this model, we may have accounted for any effect health-seeking behaviour may have had on hypertension control. For example, as depressed people use more healthcare, they are exposed to treatment and medical care that can help reduce blood pressure. This could also explain why no statistically significant association between depression and uncontrolled hypertension was found, in addition to small sample size. Further larger longitudinal studies are needed on the association between depression and uncontrolled hypertension, accounting for the potential mediating effect of healthcare utilization.

As discussed in section 7.2.3, the affordability and availability of antihypertension medication are important concerns in Kosovo. Despite depression being associated with poor adherence to antihypertension treatment in other contexts (44-46), adherence with special consideration of antihypertension medication affordability and availability needs consideration in future assessments of the association between depression and uncontrolled hypertension in Kosovo.

7.7 Challenges in studying depression

7.7.1 Heterogeneity of depression

Studying depression is highly complex as it is immensely heterogeneous. The Diagnostic and Statistical Manual for Mental Disorders (DSM-5) (69) is a formal definition of MDD, where criteria encompass the presence of symptoms and cumulative effect on functional impairment. However, there are about 10,000 ways to meet DSM-5 criteria, making a depression diagnosis quite heterogeneous in itself. Further, the DSM-5 depressive disorder definition does not distinguish biological differences or etiology, adding to the heterogeneity.

For research purposes, a multitude of operationalisations of depression has been used. In many cases, the definition includes a physician diagnosis of depression or antidepressant treatment. This is an adequate operationalization for the specificity of severe forms of depression, although it could miss meaningful depressive symptoms that do not meet DSM-5 criteria or people who do not seek healthcare, especially in low-resource settings. For this reason, many studies have used scales to screen for depressive symptoms in all participants. However, over 280 scales have been developed to screen for depressive symptoms, and only a few of them overlap with symptoms. Similarly, pathophysiological and etiological differences are not differentiated through these scales. Therefore it is plausible that if the cause and type of depression differ between populations and cultures, the effect of depression on blood pressure could also differ across studies.

Cai and colleagues (70) summarize the sources of heterogeneity that impact depression (**Figure 1 of Chapter 7**). Sources of heterogeneity that affect the main hypotheses in this dissertation to explain the findings that depression attenuates age-related blood pressure increase are the etiology, phenotype and time course of depression. Whether depressive symptoms are a response to stress or a genetic or biological source would affect blood pressure differently. One meta-analysis (71) investigated how differentiation between somatic/affective and cognitive/affective depressive symptoms affected CVD outcomes differently and found that

only somatic/affective depressive symptoms were associated with cardiovascular mortality and cardiovascular events. The subcategorization was proposed by Ormel and de Joung (72), whereby the cognitive/affective subtype is marked by psychosocial vulnerability (e.g. avoidant coping, neuroticism, stress vulnerability), and a somatic/affective subtype is characterized by vascular disease (e.g. atherosclerosis, inflammation markers, sickness behaviour, and deregulation of the HPA axis). The populations we studied may have more cognitive/affective depressive symptoms.

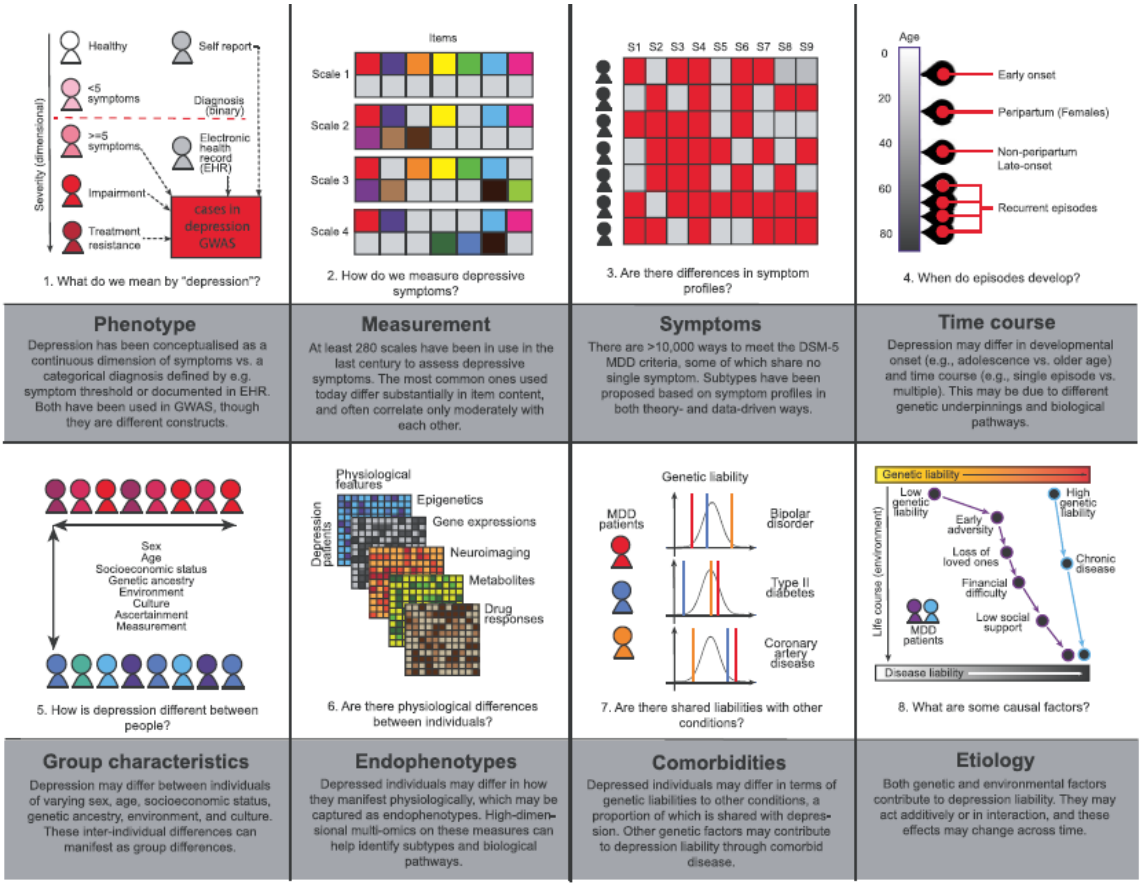


Figure 1. Sources of heterogeneity that impact depression research in terms of operationalization (phenotype, measurement), manifestation (symptoms, time course, group characteristics, endophenotypes, comorbidity), and etiology (70)

A more recent study (54) categorized depression as melancholic (typical) versus non-melancholic (atypical) and found that non-melancholic depressive symptoms increased the risk for incident CVD among CVD risk subjects. A melancholic subtype of depression is characterized by sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, irritability, loss of interest, change in sleeping, and change in appetite. The non-melancholic subtype is characterized by mood reactivity, interpersonal rejection sensitivity, hypersomnia,

fatigue, increased appetite, and weight gain. This is similar to the somatic versus cognitive forms proposed by Cai and colleagues (70). Future studies would need 24-hour blood pressure measurements to see these reactivities.

Based on the subcategorization in the above-mentioned studies, we attempted a preliminary sub-categorization in the KOSCO study, not reported in Chapter 6. We differentiated between those with low or high somatic symptoms to identify subtypes of depression. The Patient Health Questionnaire-15 (PHQ-15) is a 15-item, somatic symptom scale derived from the full Patient-Health-Questionnaire to measure the severity of somatization in patients. Patients were asked to indicate the severity of 15 physical symptoms they may have experienced during the past four weeks on a three-point scale from 0 ("not bothered at all") to 2 ("bothered a lot"). The total PHQ-15 score was obtained by summing the scores of each item and classified as minimal (0-4); mild (5-9); moderate (10-14); and high (15-30) with higher scores indicating greater severity of somatic symptoms (73). When replicating the longitudinal analysis of the fully adjusted model of depression and change in diastolic blood pressure in Chapter 6, but further disaggregated depression by the level of somatic symptoms (minimal to mild versus moderate to high), there were no meaningful differences in effect size between depressed with minimal to mild somatic symptoms (β= -2.99, 95% CI -5.39 to -0.58) and depressed with moderate to high somatic symptom level (β=-2.78, 95% CI -5.29 to -0.25) compared to the non-depressed in the fully adjusted models. The associations between depression and change in systolic blood pressure disaggregated by somatic symptom level remained non statistically significant as similar models in Chapter 6. Deeper psychological assessments are warranted in mega-cohorts though to better understand the differences between depression subtypes.

In addition to the depression subtype, the severity and time course of depressive symptoms are important characteristics of depressive symptoms that can influence the effect on change in blood pressure. The severity of depressive symptoms and how it was addressed in this dissertation has already been discussed in section 7.4.1. Duration of depressive symptoms was not accounted for in this dissertation. In the SAPALDIA study, the date of depression diagnosis was not collected and follow-ups were too far apart to assess the duration of exposure. In the KOSCO study, we used the DASS-21 which measures the presence of depressive symptoms in the last 4 weeks. However participants may differ on the onset of disease (early or later life), time course (single or multiple episodes) and comorbidities, all important factors which define the severity of depression. In other contexts, asking about history of depressive episodes may have been suitable, however it was not appropriate at baseline in the Kosovo setting. Brief

episodes of depression still increase the risk for future depression though (219,220). A next step could be a qualitative study to find out what reasons for stigmatizations are and what expectations from the people are in terms of support etc. In Chapter 6, the duration of the analyzed follow-up was only about one year. The frequent follow-ups (every 6 months) will make it possible to assess the duration and severity of depressive symptoms up to 5 years.

In summary, future epidemiological studies on the effects of depression should consider and try to address the different sources of depression heterogeneity, with a special focus on the phenotype, severity and time course.

7.7.2 Kosovo context

The use of the DASS-21 to screen for depressive symptoms in the Kosovo context was justified for several reasons. First, depression stigma is still very strong in Kosovo. Asking participants directly about their history of depression diagnosis was considered culturally offensive. This was confirmed by all four study nurses. One Kosovar study found that only 15.8% of people who stated they needed mental health support sought help from a psychologist or psychiatrist due to fear of being stigmatized (74). The DASS-21 includes questions about symptoms of depression without directly insinuating assessment for a depressive disorder, which was more acceptable to participants. Secondly, misclassification would be quite high if physician diagnosis of depression was used as an exposure definition. Primary healthcare providers are not generally trained in screening for depression. Further, because of the stigmatization, participants are hesitant to disclose their depressive symptoms or ask for a referral to a mental health professional. Seeking professional support to address mental health problems is associated with “tremendous shame” in the country, thus support is rarely requested or is kept within the family circle (75). If help related to mental health is sought outside the home, families often consulted with traditional healers or local religious people instead of mental health professionals (75). Therefore depression is suspected of being highly underdiagnosed in Kosovo. Using the DASS-21 is therefore an appropriate screening tool in the Kosovo context. Thirdly, the DASS is validated in both Albanian and Serbian, which are the local spoken languages.

7.8 Strengths and limitations of the dissertation

7.8.1 Novel evidence on the separate effects of depression on blood pressure and hypertension diagnosis

Chapter 6, to the best of our knowledge, is the first study to assess the effect of depression on blood pressure in Kosovo, where both conditions are highly prevalent. It also contributes valuable findings on cardiovascular epidemiology. Studies in Chapters 5 and 6 are the first reports, to the best of our knowledge, of the prospective association between depression and change in blood pressure and depression and hypertension diagnosis in the same study samples. The seemingly opposing findings in the same sample help disentangle the existing evidence and suggest that depression biologically has shared pathophysiology with lower blood pressure, but depression also has behavioural effects on healthcare-seeking and thus hypertension diagnosis. The dissertation therefore contributes evidence to two potential effects of depression on blood pressure-related outcomes.

7.8.2 Novel methods to assess depression effect on change in blood pressure

In Chapters 5 and 6, the use of censored regression is used as a novel approach to mitigate the effect of treatment on the prospective association between depression and change in blood pressure. It is considered a stronger approach than introducing antihypertension treatment in regression models or removing those with antihypertension treatment at follow-up as censored regression introduces the least amount of bias (43).

7.8.3 Exposure assessment

The inclusion of SF-36 MH score in Chapter 5 to identify potential cases of undiagnosed depression, minimized exposure misclassification in our study and allowed for identifying people with depressive symptoms in the absence of treatment. The association remained when we removed the SF-36 MH criteria from the exposure definition in a sensitivity analysis. The association between diagnosed depression and change in systolic blood pressure in the fully adjusted model was β=-2.65mmHg/10years (95%-CI -4.95 to -0.35) and β=-1.54mmHg/10 years (95%-CI -2.86 to -0.21) for change in diastolic blood pressure (n = 2246). Further, without the use of DASS-21 in the KOSCO study, assessment of depression would essentially not have been possible given the high level of stigma and underdiagnosis of depression.

One limitation of our study was the long elapsed time between follow-ups in the SAPALDIA study, thus could not assess the duration of exposure of depressive symptoms. Observing a dose-response effect would increase the evidence for a causal relationship for shared biological pathways, as was done in another study (26). We did not consider persistent depression in Chapter 6 to maintain the prediction perspective and to avoid reverse causation bias in the light

of only three follow-up time points. We will be able to reconsider this method once more follow-ups in the KOSCO study have passed.

7.8.4 Follow-up time

The long follow-up time (between 5.6 and 9.7 years) in the SAPALDIA study was a strength in our assessment. The KOSCO study was on the other hand implemented in 2019. Therefore the mean follow-up time for the analyses conducted for this study was 1.3 years (min 0.9 years – max 1.9 years), and may not be sufficient follow-up time to assess the effect on change in blood pressure. Follow-up of the KOSCO participants is anticipated for 5 years which would allow greater follow-up time to observe changes in blood pressure. The design of the KOSCO study with very short-term follow-ups in addition to 5 years total will also allow some mediation analyses to better understand the sequence of events.

7.8.5 Loss to follow-up

Retention between SAPALDIA follow-ups was very high: The overall participation rate at SAPALDIA1 (n=9651) was 59.3% of the sample frame (76), with a retention rate of 83% from SAPALDIA1 to SAPALDIA2 (n=8047), 76% from SAPALDIA2 to SAPALDIA3 (n=6088), and 85% from SAPALDIA3 to SAPALDIA4 (n=5149). The loss-to-follow-up in the KOSCO study was particularly evident following the outbreak of COVID-19. Retention of over 90% of participants was observed at the first follow-up (October 2019-February 2020) but was reduced to approximately 65% of the baseline sample by follow-up 3 (September 2020 to February 2021). The fear of exposure to COVID during study visits, especially before the rolling out of vaccines, was a concern vocalized by participants thus affecting the retention of participants and reducing the power of the analyses. We also may have underestimated the effect of depression in the course of blood pressure in case participants lost to follow-up in this cohort had more depression and hypertension. The participation however in the current follow-up (follow-up 5) is increasing thanks to new recruitment. Repeated cross-sectional studies will then also be possible with more statistical power.

7.8.6 Small sample size

The relatively small sample size may be a limitation to our longitudinal analyses in Chapters 5 and 6 (SAPALDIA n=3214, KOSCO n=648). However, only one similar study (26) had a much larger sample size (n=17 410), while others were equivalent or significantly smaller (n<2100) (27,28,50,77) than the SAPALDIA and KOSCO studies. The results of the dissertation can

guide research approaches in mega-cohorts established more recently and currently being followed up in various countries.

7.9 Public health and scientific impact of the KOSCO study

One important achievement of the dissertation work was the implementation of the Kosovo Non-Communicable Disease Cohort (KOSCO) in March 2019. The implementation of a non-communicable disease cohort was the first such undertaking in Kosovo as far as we know. The KOSCO study was not however only implemented for the sake of science. Due to very limited health data in Kosovo, the KOSCO study was born from the need for epidemiological data from multiple stakeholders in Kosovo, including those in public health. Apart from providing evidence for articles to be published in scientific journals, the cohort has served towards local health policy impact. As of January 2022, the KOSCO study has completed baseline and five participant follow-ups.

7.9.1 Public health relevance

Local stakeholders were involved throughout all phases of the cohort, including the preparatory phase. Medical directors of the MFMCs had voiced their data needs and the KOSCO study responded to them. For example, in the preparatory phase, MFMC directors indicated a specific need for epidemiological data on respiratory health, which was not initially considered.

KOSCO is embedded into the AQH project which works closely with the Ministry of Health and National Institute of Public Health, therefore has the power to impact health policy. Preliminary findings have been shared at least annually with the Kosovo Ministry of Health, National Institute of Public Health, medical directors of the MFMCs in 12 of 38 municipalities as well as with the AQH project. The preliminary findings of poor respiratory health not only confirm with evidence the concerns of local stakeholders but have now also been taken up as a priority by the AQH project for their second project phase. The next step would require in-depth discussions of the findings with the MoH and NIPH for consideration in their health planning.

Our study points to the need for integrating aspects of mental health into NCD prevention and treatment, given that mental health issues are prevalent and that they are interrelated with NCD risk behaviour, and care-seeking. Given the high prevalence of hypertension and diabetes, if mental health would be integrated and additionally offered to family members, and in a time

and place where people may be more open to discuss mental health issues (i.e. primary health care), a considerable percentage of the population could be reached

7.9.2 Scientific implications

The implementation of a cohort study in Kosovo sets a stage for NCD research led by local scientists. A memorandum of understanding (MoU) has been signed between the Swiss Tropical and Public Health Institute and the University of Prishtina to facilitate collaborative research with expertise from both institutions. This MoU has facilitated the initiation of doctoral studies of one Kosovar student co-supervised by both institutions and a second Kosovar student has also applied to use KOSCO data for their studies.

The KOSCO study also serves as a platform that facilitates data collection for additional scientific questions. For example, the cohort provided a structure to easily add a qualitative component to investigate perceptions of motivational counselling intervention. The qualitative work could be rapidly undertaken by the Kosovar PhD student as preliminary data on suitable candidates for the sub-study was already collected. Further, despite the rapidly evolving coronavirus pandemic, the cohort could react quickly to this research opportunity by including COVID-related questions in the questionnaire for existing participants.

7.10 Recommendations for health policy and research outlook

7.10.1 Recommendation 1: Strengthen CVD risk factor prevention in Kosovo

Chapter 3 identified that CVD risk factors such as smoking, physical inactivity, poor nutrition, obesity, hypertension and diabetes are highly common in Kosovo. A focus on improving the risk factors is of particular urgency. Risk factor modification in observational studies was associated with 44% of the decline of CVD in Finland (1) and the USA (2). A Cochrane review found that there was some evidence that multiple risk factor interventions lowered blood pressure levels, body mass index and waist circumference in populations in LMIC settings at high risk of hypertension and diabetes, but the evidence was limited (78).

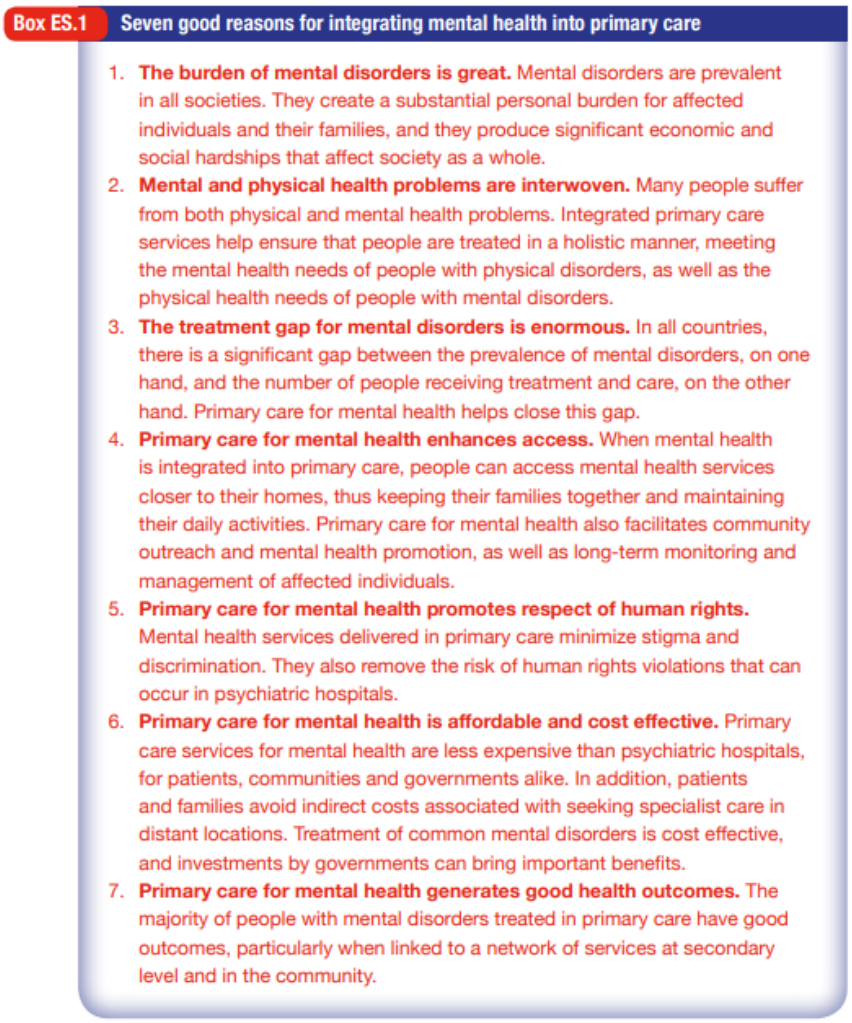
The main obstacle to health policy recommendation is the constraint of current health expenditures in the country. Kosovo spent 4.47% of its GDP on healthcare, or 158 Euros per capita in 2017 (79), whereas the European mean is 1990 Euros per capita. Risk factor modification interventions are relatively inexpensive and highly cost-effective towards the prevention of CVD in LMIC (80). Therefore risk factor modification should stay in the focus

of PHC in Kosovo, and also calls for an integrated and efficient approach to risk factor prevention.

Our study provides risk profiles for tailoring risk factor interventions, which have been shared with MFMC directors, the Ministry of Health, the National Institute of Public Health and the AQH project who can have direct impacts on improving risk factors. For example, there existed important gender differences for smoking, alcohol consumption and obesity: women were more affected by obesity, while men were more affected by smoking and alcohol consumption. Obesity and multiple unhealthy lifestyles were common among participants of low socioeconomic status, while higher socioeconomic status privileged smoking.

7.10.2 Recommendation 2: Integration of depression screening and mental health services in primary healthcare

Although the findings of this dissertation do not point towards depression being linked to CVD through increased blood pressure, depression remains by and large a risk factor for CVD in general, and acts through still unidentified mechanisms. Depression is commonly associated with considerable family, social and vocational impairment, as well as an increased economic burden. They account for 47 million DALYs. Therefore the adequate identification and treatment of depression in Kosovo should be a priority. The WHO (81) provides seven compelling arguments for the integration of mental health into PHC (**Figure 2 of Chapter 7**).



Box ES.1 Seven good reasons for integrating mental health into primary care

1. **The burden of mental disorders is great.** Mental disorders are prevalent in all societies. They create a substantial personal burden for affected individuals and their families, and they produce significant economic and social hardships that affect society as a whole.
2. **Mental and physical health problems are interwoven.** Many people suffer from both physical and mental health problems. Integrated primary care services help ensure that people are treated in a holistic manner, meeting the mental health needs of people with physical disorders, as well as the physical health needs of people with mental disorders.
3. **The treatment gap for mental disorders is enormous.** In all countries, there is a significant gap between the prevalence of mental disorders, on one hand, and the number of people receiving treatment and care, on the other hand. Primary care for mental health helps close this gap.
4. **Primary care for mental health enhances access.** When mental health is integrated into primary care, people can access mental health services closer to their homes, thus keeping their families together and maintaining their daily activities. Primary care for mental health also facilitates community outreach and mental health promotion, as well as long-term monitoring and management of affected individuals.
5. **Primary care for mental health promotes respect of human rights.** Mental health services delivered in primary care minimize stigma and discrimination. They also remove the risk of human rights violations that can occur in psychiatric hospitals.
6. **Primary care for mental health is affordable and cost effective.** Primary care services for mental health are less expensive than psychiatric hospitals, for patients, communities and governments alike. In addition, patients and families avoid indirect costs associated with seeking specialist care in distant locations. Treatment of common mental disorders is cost effective, and investments by governments can bring important benefits.
7. **Primary care for mental health generates good health outcomes.** The majority of people with mental disorders treated in primary care have good outcomes, particularly when linked to a network of services at secondary level and in the community.

Figure 2. Seven good reasons for integrating mental health in primary care (81)

People with depression often present with somatic symptoms (63), which can prompt general practitioners to identify other conditions but can also cause depression to be overlooked (82). Many general practitioners lack sufficient training in mental health disorders or have time constraints in busy primary care settings, increasing the risk of underdiagnosis of depression. A structured clinical interview (e.g., using the Diagnostic and Statistical Manual of Mental Disorders criteria) remains the gold-standard method for the assessment of depression, MDD, dysthymia, etc. However, this is not always feasible in PHC settings. Integrating a screening tool in PHC can be an effective way to improve depression detection. To become acceptable for use in medical practice, screening instruments must be valid, reliable, brief, easy to administer, available at a low cost or even free of charge, and effective in achieving improved clinical outcomes.

One review of available screening tools recommends the use of the PHQ-2 to screen patients as a first step (83), then further assessment if the person scores positively. The recommended cut-off score for MDD among adult outpatients aged 18 years is 1 for the "verbally administered" PHQ-2 (where the answer for each question is yes or no), and 3 for the "self-administered" PHQ-2 (where the answer for each question is rated from 0 to 3; sensitivity, 83%; specificity, 92%). The review suggests the PHQ-9 as a follow-up assessment which is thought by some to be the gold-standard depression screening instrument for primary care. The authors caution however that although some instruments are capable of identifying current emotional disturbances, they can fail to detect chronic illness.

PHC is an ideal setting to screen for depression and is urgently needed given that it was found that only 15.8% of those who believed that they needed professional help, actually reported receiving psychological/psychiatric help and stigma was an important barrier (74). Screening for depression by general practitioners can provide those afraid to ask for mental health services with a segue to getting help.

Adequate management and follow-up are ethical prerequisites for the utilization of any screening instrument for depression. The WHO recommends the integration of mental health into general health care to seal the existing gap between the number of patients who need mental health care and those who actually receive it. Integrated mental health services have been found to be effective in another setting (84,85). Community mental health has been developed in Kosovo but faces a lot of challenges preventing it to take off (86). Obstacles include financial and human resources; capacity building; stakeholder involvement and service availability. The financial and clinical benefits of integrated mental healthcare into primary healthcare should be brought to the attention of national stakeholders.

Our team is currently in the process of developing an intervention protocol to be adapted and tested in the Kosovo setting. The intervention will include the training of unskilled health workers to provide mental healthcare. In the long term, we hope that this intervention can be adopted by local public health stakeholders.

7.10.3 Outlook 1: Systematic review and meta-analysis of prospective studies assessing depression and change in blood pressure

There still exists ambiguity on how to consolidate the evidence on the association between depression and blood pressure. Due to the reason stated in this dissertation, it is more prudent to remove hypertension diagnosis, which is influenced by health-seeking behaviour and the

health system, in the outcome definition. More studies with larger sample sizes assessing the association between depression and blood pressure as a continuous outcome are needed. From then, a meta-analysis of the evidence can be conducted to better elucidate this relationship.

7.10.4 Outlook 2: Investigating other mechanisms between depression and CVD

The evidence of this dissertation suggests that depression and CVD are not likely causally linked by increased blood pressure. There is however preliminary evidence from this dissertation (Chapter 4) that undetected and uncontrolled diabetes is a concerning issue in the Kosovo context, and may be worthwhile to investigate as another potential link between depression and CVD. This topic through a post-doctoral study is anticipated.

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PUBLICATIONS

Obas KA, Kwiatkowski M, Bytyci-Katanolli A, Statovci S, Jerliu N, Ramadani Q, Fota N, Gerold J, Zahorka M, Probst-Hensch N. Prospective association between depressive symptoms and blood-pressure related outcomes in Kosovo. PLOS Glob Public Health. 2023 Apr 7;3(4):e0000851. doi: 10.1371/journal.pgph.0000851. PMID: 37027380; PMCID: PMC10081745.

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APPENDIX – ARTICLE 2 (CHAPTER 4)

Obas KA, Bytyci-Katanolli A, Kwiatkowski M, Ramadani Q, Fota N, Jerliu N, Statovci S, Gerold J, Zahorka M, Probst-Hensch N. Strengthening Primary Healthcare in Kosovo Requires Tailoring Primary, Secondary and Tertiary Prevention Interventions and Consideration of Mental Health. Front Public Health. 2022 Apr 5;10:794309. doi: 10.3389/fpubh.2022.794309. PMID: 35480592; PMCID: PMC9037373.

Appendix 1. Association between depressive symptoms (DASS-21 depressive symptoms score ≥14) and unhealthy lifestyle behaviours (smoking, physical, inactivity, poor nutrition, alcohol consumption, obesity, and unhealthy lifestyle index), undetected and uncontrolled hypertension, diabetes and COPD (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019).

	Adjusted association with depression symptoms as a binary score (DASS-21 depressive symptoms score ≥14)		
Outcome	**Odds Ratio**	**95 % confidence interval**	
Currently smoking (n=977)	0.85	0.49	1.49
Physical inactivity (n=977)	1.40	0.86	2.29
Poor nutrition (n=977)	0.83	0.47	1.44
Alcohol consumption	-	-	-
Obesity (n=977)	0.95	0.63	1.45
Unhealthy lifestyle index (n=977)	1.01	0.69	1.47
Undetected hypertension (n=743)	0.63	0.31	1.54
Undetected diabetes (n=601)	0.69	0.31	17.76
Undetected chronic obstructive pulmonary disease (n=108)	4.37	1.07	2.41
Uncontrolled hypertension (n=605)	1.42	0.83	1.27
Uncontrolled diabetes (n=506)	0.67	0.36	1.49
Uncontrolled chronic obstructive pulmonary disease	-	-	-

A Depression, Anxiety, Stress Scale-21 score of ≥14 indicated having depressive symptoms. Mixed ordinal logistic regression models quantified the association between depressive symptoms and lifestyle index. The associations between depressive symptoms and all other outcomes were quantified with mixed logistic regression models. All models included municipality as a random effect and were adjusted for age, sex, work status, education level, living in a rural or urban setting, and ethnicity except only adjustments for age and sex were included in the model of the association between depression and undetected chronic obstructive pulmonary disease due to few cases. We did not include a regression for the association between depressive symptoms and alcohol consumption because there were no cases of depressed people drinking alcohol in the last 30 days, therefore depressive symptoms predicted the outcome perfectly. We also did not include a regression model for the association between depressive symptoms and uncontrolled COPD because there were too few cases. Subsamples for undetected hypertension, diabetes and COPD included all participants with a self-reported physician diagnosis or pathological findings for the given disease (systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg for hypertension; HbA1c ≥ 6.5% for diabetes; PEF < 80% Predicted with breathlessness for six months or longer or cough for at least 3 months for COPD). Subsamples for uncontrolled disease included all participants with a self-reported physician diagnosis for the given disease. The vertical red line indicates the limit of the odds ratio of one.

Appendix 2. Association between depressive symptoms (continuous score) and non-communicable disease risk factors (smoking, physical, inactivity, poor nutrition, alcohol consumption, obesity, and unhealthy lifestyle index), undetected and uncontrolled hypertension, diabetes and COPD (Kosovo Non-Communicable Disease Cohort, Kosovo, 2019)

Outcome	**Odds Ratio per one-point increase of depressive symptoms**	**95 % confidence interval**	
Currently smoking (n=977)	1.00	0.97	1.02
Physical Inactivity (n=977)	1.02*	1.00	1.05
Poor nutrition (n=977)	1.00	0.97	1.02
alcohol (n=977)	0.90	0.81	1.01
Obesity (n=977)	1.00	0.98	1.02
lifestyl index (n=977)	1.01	0.99	1.03
undetected hypertension (n=743)	0.98	0.95	1.01
undetected diabetes (n=601)	0.95*	0.91	1.00
undetected chronic obstructive pulmonary disease (n=108)	1.07*	1.00	1.15
uncontrolled hypertension (n=605)	1.01	0.98	1.04
uncontrolled diabetes (n=506)	1.00	0.97	1.03
uncontrolled chronic obstructive pulmonary disease (n=59)	-	-	-

Depressive symptoms were assessed using the Depression, Anxiety, Stress Scale-21. Mixed ordinal logistic regression models quantified the association between depressive symptoms and lifestyle index. The associations between depressive symptoms and all other outcomes were quantified with mixed logistic regression models. All models included municipality as a random effect and were adjusted for age, sex, work status, education level, living in a rural or urban setting, and ethnicity with exception of alcohol, which was reduced to adjustment for only age, sex and ethnicity. Subsamples for undetected hypertension, diabetes and COPD included all participants with a self-reported physician diagnosis or pathological findings for the given disease (systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg for hypertension; HbA1c ≥ 6.5% for diabetes; PEF < 80% Predicted with breathlessness for six months or longer or cough for at least 3 months for COPD). Subsamples for uncontrolled disease included all participants with a self-reported physician diagnosis for the given disease. The vertical red line indicates the limit of the odds ratio of one.

APPENDIX – ARTICLE 3 (CHAPTER 5)

Obas KA, Kwiatkowski M, Schaffner E, Lang UE, Stolz D, Eze IC, Imboden M, Probst-Hensch N. Depression and cardiovascular disease are not linked by high blood pressure: findings from the SAPALDIA cohort. Sci Rep. 2022 Apr 1;12(1):5516. doi: 10.1038/s41598-022-09396-2. PMID: 35365701; PMCID: PMC8975826.

Appendix 1. Prospective association between baseline [a] depression (binary, disaggregated by antidepressant use and antidepressant class) and age-related increase in systolic and diastolic blood pressure over 10 years among normotensives at baseline a (n=3214), with adjustment for baseline blood pressure.

	Change in systolic blood pressure over 10 years				**Change in diastolic blood pressure over 10 years**			
	Lightly adjusted [b]		Fully Adjusted [c]		Lightly adjusted [b]		Fully Adjusted [c]	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Presence of depression								
Not depressed (n=2851)	(reference)		(reference)		(reference)		(reference)	
Depressed (n=363)	-2.6	(-4.20, -0.23)	-2.30	(-4.26, -0.35)	-0.98	(-2.19, 0.24)	-1.05	(-2.23, 0.14)
Depression, disaggregated by antidepressant medication use								
Not depressed (n=2851)	(reference)		(reference)		(reference)		(reference)	
Depressed, not medicated (n=242)	-1.77	(-4.15, 0.60)	-1.69	(-4.04, 0.65)	-0.69	(-2.18, 0.80)	-0.59	(-2.06, 0.87)
Depressed, medicated (n=121)	-3.10	(-6.38, 0.19)	-3.50	(-6.73, -0.26)	-1.55	(-3.45, 0.35)	-1.94	(-3.76, -0.11)
Depression, disaggregated by type of antidepressant								
Not depressed (n=2851)	(reference)		(reference)		(reference)		(reference)	
Depression, not medicated	-1.79	(-4.16, 0.59)	-1.71	(-4.05, 0.63)	-0.70	(-2.18, 0.79)	-0.60	(-2.07, 0.87)
(n=242)	-6.66	(-13.27, -0.06)	-6.67	(-12.92, -0.41)	-5.37	(-9.74, -1.00)	-5.48	(-9.57, -1.39)
Depressed, on N06AA [d] (n=16)	-4.59	(-9.19, 0.01)	-4.88	(-9.46, -0.29)	-1.70	(-4.45, 1.05)	-1.85	(-4.47, 0.78)
Depressed, on N06AB [e] (n=55)	0.07	(-5.66, 5.79)	-0.62	(-6.22, 4.98)	0.02	(-3.18, 3.22)	-0.79	(-3.90, 2.32)
Depressed, on other or multiple antidepressants (n=46)								

[a]First time point of each wave is defined as baseline, [b] Censored normal regression models "lightly adjusted" included baseline blood pressure, age, quadratic age term, cubic age term, sex, age and sex interactions, education, employment, SSEP, study area, and wave. [c] Fully adjusted models included all of the above and BMI, pulse, sleepiness, physical activity, fruit consumption, vegetable consumption, alcohol, and smoking. [d] N06AA –Non-selective monoamine reuptake inhibitors; [e] N06AB - Selective serotonin reuptake inhibitor.

APPENDIX – ARTICLE 4 (CHAPTER 6)

Obas KA, Kwiatkowski M, Bytyci-Katanolli A, Statovci S, Jerliu N, Ramadani Q, Fota N, Gerold J, Zahorka M, Probst-Hensch N. Prospective association between depressive symptoms and blood-pressure related outcomes in Kosovo. PLOS Glob Public Health. 2023 Apr 7;3(4):e0000851. doi: 10.1371/journal.pgph.0000851. PMID: 37027380; PMCID: PMC10081745.

Appendix 1. Baseline characteristics disaggregated by participant and non-participant status

Sociodemographic factors	**Participant n=648**	**Non-participant n =363**	
Age, mean (SD)	59.4 (8.9)	60.4 (10.0)	p=0.087 [a]
Sex, frequency (%)			p=0.269 [b]
Male	273 (42.1)	140 (38.6)	
Female	375 (57.9)	223 (61.4)	
Education, frequency (%)			p=0.185 [b]
Primary school or less	399 (61.6)	239 (65.8)	
Secondary school	204 (31.5)	108 (29.8)	
University/College	45 (6.9)	16 (4.4)	
Work status, frequency (%)			p=0.073 [b]
Currently working	119 (18.4)	52 (14.3)	
House person	303 (46.8)	175 (48.2)	
Retired or disabled	208 (32.0)	116 (32.0)	
Unemployed	18 (2.8)	20 (5.5)	
Residence, frequency (%)			p=0.588 [b]
Rural	372 (57.4)	202 (55.7)	
Urban	276 (42.6)	161 (44.3)	
Municipality, frequency (%)			p=0.054 [b]
Drenas	63 (9.7)	40 (11.0)	
Fushe Kosova	64 (9.9)	46 (12.7)	
Gjakova	51 (7.9)	23 (6.3)	
Gračanica	36 (5.6)	19 (5.2)	
Junik	11 (1.7)	11 (3.0)	
Lipjan	106 (16.4)	71 (19.6)	
Malisheva	51 (7.9)	29 (8.0)	
Mitrovica	65 (10.0)	19 (5.2)	
Obiliq	37 (5.7)	33 (9.1)	
Rahovec	53 (8.2)	24 (6.6)	
Skenderaj	69 (10.7)	29 (8.0)	
Vushtrri	42 (6.5)	19 (5.2)	
Ethnicity, frequency (%)			p=0.908 [b]
Albanian	589 (90.9)	331 (91.2)	
Serbian	34 (5.2)	17 (4.7)	
Roma, Ashkali, Egyptian, Other	25 (3.9)	15 (4.1)	
Main Family Medicine Center visits in the last 6 months, median (IQR)	3 (2-6)	3 (2-7)	p=0.685 [a]
Smoking, frequency (%)			p=0.412 [b]
Never or ex-smoker	521 (80.4)	284 (78.2)	
Current smoker	127 (19.6)	79 (21.8)	

Physical activity, frequency (%)			p=0.002 [b]
Sufficiently active	211 (32.6)	85 (23.4)	
Insufficiently active	437 (67.4)	278 (76.6)	
Alcohol, frequency (%)			p=0.316 [b]
No alcohol in past 30 days	616 (95.1)	350 (96.4)	
Consumed alcohol in past 30 days	32 (4.9)	13 (3.6)	
Nutrition, frequency (%)			p=0.732 [b]
Adequate nutrition	98 (15.1)	52 (14.3)	
Poor nutrition	550 (84.9)	311 (85.7)	
Sleep, frequency (%)			p=0.943 [c]
Very good	175 (27.0)	102 (28.1)	
Fairly good	236 (36.4)	127 (35.0)	
Fairly bad	173 (26.7)	96 (26.5)	
Very bad	64 (9.9)	38 (10.5)	
Obesity			p=0.024 [b]
BMI <30	286 (44.1)	187 (51.5)	
BMI ≥ 30	362 (55.9)	176 (48.5)	
Systolic blood pressure (mmHg), mean (SD)	135.7 (17.9)	134.5 (19.2)	p=0.342 [a]
Change in systolic blood pressure, mean (SD)	2.2 (14.0)	N/A	N/A
Diastolic blood pressure (mmHg), mean (SD)	86.4 (9.9)	86.1 (10.2)	p=0.692 [a]
Change in diastolic blood pressure, mean (SD)	0.4 (7.8)	N/A	N/A
Hypertension, freq (%)			p=0.987 [b]
Never diagnosed	246 (38.0)	138 (38.0)	
Diagnosed	402 (62.0)	225 (62.0)	
Antihypertensive treatment, freq (%)			p=0.618 [b]
Not taking	359 (55.4)	207 (57.0)	
Taking	289 (44.6)	156 (43.0)	
Depressive symptoms at baseline			p=0.138 [b]
Normal-mild (DASS <14)	575 (88.7)	307 (85.5)	
Moderate to very severe (DASS≥14)	73 (11.3)	52 (14.5)	

mmHg: millimetres of mercury, DASS: Depression Anxiety Stress Scale, BMI: body mass index, SD: standard deviation, IQR: interquartile range. Normal to mild depressive symptoms if depression subscale of 21-item Depression Anxiety Stress Scale score was <14. Moderate to very severe depressive symptoms if depression subscale of 21-item Depression Anxiety Stress Scale score was ≥14. [a]t-test; [b]Chi^2 test; [c]Kruskall-Wallis test

Appendix 2. Prospective association between depression and change in systolic and diastolic blood pressure per year, without adjustment for baseline systolic and diastolic blood pressure

	Change in systolic blood pressure						Change in diastolic blood pressure					
	Minimally [a] adjusted			Fully [b] adjusted			Minimally [a] adjusted			Fully [b] adjusted		
	Coef	95%-CI	p-value	Coef	95%-CI	p-value	Coef	95%-CI	p-value	Coef	95%-CI	p-value
Depression												
Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)			(Ref)			(Ref)		
Moderate to very severe depressive symptoms (DASS ≥14)	-2.64	(-6.32, 1.03)	p=0.155	-2.27	(-6.04, 1.50)	p=0.238	-3.48	(-5.48, -1.49)	p=0.001	-3.23	(-5.26, -1.19)	p=0.002
Depression severity (categorical)												
Normal (DASS-21 score 0-9)	(Ref)			(Ref)			(Ref)		p=0.427	(Ref)		
Mild (DASS-21 score 10-13)	-0.63	(-4.93, 3.67)	p=0.773	-0.24	(-4.58, 4.09)	p=0.913	0.93	(-1.36, 3.22)	p=0.001	1.19	(-1.12, 3.49)	p=0.314
Moderate (DASS-21 score 14-20)	-4.14	(-8.49, 0.21)	p=0.062	-3.95	(-8.37, 0.46)	p=0.079	-4.09	(-6.43, -1.75)	p=0.271	-3.93	(-6.31, -1.56)	p=0.001
Severe (DASS-21 score 21-27)	-1.47	(-9.92, 6.99)	p=0.733	-0.19	(-8.64, 8.27)	p=0.966	-2.55	(-7.10, 1.99)	p=0.677	-2.07	(-6.61, 2.48)	p=0.373
Very severe (DASS-21 score ≥ 28)	2.30	(-6.33, 10.94)	p=0.601	2.99	(-5.74, 11.71)	p=0.503	-1.01	(-5.62, 3.60)		-0.12	(-4.79, 4.54)	p=0.958

Results from multivariable censored regression models. [a] minimally adjusted: age (in years), sex (male, female), highest level of education completed (primary school or less, secondary school, university/college or more), work (working, home-person, retired/disabled, unemployed), urban-rural classification (rural, urban), ethnicity (Albanian, Serbian, Roma/Ashkali/Egyptian/Other). [b] fully adjusted: minimally adjusted covariates and additionally, smoking status (current smoker), physical inactivity (<150 min of moderate-intensity physical activity per week, or <75 min of vigorous-intensity physical activity per week, or less than an equivalent combination of moderate-intensity and vigorous-intensity activity; poor nutrition (<5 fruits and/or vegetables per day), alcohol consumption (any alcohol in the last 30 days), obesity (BMI≥30), heart rate (beats per minutes), number of main family medicine center visits in the last 6 months. DASS-21: 21-item Depression Anxiety Stress Scale; Ref: Reference group; mmHg: millimetres of mercury

Appendix 3. Prospective association between depression and change in systolic and diastolic blood pressure, minimally adjusted model and introduction of potential mediators individually

		Change in systolic blood pressure			Change in diastolic blood pressure		
		Coef	95%-CI	p-value	Coef	95%-CI	p-value
Minimally[a] adjusted	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.31	(-5.48, 0.87)	p=0.155	-2.93	(-4.68, -1.18)	p=0.001
Minimally[a] adjusted + adjustment for **physical inactivity**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.30	(-5.48, 0.87)	p=0.155	-2.93	(4.68, -1.17)	p=0.001
Minimally[a] adjusted + adjustment for **smoking**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.44	(-5.62, 0.75)	p=0.134	-3.02	(-4.78, -1.25)	p=0.001
Minimally[a] adjusted + adjustment for **alcohol**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.27	(-5.45, 0.91)	p=0.161	-2.91	(-4.66, -1.16)	p=0.001
Minimally[a] adjusted + adjustment for **poor nutrition**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.25	(-5.43, 0.94)	p=0.166	-2.85	(-4.60, -1.09)	p=0.001
Minimally[a] adjusted + adjustment for **sleep quality**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.04	(-5.28, 1.21)	p=0.219	-2.81	(-4.61, -1.01)	p=0.002
Minimally[a] adjusted + adjustment for **obesity**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.29	(-5.46, 0.89)	p=0.158	-2.93	(-4.69, -1.16)	p=0.001
Minimally[a] adjusted + adjustment for **heart rate**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.43	(-5.60, 0.74)	p=0.133	-3.05	(-4.80, -1.31)	p=0.001
Minimally[a] adjusted + adjustment for **visits to Main Family Medicine Centers**	**Depression**						
	Normal to mild depressive symptoms (DASS<14)	(Ref)			(Ref)		
	Moderate to very severe depressive symptoms (DASS ≥14)	-2.13	(-5.31, 1.05)	p=0.188	-2.87	(-4.64, -1.10)	p=0.002

Smoking status (current smoker), physical inactivity (<150 min of moderate-intensity physical activity per week, or <75 min of vigorous-intensity physical activity per week, or less than an equivalent combination of moderate-intensity and vigorous-intensity activity; poor nutrition (<5 fruits and/or vegetables per day), alcohol consumption (any alcohol in the last 30 days), obesity (BMI≥30), heart rate (beats per minutes), number of main family medicine center visits in the last 6 months. DASS-21: 21-item Depression Anxiety Stress Scale

Appendix 4. P-values of the interaction term between depression and sex in main fully adjusted models

	p-value of interaction term between depression and sex
Prospective association between depression and change in systolic blood pressure	p=0.827
Prospective association between depression and change in diastolic blood pressure	p=0.977
Prospective association between depression and hypertension diagnosis	p=0.354
Prospective association between depression and uncontrolled hypertension	p=0.919