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

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4 1 **TITLE:** Study Protocol: A prospective cohort on non-communicable diseases among primary  
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29 **KEYWORDS:** Kosovo, non-communicable disease, cohort study, depression, cardiovascular  
30 disease, hypertension, Balkans

31 **ABSTRACT 295/300**

32 **Introduction:** With the lowest life expectancy in the Balkans, underlying causes of morbidity in  
33 Kosovo remain unclear due to limited epidemiological evidence. Cardiovascular disease is a  
34 non-communicable disease which causes the greatest burden of disease globally. Some  
35 studies suggest that depression may worsen the incidence and outcome of hypertension,  
36 which is the most important risk factor for cardiovascular disease. Given the high prevalence  
37 of depression in Kosovo, understanding its relationship with hypertension is of great relevance  
38 for the prevention of cardiovascular disease in the country. The aim of this cohort is to  
39 contribute epidemiological evidence for the prevention of non-communicable diseases in  
40 Kosovo as the basis for policy and decision making, with a spotlight on the relationship  
41 between depression and hypertension.

42 **Methods and Analysis:** Patients exiting 12 Main Family Medicine Centers in Kosovo were  
43 consecutively recruited. Patients aged 40 years and above and who consulted healthcare  
44 services on the day of recruitment were included in the study. The data collected includes:  
45 socio-demographic characteristics, social and environmental factors, comorbidities, health  
46 system, lifestyle, psychological factors, and clinical attributes (blood pressure, height, weight,  
47 waist/hip/neck circumferences, peak expiratory flow and HbA1c measurements). The data was  
48 collected in two phases, with a 6 month interval. Recruitment began on 18 March 2019.

49 **Ethics and dissemination:** Ethical approvals for the study were obtained from Ethics Committee  
50 Northwest and Central Switzerland (Ref. 2018-00994) and the Kosovo Doctors Chamber (Ref.  
51 11/2019). Cohort results will provide novel epidemiological evidence on non-communicable

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1  
2  
3 52 diseases and their relation to mental health in Kosovo, which will be published in scientific  
4  
5  
6 53 journals. The study will also examine the health needs of the people of Kosovo and provide  
7  
8 54 evidence for health sector decision makers to improve service responsiveness, which will be  
9  
10 55 shared with stakeholders through reports and presentations.  
11  
12  
13

14 56 **Registration:** not applicable  
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16

## 17 57 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 21 58 • As the first prospective cohort in Kosovo, the study will provide important evidence on  
22  
23 59 the course of non-communicable diseases in a country with limited epidemiological  
24  
25 60 evidence.  
26  
27
- 28 61 • The longitudinal study design will allow us to observe changes over time in individuals  
29  
30 62 and analyze the temporal sequence of changes, thus providing stronger evidence in  
31  
32 63 investigating causal relationships, for example between depression and hypertension.  
33  
34
- 35 64 • This study will assess the long-term effect of primary healthcare interventions and study  
36  
37 65 results can be immediate applied in designing targeted behaviour change interventions  
38  
39 66 by healthcare stakeholders.  
40  
41
- 42 67 • This study is not population-based due to the recruitment scheme in primary healthcare  
43  
44 68 facilities, which limits its generalizability and may overestimate the prevalence of health  
45  
46 69 conditions, however healthy persons are included in the study because PHC patients  
47  
48 70 visit centers for an array of conditions including general check-ups.  
49  
50  
51

## 52 71 **INTRODUCTION**

56 72 The burden of disease in the Balkan region falls heaviest on Kosovo, suggested by a life  
57  
58 73 expectancy of 72 [1], which is lower than neighbouring countries such as Albania (78 years),  
59  
60 74 Montenegro (77 years), Macedonia (76 years), and Serbia (76 years) [1]. It is a challenge,

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3 75 however, to get a better understanding of the main culprits of Kosovo's disease burden due  
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5  
6 76 in part to limited epidemiological evidence given the country's health information system is  
7  
8 77 still in its initial developmental phase [2].  
9

## 10 11 78 **The burden of disease in Kosovo**

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13  
14  
15 79 Although it is well known that non-communicable diseases (NCDs) are the greatest contributor  
16  
17 80 to health loss in the world, accounting for 61% (or 1.5 billion) of Disability Adjusted Life-Years  
18  
19 81 (DALY), only a few estimates on NCDs in Kosovo are available. A national population-based  
20  
21 82 study conducted in 2010 in Kosovo of adults over the age of 65 (n=1890) indicated that the  
22  
23 83 most common self-reported NCD was cardiovascular disease (CVD), with a prevalence of  
24  
25 84 63%, followed by stomach and liver disease (21%), then diabetes mellitus (DM) (18%) [3].  
26  
27  
28  
29

30 85 CVD is a major health concern globally, accounting for 353 million DALYs (14.8% of all DALYs  
31  
32 86 globally), over 471 million prevalent cases and 17.6 million deaths annually [4]. The situation  
33  
34 87 is dire in the Balkans, where the burden of CVD is nearly double that of the global prevalence  
35  
36 88 (27.7% of all DALYs for the Balkans). CVDs include coronary artery disease, cardiomyopathy,  
37  
38 89 cerebrovascular disease, peripheral vascular disease, rheumatic heart disease, arrhythmias,  
39  
40 90 and endo/myocarditis. Acute CVD events include myocardial infarctions and strokes. The  
41  
42 91 Kosovo Agency of Statistics reports that CVD was responsible for 57.9% of deaths in 2012;  
43  
44 92 18% of these occurring under the age of 60 [5].  
45  
46  
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49

50 93 Although CVD is the principal cause of death worldwide, mental disorders are now among the  
51  
52 94 leading causes of disability [4]. Among mental disorders, depression is the most common with  
53  
54 95 over 300 million prevalent cases worldwide (4.4% global prevalence) [6]. Depression results  
55  
56 96 from a complex interaction of social, psychological and biological factors and is characterized  
57  
58 97 by persistent sadness, loss of interest in activities a person normally enjoys, and inability to  
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3 98 carry out daily activities. People who have gone through adverse life events (unemployment,  
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5 99 bereavement, psychological trauma) are more likely to develop depression as well as post-  
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7  
8 100 traumatic stress disorder (PTSD). PTSD differs from depression in that the person must have  
9  
10  
11 101 experienced a traumatic event and experiences intense, disturbing thoughts and feelings  
12  
13 102 related to their trauma that last long after the event has ended.

14  
15  
16 103 Depression and PTSD in Kosovo have been studied more extensively in the past two decades  
17  
18 104 as a result of the scientific interest to study psychological effects following the war in the late  
19  
20  
21 105 1990s. One nationally representative study (n=1161) of persons aged 15 years or older found  
22  
23  
24 106 that 41.7% had moderate to severe depressive symptoms and 41.6% had severe anxiety,  
25  
26 107 measured by the Hopkins Symptoms Checklist (HSCL) [7]. PTSD was present in 22% of  
27  
28 108 respondents, measured by the Harvard Trauma Questionnaire, and was predictive of suicidal  
29  
30  
31 109 ideation which was measured with a suicidal ideation index created using items from the  
32  
33 110 General Health Questionnaire and HSCL [7]. Other studies, which focused on specific regions  
34  
35  
36 111 of the country or specific subgroups, found a prevalence of depression which ranged from  
37  
38 112 29.7% to 66.5% [8–11]. It is clear that depression is extremely common in Kosovo, far  
39  
40 113 exceeding the global average. Some interpret the high rates of depression as an aftermath to  
41  
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43 114 the stressful conditions following the war [12].

#### 115 **NCD prevention and control through primary healthcare**

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48  
49 116 An important way to prevent the development of NCDs is to reduce their risk factors, which is  
50  
51  
52 117 the focus of Primary Healthcare (PHC) [13]. In Kosovo, the PHC system is divided into three  
53  
54 118 tiers: Main Family Medicine Centers (MFMC), Family Medicine Centers (FMC) and Family  
55  
56 119 Medicine Ambulancias (FMA). MFMCs, which form the basis for the recruitment of the study  
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59 120 participants, are the largest facilities at the highest level of PHC, which offer more services,  
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3 121 staff, and medical equipment and therefore have a higher patient flow compared to the  
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6 122 second level FMCs and third level FMAs. The Accessible Quality Healthcare (AQH)  
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8 123 implementation project, which is funded by the Swiss Agency for Development and  
9  
10 124 Cooperation (SDC) and led by the Swiss Tropical and Public Health Institute (Swiss TPH), is  
11  
12  
13 125 one of the prominent projects in Kosovo, working within the PHC. The AQH project has been  
14  
15 126 devoted to working with local stakeholders to improve the quality of PHC in the public health  
16  
17 127 sector through a health system strengthening approach, with a focus on the prevention of  
18  
19  
20 128 NCDs. One of the AQH interventions for improvement of PHC services is the implementation  
21  
22 129 of service packages (SPs). This intervention aims to improve the quality of care by setting  
23  
24 130 standards that should be provided at PHC facilities, based on the World Health Organization  
25  
26  
27 131 (WHO) 'Packages of Essential Non-Communicable Disease (PEN) Protocols,' which have  
28  
29 132 been adapted to the Kosovo context by national experts. The SPs ensure a continuum of  
30  
31  
32 133 care with the family physician in a gatekeeper role, where patients who are at risk of  
33  
34 134 developing diabetes or hypertension, or those who have already been diagnosed are  
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36  
37 135 referred to the health educator for one-to-one motivational interviewing session to facilitate  
38  
39 136 behaviour change.

40  
41  
42 137 Behaviour change is facilitated through lifestyle medicine, which is "evidence based practice  
43  
44 138 of assisting individuals and families to adopt and sustain behaviors that can improve health  
45  
46 139 and quality of life (QoL). Healthy behaviors could greatly influence future health and well-  
47  
48 140 being, especially among patients with NCDs" [14]. In the long run, improving the health of  
49  
50 141 populations means that individuals, communities and organizations need to change their  
51  
52 142 behaviour to become healthier [15]. The principal modifiable risk factors for CVD include:  
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54 143 tobacco use, an unhealthy diet and physical inactivity (which together result in obesity),  
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57 144 hypertension, dyslipidemia and diabetes [16]. Prevention, management, or reversal of the  
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3 145 modifiable risk factors can be achieved through leading a healthier lifestyle [17]. When  
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6 146 considering the reduction of CVD risk factors, the most damaging one in terms of attributable  
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8 147 DALYs is hypertension [4]. The prevalence of hypertension is available in a few Kosovar  
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10 148 studies, but no data on hypertension control is yet available. One cross-sectional study  
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12  
13 149 (n=423, mean age 51 years) of two rural predominantly ethnic-Serb communities in Kosovo  
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15 150 found a hypertension prevalence of 42% [18]. Another cross-sectional study of primary  
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17  
18 151 healthcare users (n=1793, mean age 51 years) in the capital city of Pristina found a  
19  
20 152 prevalence of hypertension at 33.6% (39% in men and 29% in women) [19]. A third cross  
21  
22  
23 153 sectional study in 20 villages with a mixture of ethnic-Serbs and ethnic-Albanians found a  
24  
25 154 hypertension prevalence of 30.6% (mean age men =62 years, women=49 years) [20].

26  
27  
28 155 The state of other CVD risk factors is even less well known in Kosovo. Although one study  
29  
30 156 showed that 18% of older adults self-reported a diagnosis of diabetes mellitus (DM) [3], it is  
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32  
33 157 suspected that DM is highly underdiagnosed in Kosovo. For example, another population  
34  
35 158 study (n=423) conducted in 2006 assessing the prevalence of kidney disease (a positive  
36  
37  
38 159 family history for Balkan Endemic Nephropathy (BEN), mild proteinuria, alpha 1-  
39  
40 160 microglobulinuria, eGFR<60mL/min/1.73m<sup>2</sup>, anemia, low specific gravity of urine, and  
41  
42  
43 161 reduced kidney length) in adults aged 18 years and older living in 2 Serbian settlements in  
44  
45 162 the municipality of Rahovec found that 13% of participants had a previous diagnosis of  
46  
47 163 diabetes but 21% (n=89) had a pathological glycaemia finding (fasting blood glucose  
48  
49  
50 164 >6.1mmol/L) [21]. Although all residents aged 18 years and above in the 2 settlements were  
51  
52 165 eligible to participate in the study, the methodology in recruitment was not specified. Some  
53  
54  
55 166 studies on physical activity are available on Kosovar adolescents [22], but no evidence is  
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57 167 available for adults. Similarly, evidence on tobacco use in Kosovo has been focused on  
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59 168 schoolchildren and adolescents. However, a recent publication on the WHO Stepwise

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3 169 approach to surveillance (STEPS) survey conducted in 2010 results of persons aged 15 to  
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6 170 64 years (n= 6400) showed that 37% of men and 20% of women in Kosovo smoke [23]. The  
7  
8 171 prevalence increased with age until it dropped at aged 45. The results from the same STEPS  
9  
10 172 survey on physical activity, diet and cholesterol have not yet been published. The AQH  
11  
12 173 project conducted a population-based study in the 12 municipalities, with the aim to collect  
13  
14 174 primary data on project indicators for a baseline against which the impact of the project  
15  
16 175 activates will be measured. The study found that 20.6% of respondents said they smoked,  
17  
18 176 15% had ever consumed alcohol, 46% did not meet WHO recommendations on physical  
19  
20 177 activity [24]. More information is needed about the control of CVD and their risk factors for a  
21  
22 178 better understanding of where to target PHC services.  
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### 28 179 **Mental disorders and their relationship with hypertension**

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31 180 The bidirectional relationship between cardiovascular diseases such as coronary artery  
32  
33 181 disease and depression is well established [25]. In PHC, the prevention of CVD is a high  
34  
35 182 priority. Thus the relationship between depression and risk factors of CVD such as  
36  
37 183 hypertension is of great relevance for the public health sector. According to a meta-analysis  
38  
39 184 of 41 cross-sectional studies [26], the prevalence of depression in patients with hypertension  
40  
41 185 was much higher than in the general population (26.8% compared to 4.4%), suggesting that  
42  
43 186 the two are strongly connected.  
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49 187 *Mechanisms linking depression and hypertension.* Some mechanisms have been proposed to  
50  
51 188 explain how depression may cause hypertension. Firstly, people living with depression tend to  
52  
53 189 have unhealthy lifestyles which include habits such as smoking, alcohol abuse and physical  
54  
55 190 inactivity [27], all of which are risk factors for hypertension and CVD. Secondly, depression  
56  
57 191 can cause autonomic nervous system dysfunctions which activates sympathetic activities [28]  
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3 192 thereby elevating blood pressure. Insomnia and short sleep duration, which are typical  
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6 193 symptoms of some forms of depression, have been found to significantly increase the risk of  
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8 194 hypertension incidence [29,30]. Little sleep can activate the hypothalamic–pituitary–adrenal  
9  
10 195 axis, which raises blood pressure in the short term, and can lead to long term structural  
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12  
13 196 adaptation that gradually reset the cardiovascular system to operate at an elevated pressure  
14  
15 197 equilibrium. Finally, beyond its role in the etiology of hypertension and CVD, the presence of  
16  
17 198 depression may also affect the control of hypertension and CVD. Medications may play a role;  
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19  
20 199 it was found that physicians are often cautious with augmenting antihypertensive treatment in  
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22  
23 200 people with depression [31] because some antihypertensive medications have been found to  
24  
25 201 cause or worsen depression [32]. This means that depressed persons may be less likely to  
26  
27 202 receive adequate treatment from their physician for their blood pressure. In another sense,  
28  
29  
30 203 depression is a risk factor for poor adherence to antihypertensive medication [33].

31  
32  
33 204 *Evidence on depression and hypertension incidence.* According to a meta-analysis of  
34  
35 205 longitudinal studies, depression significantly increases the risk of incident hypertension (RR  
36  
37 206 1.42, 95% CI 1.09-1.86,  $p=0.009$ ) [34]. However, authors caution that the limited number of  
38  
39  
40 207 longitudinal studies available may have impacted conclusions. The inverse relationship  
41  
42 208 (hypertension as a risk factor for incident depression) was assessed in another meta-analysis,  
43  
44  
45 209 which did not find a significant association [35]. One possible explanation is that hypertension  
46  
47 210 is often asymptomatic, having less impact on quality of life and thus depression when  
48  
49  
50 211 compared to more advance stages of CVD.

51  
52  
53 212 *Evidence on depression and hypertension control.* Hypertension control occurs when a person  
54  
55 213 previously diagnosed with hypertension is able to maintain a normal level of blood pressure  
56  
57 214 over time through lifestyle changes or adhering to prescribed medication. Uncontrolled  
58  
59  
60 215 hypertension is the persistence of hypertension after diagnosis, a risk factor for CVD. Despite

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3 216 being of great relevance for secondary prevention in the public health sector, few studies have  
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6 217 assessed the effect of depression on the control of hypertension over time among hypertensive  
7  
8 218 patients. Depression was found to be positively associated with uncontrolled hypertension in  
9  
10 219 a small cross-sectional study ( $r = 0.71$ ,  $n=40$ ) [36], and a case-control study ( $RR=2.02$ ,  $n=590$ )  
11  
12 [37]. In contrast, another cross-sectional study ( $n=1300$ ) reported that among hypertensive  
13 220  
14  
15 221 persons, depression was associated with lower systolic blood pressure, however the effect  
16  
17 222 size was small ( $r=-0.083$ ) and may be related to the high prevalence of patients with heart  
18  
19 223 failure in this study, a condition which is associated with low blood pressure [38]. The  
20  
21 224 longitudinal association of depression on hypertension control is unclear. A recent longitudinal  
22  
23 225 study in Germany ( $n=1887$ ) found that after 12 years of follow-up, a history of major depressive  
24  
25 226 disorder (MDD) was not significantly associated with the time course of blood pressure in  
26  
27 227 hypertensive patients [39]. Since depressive symptoms vary over time, this study was limited  
28  
29 228 by its definition of depression (a lifetime history of depression) because conclusions about the  
30  
31 229 relative effect of short and long-term depressive symptoms could not be made. In a large  
32  
33 230 retrospective cohort study ( $n=210\ 482$ ), the authors found a significant association between  
34  
35 231 depression and uncontrolled hypertension in their secondary analysis [40], however the study  
36  
37 232 did not specify if the single score of depression was measured at the end of the cohort or at  
38  
39 233 baseline. The importance of evaluating depressive symptoms in parallel to blood pressure over  
40  
41 234 time was noted in another longitudinal study [41], which found a negative association between  
42  
43 235 change in depression score and change in blood pressure, with an effect size of  $-0.46$  for  
44  
45 236 systolic blood pressure and  $-0.20$  for diastolic blood pressure, in their linear regression  
46  
47 237 analysis. When linear regression was performed with depression as a categorical variable,  
48  
49 238 results were no longer significant. Although the cross-sectional association of depression and  
50  
51 239 blood pressure control has been postulated, there is a strong need to further evaluate this  
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53 240 relationship longitudinally in well-controlled settings.  
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3 241 Other emotional states such as anxiety and stress have overlapping symptomology with  
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6 242 depression but are distinct negative emotional states. Different mechanisms of their linkage  
7  
8 243 have been postulated, for example, anxiety and depression are thought to be maladaptive  
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10  
11 244 responses to psychological stressors, and thus in a chain of causation for hypertension. The  
12  
13 245 independent associations between anxiety and stress with hypertension have been studied.

16 246 *Evidence on anxiety and hypertension.* According to the Depression Anxiety Stress Scale  
17  
18 247 (DASS), which differentiates the three emotional states, symptoms of anxiety include  
19  
20  
21 248 autonomic arousal (heart rate increase, mouth dryness, etc.), skeletal muscle effects  
22  
23 249 (trembling), feelings of panic, faintness or being terrified for no good reason [42]. A meta-  
24  
25  
26 250 analysis which pooled 13 cross-sectional studies with 151 389 subjects found a significant  
27  
28 251 positive association between anxiety and hypertension (OR 1.40, 95% CI 1.20-1.62) [43].  
29  
30  
31 252 Although significant publication bias was detected, the OR remained significant after trim and  
32  
33 253 fill analysis (OR 1.18, 95% CO 1.02-1.37). In the same meta-analysis, eight prospective studies  
34  
35  
36 254 on baseline anxiety and incident hypertension were pooled (n=80 146) and presented a hazard  
37  
38 255 ratio by random effect model of 1.55 (95% CI 1.24-1.94) with strong heterogeneity ( $p < .001$ ,  
39  
40 256  $I^2 = 84.6\%$ ) but no publication bias was detected ( $p = .663$ ). Although there are clear  
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42  
43 257 relationships, the mechanisms for them are not yet well understood.

46 258 *Evidence on stress and hypertension.* Symptoms of stress included in the DASS are difficulty  
47  
48 259 relaxing, nervous arousal, getting easily upset or agitated, irritable/over-reactive, and  
49  
50  
51 260 impatience [42]. In a recent meta-analysis (n=5696) of 11 studies, domains of mental stress  
52  
53 261 were defined as psychological stress, anxiety/depression or work stress [44]. Two studies  
54  
55  
56 262 (n=622) looked at the association of mental stress on the risk of increased hypertension (OR  
57  
58 263 2.40, 95%CI 1.65-3.49,  $I^2 = 0\%$ ,  $p = 0.33$ ) and the other 9 studies looked at the association of  
59  
60 264 hypertension on the risk of mental stress (OR=2.69, 95%CI 2.32-3.11). The limitation of studies

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1  
2  
3 265 on stress and hypertension, as seen in the meta-analysis, are that they are few in numbers  
4  
5  
6 266 and have varying definitions of stress, which in some cases include depression and anxiety.  
7  
8 267 Therefore, more studies are needed on the relationship between stress and hypertension, with  
9  
10 268 a clear definition of stress as a distinct emotional state.

11  
12  
13  
14 269 *Mental health care in Kosovo.* In Kosovo, supporting persons with mental illness (depression  
15  
16 270 or other mental problems) is a challenge as mental health services are only available upon  
17  
18 271 referral to a specialist, which may deter persons with mental illness from seeking care as it  
19  
20 272 remains highly stigmatized in the country. Seeking professional support to address mental  
21  
22 273 health problems is associated with “tremendous shame” in the country, thus support is rarely  
23  
24 274 requested or is kept within the family circle [45]. Indeed, only 15% of people who stated they  
25  
26 275 needed help actually sought the help from a psychologist or psychiatrist due to fear of being  
27  
28 276 stigmatized [11]. If help for mental illness is sought outside the home, families often consult  
29  
30 277 with traditional healers or local religious persons instead of mental health professionals [45].  
31  
32  
33  
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35

36 278 In summary, both hypertension and depression are chronic conditions which cause a great  
37  
38 279 deal of health loss. Some evidence appears to suggest that depression is associated with an  
39  
40 280 unfavourable course of blood pressure; however additional longitudinal studies are needed to  
41  
42 281 help determine such causal relationships. Understanding potential mutual influences between  
43  
44 282 depression and hypertension could indicate the need for integrated mental health services in  
45  
46 283 primary healthcare, which has been found to be effective in another setting [46], for more  
47  
48 284 effective control of both conditions where standalone mental health services are stigmatized.  
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54 285 **Objectives of the KOSCO study**  
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3 286 The overarching goal of the KOSCO study is to contribute epidemiological evidence to the  
4  
5  
6 287 prevention and control of NCDs in Kosovo as the basis for policy and decision making, which  
7  
8 288 is currently lacking in the country. Specific objectives include  
9

10  
11 289 1. To conduct a patient-based cross-sectional survey of adults living in 12 municipalities  
12  
13  
14 290 in Kosovo to assess (a) the prevalence of NCDs and their risk factors; and (b) the  
15  
16 291 prevalence of NCD control.

17  
18 292 2. To assess the effect of primary healthcare service quality on patient satisfaction and  
19  
20  
21 293 NCD outcomes.

22  
23 294 3. To assess the longitudinal effect of primary care interventions (such as health  
24  
25  
26 295 education and service packages) in 12 Main Family Medicine Centers in Kosovo on the  
27  
28 296 course on non-communicable diseases, as well as the mediators and modifiers of the  
29  
30 297 associations.

31  
32 298 4. To assess the predictors of NCD incidence and NCD control, with a focus on the  
33  
34  
35 299 predictive association between depression and hypertension in adult primary  
36  
37 300 healthcare users living in Kosovo, as well as the mediators of the association.  
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## 41 301 **METHODS AND ANALYSIS**

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43  
44 302 This is a prospective longitudinal study of primary healthcare users in Kosovo.  
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46  
47

### 48 303 **Location**

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50  
51 304 The study is being conducted in Kosovo, which is located in the center of the Balkans and the  
52  
53  
54 305 newest independent state in Europe, albeit not accepted as such by all countries. It has a  
55  
56 306 population of 1.8 million and is divided into 38 municipalities over a surface area of nearly  
57  
58 307 11,000km<sup>2</sup>. The country has mainly rural settlements (62%), ethnic-Albanians with minorities  
59  
60 308 of Serbian and Roma, Ashkali, Egyptian (RAE) Bosnians, and Turkish ethnicities and has a

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309 male to female ratio of 1.06 [5]. MFMCs in twelve municipalities in Kosovo were selected as  
310 sites for recruitment for the purpose of this study. Participating municipalities include: Fushë  
311 Kosovë, Drenas, Gračanica, Gjakovë, Junik, Lipjan, Malishevë, Mitrovicë, Obiliq, Rahovec,  
312 Skënderaj, and Vushtrri.

### 313 **Accessible Quality Healthcare Project**

314 The current study is embedded within the AQH project and the selection of municipalities was  
315 based on the project's established stakeholder collaboration. The AQH project engaged with  
316 these municipalities based on 9 indicators (RAE population as percentage of total population,  
317 per capita public expenditure, per capita total primary healthcare financing, social welfare  
318 beneficiaries per 100 inhabitants, female lone parent as percentage of female population,  
319 doctors per 1000 inhabitants, nurses per 1000 inhabitants, total PHC visits per capita, diarrhea  
320 per 1000 inhabitants, and applying a convenience sample to ensure geographic clustering and  
321 representation of ethnic-Serbs.

322 Health systems strengthening interventions implemented by the AQH project in Kosovo are  
323 broad and complex. The interventions are focused on strengthening PHC alongside the  
324 prevention and control of NCDs. The three project outcomes are as follows: 1) PHC providers  
325 deliver quality services for NCDs to informed citizens, 2) Health managers ensure delivery of  
326 PHC services that respond to community needs, 3) The population improves its health literacy  
327 and is empowered to demand the right to quality services and better access to care.

### 328 **Study preparation**

329 *Research nurse training.* Four research nurses were hired to conduct the data collection. They  
330 participated in a 3-day training certified by the Kosovo Nursing Chamber which covered  
331 standard operating procedures to perform interviews and health assessments. One week prior

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1  
2  
3 332 to recruitment, research nurses and the field research coordinator visited all sites to meet and  
4  
5  
6 333 inform relevant staff about the study and ensure necessary on-site equipment were ready for  
7  
8 334 use. A plan of the recruitment schedule which rotated between study sites was provided to all  
9  
10 335 directors.

### 13 336 **Patient and Public Involvement**

16 337 *Public stakeholder involvement in study design.* Directors of the MFMCs were invited for  
17  
18 338 meetings to discuss the study in October 2018 and in February 2019 (5 months and again 3  
19  
20 339 weeks prior to the launch of the recruitment of participants respectively). In these meetings,  
21  
22 340 the purpose and methods of the study were presented. Stakeholder feedback on logistical  
23  
24 341 issues and health priorities in the regions were adapted into the protocol. For example,  
25  
26 342 directors of primary healthcare facilities asked to include data collection on respiratory health  
27  
28 343 since their clinical experience indicated that it was a public health concern with lacking  
29  
30 344 epidemiological evidence in the area. Considering the decentralized system, a signed  
31  
32 345 agreement with all 12 directors of the MFMCs was established for their voluntary participation  
33  
34 346 in the cohort.

37  
38 347 *Patient involvement in piloting the interview guide.* The interview guide was piloted on a  
39  
40 348 convenience sample of 9 PHC patients from the MFMC in Obiliq. The questions were adapted  
41  
42 349 according to patient feedback (for example some questions were repetitive or not culturally  
43  
44 350 appropriate). The first follow-up questionnaire was piloted on 42 cohort participants and the  
45  
46 351 questionnaire was again modified based on feedback.

### 54 352 **Recruitment**

57  
58 353 Participant recruitment began on 18 March 2019 and is expected to end in the last week of  
59  
60 354 November 2019, however, baseline data collection will continue until March 2019 as it is

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1  
2  
3 355 divided into two parts (see section on data collection for further details). Patients exiting the 12  
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5  
6 356 participating MFMCs were approached consecutively and **included** in the study if they were  
7  
8 357 aged 40 years or older and consulted healthcare services at one of the 12 MFMCs on the day  
9  
10 358 of recruitment. Persons were **excluded** from participating in the study if they had a terminal  
11  
12  
13 359 illness, were not able to understand or respond to pre-screening questions, did not live in one  
14  
15 360 of the 12 study municipalities or live abroad for more than 6 months of the year. During  
16  
17 361 recruitment, research nurses first pre-screen potential participants exiting the MFMC, then  
18  
19 362 obtain informed consent in a quiet room of the MFMC where the participant is also informed  
20  
21 363 that as a participant of the cohort, they are entitled to the following **incentives**: the co-payments  
22  
23 364 of one health consultation and associated blood tests are waived once per year, and an HbA1c  
24  
25 365 test is free of charge on the day of the in-person interview. Research nurses alternated  
26  
27 366 municipalities in their study clusters each week of recruitment (Cluster 1: Gračanica, Drenas,  
28  
29 367 Skënderaj. Cluster 2: Malishevë, Rahovec, Gjakovë, Junik. Cluster 3: Fushë Kosovë, Vushtrri,  
30  
31 368 Mitrovicë. Cluster 4: Lipjan, Obiliq). Clusters were developed based on the proximity of  
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33  
34 369 municipalities to each other and number of participants to be recruited per municipality to  
35  
36  
37 370 balance the workload of each research nurse.  
38  
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## 43 371 **Data collection**

### 44 45 46 372 *Interviews*

47  
48  
49 373 The interview guide of the cohort addresses many objectives and is therefore lengthy. To  
50  
51 374 reduce the risk of participant fatigue, the interview guide was divided into two parts, spaced by  
52  
53 375 an interval of 6 months. Part 1 of the interview will be conducted in-person at the MFMC by a  
54  
55 376 trained research nurse (approximately 30 minutes duration) and part 2 of the interview will be  
56  
57 377 conducted by telephone (approximately 20 minutes duration). Refer to **Table 1** for variables  
58  
59  
60

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378 measured in each of the two parts of baseline data collection which are grouped by theme,  
 379 and **Table 2** for a description of instruments used. Part 1 of the data collection began on 18  
 380 March 2019 and is expected to end in the last week of November 2019. Part 2 of data collection  
 381 began on 1 October 2019 and is expected to end in the first week of March 2020.

382 **Table 1.** Cohort variables measured in participant interviews and health examinations

Theme	Variables	Part 1: In-person interview	Part 2: Telephone interview
Socio-demographic 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 CVD	x	Repeat only: comorbidities, symptoms, complications of CVD
Health factors, block II	Somatic symptoms		x
Health system factors	Provider adherence to treatment protocol, healthcare utilization, patient satisfaction with services	x	Repeat only: provider adherence to protocol, healthcare utilization
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	

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383 *Data collection is divided into two parts: in-person interviews with health examination (part 1) and*  
 384 *telephone interviews (part 2). Variables assessed are grouped by theme, and timing of their*  
 385 *assessment (either in part 1 or 2) is indicated with an “x” or with comments.*

386 **Table 2.** Validated instruments used in interviews

Theme	Questionnaire	Description
Socio-demographic factors	None	
Social and environmental factors	Modified Medical Outcome Survey Social Support Scale (mMOS-SSS)	The modified Medical Outcome Study-Social Support Scale (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 [1].
Health factors, part I	self-report generated Charlson Comorbidity Index (SRG-CCI)	The self-report generated Charlson Comorbidity Index (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 [2]. 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)	Rose Angina Questionnaire (RAQ) was developed to detect ischemic heart pain (angina pectoris and myocardial infarction) for epidemiological field-surveys [3]. 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 European Community Respiratory Health Survey II (ECRHS II) Main questionnaire was included to assess respiratory symptoms. Items assess presence of wheezing, tightness in chest, shortness of breath, cough and phlegm with binary responses [4].
	Medical Research Council (MRC) Dyspnea Scale	The Medical Research Council (MRC) Dyspnea Scale was developed to categorize the level of disability in Chronic Obstructive Pulmonary Disease (COPD) [5]. The scale has one item with 5 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)	Patient Health Questionnaire (PHQ 15) is a 15-item somatic symptom scale which measures the severity of somatization in patients [6]. 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 to 30 and classified as minimal (0-4); mild (5-9); moderate (10-14) and high (15-30) severity of somatic symptoms.
Health system factors	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 co-operation, and accessibility [7]. All items are aggregated into two dimensions: clinical behaviour (items 1-16) and organization of care (items 17-23). Responses are rated on a 5 point Likert scale 1 (poor) to 5 (excellent).
Lifestyle behaviour, part I	None	
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 5 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 [8].
	Smoking Abstinence Self-Efficacy Questionnaire (SASEQ)	Smoking Abstinence Self-Efficacy Questionnaire (SASEQ) has 6 items with statements of various situations where a one might be tempted to smoke and asks for the participant's confidence level that they will not smoke [9]. Response options are on a 5-point Likert scale ranging from certainly (4) to certainly not (0).
	Health-Specific Self-Efficacy Scales (HSSES)	The Health-Specific Self-Efficacy Scales (HSSES) assesses a person's optimistic self-belief about being capable to resist temptations and to adopt a healthy lifestyle [10]. 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 (5 items), physical exercise (5 items) and alcohol consumption (3 items). Response options range on a 4-point Likert scale from (1) very uncertain to (4) very certain.
	Short Form Health Survey version 2 (SF12v2)	The Short Form Health Survey version 2 (SF12v2) is a 12-item questionnaire which measures health-related quality of life. 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 4 through 7 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 through 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 (PCS & MCS) using a norm based method and transformed to each have a mean of 50. The total score ranges from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health [11].
Psychological factors, part I	Depression, Anxiety, Stress Scale (DASS-21)	Depression, anxiety and stress were measured using the Depression, Anxiety Stress Scale-21 (DASS-21) [12,13], a 21-item questionnaire consisting of three subscales, each containing 7 items scored on a four-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much). The scores are classified as; depression 0-4 (normal), 5-10 (mild to moderate), >11 (severe to very severe); anxiety 0-3 (normal), 4-7 (mild to moderate), >8 (severe to very severe); stress 0-7 (normal); 8-12 (mild to moderate), >13 (severe to very severe).
	Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)	Primary Care PTSD Screen for DSM-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; $\leq 2$ (improbable PTSD) and $\geq 3$ (probably PTSD) [14].
	Resilience Scale (RS-14)	Resilience Scale (RS-14) is a 14-item questionnaire that assesses individual resilience in a general population [15]. Items are scored on a 7 point Likert scale from 1 (strongly disagree) to 7 (strongly agree). Scores are categorized 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).
	Self-esteem (SE)	Self-esteem (SE) is a 1-item scale developed as an alternative to the Rosenberg self-esteem scale [16]. It is measured on a 7 point Likert scale from 1 (not true of me) to 7 (very true of me).
Psychological factors, part II	None	
Health examination		

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

390 *Physical examination*

391 Immediately following interview - part 1, the research nurse performs a brief health examination  
 392 of about 10 minutes. Height and weight are measured using stadiometers and scales which  
 393 are available at the MFMCs (various brands). The precision of scales are assessed regularly  
 394 with a weight of 10 kilograms. Circumferences of the waist, hip and neck are measured using  
 395 the SECA 201 measuring tape (Seca GmbH & Co. KG., Switzerland). Peak expiratory flow is  
 396 measured 3 times with 30 seconds pause between attempts, using the OMRON Peak Flow  
 397 Meter PFM20 (Omron Healthcare, Switzerland). Systolic and diastolic blood pressure are  
 398 measured three times, at least 3 minutes apart, after sitting quietly for about 10 minutes, using  
 399 an M3 model Omron blood pressure monitor (Omron Healthcare, Switzerland). The research  
 400 nurses place the blood pressure cuff 2 centimeters above the elbow on the bare left upper arm  
 401 (in the case of arteriovenous fistula, radiotherapy or removal of lymph nodes in the armpit of  
 402 the left arm, the right arm is used) of the seated participant and elevates the arm on the table  
 403 to the level of the fourth intercostal space. Towards the end of the battery of tests, the research



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2  
3 404 nurse then accompanies participants to the laboratory of the MFMC for a finger-prick (non-  
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5  
6 405 invasive) glycated haemoglobin test (HbA1c). The HbA1c test is performed by a staffed  
7  
8 406 laboratory technician who received training by the supplier on how to use the SUPER ID  
9  
10 407 clinchem device (Dr. Müller Gerätebau GmbH, Germany). Participants are then given a self-  
11  
12  
13 408 care passport, which was developed by local experts in collaboration with the AQH project.  
14  
15 409 The research nurses transcribe the participants' health examination results in the passport  
16  
17 410 which also has additional space for participants to write blood pressure or blood glucose  
18  
19 411 measurements taken at home. Participants are instructed that they will be re-contacted in 6  
20  
21  
22 412 months for a telephone interview.  
23  
24  
25

#### 26 413 *Follow-up interval*

27  
28  
29 414 Each full round of data collection lasts 12 months, with two participant contacts per year,  
30  
31 415 spaced by 6 months. Baseline data collection part 1 began in March 2019 and part 2 began in  
32  
33 416 October 2019. The second round of data collection (follow-up) is expected to start in March  
34  
35  
36 417 2020.  
37  
38  
39

#### 40 418 *Non-participants*

41  
42  
43 419 Non-participants (patients approached who decline to participate or who do not meet inclusion  
44  
45 420 criteria) were asked 9 optional questions with the purpose to understand if participants differ  
46  
47 421 from non-responders. The optional questions provide information on sex, age, education level,  
48  
49 422 diagnosis of diabetes, lung disease, cardiovascular disease, smoking status, weight, level of  
50  
51 423 satisfaction with PHC services and reason for non-participation.  
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#### 56 424 **Data Management**

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3 425 Data from in-person and telephone interviews were collected using Open Data Kit (ODK)  
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5  
6 426 software. Results from health examinations were also entered into ODK. Data quality was  
7  
8 427 assured through (1) formulation of standard operating procedures for all aspects of the study,  
9  
10 428 (2) extensive and careful training of the study team according to the standard operating  
11  
12  
13 429 procedures, (3) onsite supervision of field activities ensuring adherence to protocol, and (4)  
14  
15 430 regular monitoring and internal evaluation of data entry during the field visits. The ODK and  
16  
17  
18 431 STATA programs will keep track of all changes made to the data. All data will be merged into  
19  
20 432 a single database at the end of data entry using STATA version 15.1 (STATA Corporation).  
21  
22

### 23 433 **Power calculation without local effects**

24  
25  
26  
27 434 The following is a power calculation for the study of the association of blood pressure with  
28  
29 435 depression in the case of a single homogenous population with the prevalence of depression  
30  
31 436  $d=40\%$ . We denote the cross-sectional effect size of depression on blood pressure relative to  
32  
33  
34 437 the population standard deviation as  $\tau$ . For  $\tau=0.4$ , which under the normal distribution  
35  
36  
37 438 assumption corresponds to the shift from the median to the 66<sup>th</sup> percentile, we obtain the  
38  
39 439 sample sizes of 208 and 278 patients for the power of 80% and 90%, respectively. For a  
40  
41 440 smaller effect  $\tau=0.25$  (shift to the 60<sup>th</sup> percentile), the corresponding samples are 528 and  
42  
43  
44 441 706 people. For the longitudinal study, the calculation is identical but this time  $\tau$  stands for  
45  
46 442 the relative effect of the depression at baseline on the change of blood pressure at follow-up.  
47  
48  
49 443 Assuming a 20% loss to follow-up, we arrive at the minimal cohort size of 883 people for 90%  
50  
51 444 power in the case of the small effect  $\tau=0.25$ . The control for confounding variables will lead  
52  
53  
54 445 to a reduction of power, as will the discretisation of the blood pressure measurement to study  
55  
56 446 hypertension as a binary outcome, and so we aim to recruit a total of 1000 patients into the  
57  
58 447 cohort. The number of participants to be recruited by MFMC was proportional to the mean of  
59  
60 448 proportions using the number of medical visits in the month of June 2018 and October 2018.

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3 449 **Power in the presence of clustering**  
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6  
7 450 To take into account the potential local variation in the effect of depression on blood pressure,  
8  
9 451 we performed explicit simulations to make sure that the study has sufficient power under a  
10  
11 452 range of plausible scenarios. Specifically, we posited that the mean blood pressure can vary  
12  
13 453 between the 12 municipalities (random effect with variance  $\sigma^2$ ), and also that the effect  
14  
15 454 of depression on blood pressure can be different in each municipality (random effect with  
16  
17 455 variance  $\rho^2$ ). The magnitudes  $\sigma$  and  $\rho$  of these local effects were tunable parameters  
18  
19 456 of the simulation, as was the overall effect size  $\tau$ . Preliminary analyses showed that the  
20  
21 457 power of the study is driven by the relationship of  $\tau$  and  $\rho$ , and is not sensitive to  $\sigma$ ;  
22  
23 458 this is because the municipality-level effect affects depressed and non-depressed people  
24  
25 459 equally. Thus we fixed  $\sigma=\tau$  in what follows.  
26  
27  
28  
29  
30

31  
32 460 For 18 combinations of plausible values of  $\tau$  and  $\rho$ , we simulated normal data on 800  
33  
34 461 participants (i.e. the target cohort size minus 20% loss to follow-up) 10'000 times and  
35  
36 462 computed the fraction of instances when the mixed regression model fitted on this synthetic  
37  
38 463 data reported depression as a significant factor. This fraction can be interpreted as the  
39  
40 464 statistical power of the study for the given  $\tau$  and  $\rho$ . The results of the simulations are  
41  
42 465 reported in table 3 below (rounded down to the nearest percent). We found that the study  
43  
44 466 retains sufficient power for as long as the overall effect of depression dominates the local  
45  
46 467 variation in that effect (that is  $\tau$  is much greater than  $\rho$ ), which is likely. This requirement is  
47  
48 468 progressively relaxed as the overall effect size grows.  
49  
50  
51  
52  
53

54 469 The simulations did not take into account the loss of power due to adjustment for  
55  
56 470 confounders.  
57  
58  
59

60 471 **Table 3.** Simulation of statistical power

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	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%

472

### 473 **Statistical Analysis Plan**

474 The statistical analysis plan is provided for the example of the association between depression  
 475 and blood pressure control. Given the fact that the data collected serves to address multiple  
 476 objectives it is not possible to describe statistical analyses towards all of these objectives, but  
 477 the principles remain the same. Figure 1 provides an overview of associations under study.

### 478 **Figure 1.** Hypothesized associations between variables

#### 479 *Descriptive statistics*

480 Categorical variables will be presented as numbers and percentages. Normally distributed  
 481 quantitative variables will be presented as mean and standard deviation. Other quantitative  
 482 variables will be presented as medians and interquartile ranges. Chi-squared tests, t-tests and  
 483 Wilcoxon rank-sum tests will be used for bivariate analysis where appropriate.

#### 484 *Cross sectional analysis*

485 The main outcome for these analyses is considered to be hypertension. We will use an  
 486 explanatory model with a focus on depression among predictor variables. The cross sectional  
 487 association of depression with dichotomous, polytomous or continuous health outcomes will  
 488 be investigated using regression models, adjusting for health center (fixed effect) as well as a

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2  
3 489 set of covariates identified a priori as potential confounders. Covariates systematically  
4  
5  
6 490 considered as confounders as well as effect modifiers in all models will be sex, age,  
7  
8 491 urban/rural, ethnicity, education level and employment status. Additional covariates considered  
9  
10 492 in some models as either confounders, effect modifiers or mediators include: *smoking, alcohol,*  
11  
12 493 *physical activity, obesity, family history, anxiety, stress, resilience, social support, self-esteem,*  
13  
14 494 *health literacy, healthcare seeking, patient satisfaction, comorbidity, sleep quality and duration,*  
15  
16 495 *and medication.*

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20  
21 496 *Longitudinal analyses*  
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24 497 Two approaches will be explored to assess the longitudinal association between depression  
25  
26 498 and the course of blood pressure.  
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29

- 30 499 1. Predictive perspective: A regression model will be constructed with the outcome of  
31  
32 500 **change in blood pressure from baseline (continuous)**. Baseline blood pressure will be  
33  
34 501 adjusted for by including it as a covariate in the model. This model will allow predicting  
35  
36 502 the future course of blood pressure, based on a set of variables observed at baseline.  
37  
38 503 This model is of value for a provider perspective: based on what the provider observes  
39  
40 504 at a specific point in time, what is the predicted course of blood pressure?  
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43  
44 505 2. Change perspective: The effect of **change in depression** (predictor) on **change in blood**  
45  
46 506 **pressure** (outcome) will be assessed with a repeated measures model. This model will  
47  
48 507 allow assessing the parallel change in depression and blood pressure and in that sense  
49  
50 508 takes cross-sectional short-term associations at baseline and follow-up into  
51  
52 509 consideration.  
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57 510 The same covariates considered in the cross-sectional analysis will be considered in the  
58  
59 511 longitudinal analysis models.  
60

## 512 STRENGTHS AND LIMITATIONS

513 Given the limited evidence on NCDs in Kosovo, the cohort is of great benefit for healthcare  
514 decision makers which rely on health data. Results from this cohort study will provide an overall  
515 insight into the relationship between NCDs and their determinants through study objective 1.  
516 Considering that this study is assessing the long-term effect of PHC interventions (such as  
517 delivery of motivational counselling sessions for behavior change) in study objective 2, the  
518 scientific findings of this study can be applied in designing targeted behaviour change  
519 interventions. Behaviours affect morbidity, and extremely unhealthy behaviours may lead to  
520 mortality, therefore understanding what causes patients to do certain behaviours and what  
521 motivates them to change (in study objective 3), provides information which could be useful  
522 for populations with similar characteristics [14]. Further, understanding potential mutual  
523 influences between depression and hypertension could indicate the need for integrated mental  
524 health services in primary healthcare for more effective control of both conditions [46], and will  
525 be addressed through objective 4.

526 Embedding this cohort in an existing local implementation project, namely AQH which builds  
527 on strong partnerships with local stakeholders, has greatly increased the ease of  
528 implementation and acceptability of this study. For example, the study population is living in  
529 mostly rural areas, with high levels of poverty and low levels of education which means that  
530 there was little awareness of research and their benefits. Being embedded within the AQH  
531 project, which has established trust with municipalities, has helped in the recruitment process.  
532 Further, given that the healthcare system is decentralized, getting directors of MFMCs from  
533 multiple municipalities on board to participate in the cohort study would normally be a long and  
534 complicated process, but was simplified since the directors have a longstanding relationship  
535 with the AQH project.

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3 536 A pilot of the questionnaire with 9 primary healthcare users aged 40 years and above  
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6 537 conducted in March 2019 and in the MFMC of Obiliq and again in October 2019 with 42 cohort  
7  
8 538 participants from various municipalities served to identify the understanding and flow of  
9  
10 539 questions. Some questions were identified as inappropriate or irrelevant in the cultural context  
11  
12  
13 540 and were omitted. For example, the original PC-PTSD-5 questionnaire lists sexual abuse as  
14  
15 541 an example of a traumatic event and this was considered offensive by one person in the pilot  
16  
17 542 survey. Thus the example was removed. One question asked if the participant has ever been  
18  
19 543 diagnosed with a mental disorder by a physician. Local research nurses unanimously stated  
20  
21 544 that this question was highly offensive and was therefore removed from part 1 of the baseline  
22  
23 545 data collection (initial contact with participants) and moved to part 2 to allow participants time  
24  
25 546 to grow trust with research nurses. The PHQ asks questions about menstruation pain during  
26  
27 547 intercourse, which were considered offensive to ask in an interview and a disclaimer statement  
28  
29 548 was added before the items to preface the question. A question in the EUROPEP which  
30  
31 549 assesses satisfaction with "Getting through to the practice on telephone" was removed as it is  
32  
33 550 not common practice in Kosovo. Given that the average level of education in Kosovo's older  
34  
35 551 population is of primary school or lower, some instruments' questions were abstract and  
36  
37 552 difficult to understand by participants. In particular, respondents of the pilot survey noted that  
38  
39 553 multiple questions in the Resilience Survey (RS-14) were difficult to understand, such as "I am  
40  
41 554 friends with myself" which was considered a Western ideal and "I keep interested in things"  
42  
43 555 often yielded participant questions like "what things?" A debriefing with research nurses  
44  
45 556 ensured that these questions were clarified with participants in a uniform way. It was confirmed  
46  
47 557 through the pilot that the questionnaire was too lengthy, demonstrated by participants asking  
48  
49 558 to end the interview before the end. It was decided to separate questions into two parts, asked  
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51 559 with an interval of 6 months.  
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3 560 During the preparation period which involved site visits before the launch of recruitment, the  
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6 561 first author learned that lab hours were shorter than anticipated, which limited the amount of  
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8 562 hours of recruitment (from 7:00 to 13:00). This meant that the original estimated recruitment  
9  
10 563 timeline was extended from 3 months to 8 months. Further, participation rates were low, which  
11  
12  
13 564 extended recruitment time.

14  
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16 565 Due to the recruitment scheme in PHC facilities, the study is not population-based. Thus the  
17  
18 566 study is limited in its generalizability as well as it may overestimate the prevalence of health  
19  
20 567 conditions. However, patients visit MFMCs for an array of conditions as well as for general  
21  
22 568 check-ups, thus healthy persons are also included in the study. Providing participants  
23  
24 569 incentives with free health consultations may bias towards participation of persons with chronic  
25  
26 570 conditions, and thus may also overestimate the prevalence of NCDs and their determinants.  
27  
28 571 The relevance of the study, in the absence of being entirely representative for Kosovo as  
29  
30 572 whole, lies in the longitudinal design; furthermore it evaluates care and its perception and  
31  
32 573 utilization in a large number of relevant health service infrastructures. The findings will  
33  
34 574 therefore be relevant and guiding for other similar structures in the country.  
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## 41 575 **ETHICS AND DISSEMINATION**

### 42 43 44 576 **Ethics approval and Consent to Participate**

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46  
47  
48 577 Ethical approvals for the study were obtained from Ethics Committee Northwest and Central  
49  
50 578 Switzerland (Reference number 2018-00994) obtained 11 December 2018 and the Kosovo  
51  
52 579 Doctors Chamber (Reference number 11/2019) obtained on 30 January 2019 and expiring on  
53  
54 580 31 December 2023. Before any data is collected, participants are asked for their verbal and  
55  
56 581 written consent. To obtain consent, participants are informed that a) their participation is  
57  
58  
59 582 voluntary, b) they can withdraw from participation at any time, and c) non-participation will not



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1  
2  
3 583 have any negative effects. The participants were asked for additional consent whether, in the  
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5  
6 584 case a previously unrecognised medical problem is detected, they approve that qualified staff  
7  
8 585 or the research team will inform them of the results and provide advice on what the participant  
9  
10 586 should do next. Standard Operating Procedures (SOP) developed by the study team and  
11  
12  
13 587 approved by MFMC directors (who are physicians), were provided to research nurses to guide  
14  
15 588 them in referring participants to appropriate care. Severe findings (systolic blood pressure  
16  
17 589  $\geq 180$ mmHg and diastolic blood pressure  $\geq 110$ ) were referred immediately to emergency  
18  
19  
20 590 services in the MFMC. Participants were informed how the data will be used and that  
21  
22 591 confidentiality is ensured as their data will be coded. Potential risks and benefits of participation  
23  
24  
25 592 were also discussed with participants, and ample time was given to ask questions. Once  
26  
27 593 consent was obtained, the research nurse proceeded to data collection.

#### 30 31 594 **Data Protection**

32  
33  
34 595 Data entry is done using a tablet (Samsung Galaxy Tab A, Samsung Group, Switzerland),  
35  
36 596 where data is sent to a server and erased from tablets daily. Only participant identifiers, but  
37  
38  
39 597 not names of the participants will be included in electronic health databases. HbA1c results  
40  
41 598 are recorded in laboratories as per facility protocol with participant name, but not participant  
42  
43  
44 599 ID. Consent forms are kept in a locked file cabinet in Pristina, with restricted access to project  
45  
46 600 personnel. Each participant has a code which is linked to their personal identifying data (PID)  
47  
48  
49 601 and a code linked to the study data (DID). The participant identifying information with PID is  
50  
51 602 kept in one document stored by the Deputy Team Leader of the AQH project in Pristina,  
52  
53 603 Kosovo. The DID, study data, and key which links PID and DID are kept in a password  
54  
55  
56 604 protected document with the principal investigator (NPH) in Basel, Switzerland.

#### 57 58 59 605 **Data sharing** 60

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606 The datasets will be available from the corresponding author on reasonable request.

## 607 **Collaboration**

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

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

## 614 **DECLARATIONS**

### 615 **Competing Interests**

616 Mrs. Obas, Mrs. Bytyci-Katanolli, and Dr. Ramadani, reports personal fees from Swiss Agency for Development  
617 and Cooperation (SDC), during the conduct of the study;

618 Mrs. Bytyci-Katanolli reports grants from Swiss Confederation, during the conduct of the study.

619 The remaining authors declare that they have no competing interests.

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622 first year of salary for the doctoral studies of KO and the implementation and running costs of  
623 the cohort were funded by SDC, which is an agency in the federal administration of Switzerland  
624 and part of the Federal Department of Foreign Affairs, whom are responsible for coordinating  
625 Swiss international development projects in Eastern Europe. They are the core funders of the  
626 AQH implementation project in which the cohort is embedded. Local SDC representatives were

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627 responsible for approving the cohort budget and the study proposal. SDC contributed to the  
628 direction of study objectives.

629 The Swiss Tropical and Public Health Institute (Swiss TPH) has internally funded the salary of  
630 KO in the second and third years of the doctoral studies. Co-authors associated with Swiss  
631 TPH include KO, JG, ABK, MZ and NPH and contributed to the study in various capacities,  
632 specified in authors' contributions declaration.

633 The Swiss Government Excellence Scholarship for Foreign Scholars and Artists was awarded  
634 to Ariana Bytyci-Katanolli for the time period of 2019-2022 (Reference number 2019.0234),  
635 which will fund her doctoral studies salary.

#### 636 **Authors' contributions**

637 **KO** –co-developed and implemented the study protocol, coordinated and supervised data  
638 collection, will analyze and interpret data.

639 **NJ** contributed to study objectives related to non-communicable diseases in Kosovo

640 **SS** contributed to study objectives related to mental health in Kosovo

641 **MK** conducted statistical power calculations and will supervise data analysis

642 **MZ, QR, ABK, and JG** contributed to the study objectives related to the evaluation of health  
643 service provision and to the integration of the study protocol within the AQH framework.

644 **NPH** developed the KOSCO cohort concept, study objectives, and protocol, directed the  
645 implementation, data analysis and result interpretation.

646 All authors read and approved the final protocol.

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 654 (Mitrovica), Dr. Haki Jashari (Obiliq), Dr. Jusuf Korenica (Rahovec) , Dr. Fazli Kadriu  
 655 (Skenderaj), Dr. Luljeta Zahiti-Preteni (Vushtrri). The KOSCO research nurses were  
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 657 Igrishta, Selvete Zyberaj, Shqipe Agushi and Alma Stojanović.

## 658 **List of Abbreviations**

659	AQH	Accessible Quality Healthcare Project
660	BEN	Balkan Endemic Nephropathy
661	CVD	Cardiovascular Disease
662	DALY	Disability Adjusted Life-Years
663	DASS	Depression Anxiety Stress Syndrome
664	DM	Diabetes Mellitus
665	FMA	Family Medicine Ambulantas
666	FMC	Family Medicine Center
667	HbA1c	glycosylated haemoglobin
668	HSCL	Hopkins Symptoms Checklist
669	KOSCO	Kosovo Non-Communicable Disease Cohort

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1			
2			
3	670	MDD	Major Depressive Disorder
4			
5			
6	671	MFMC	Main Family Medicine Center
7			
8			
9	672	NCD	Non-communicable diseases
10			
11	673	NIPH	National Institute of Public Health
12			
13			
14	674	ODK	Open Data Kit
15			
16	675	PEN	Packages of Essential Non-Communicable Disease Protocols
17			
18			
19	676	PHC	Primary Healthcare
20			
21			
22	677	PTSD	Post-Traumatic Stress Disorder
23			
24	678	QoL	Quality of Life
25			
26			
27	679	RAE	Roma, Ashkali, Egyptian ethnicity
28			
29			
30	680	SDC	Swiss Agency for Development and Cooperation
31			
32	681	SOP	Standard Operating Procedures
33			
34			
35	682	SPs	Service Packages
36			
37	683	STEPS	Stepwise approach to surveillance survey
38			
39			
40	684	Swiss TPH	Swiss Topical and Public Health Institute
41			
42	685	UP	University of Prishtina
43			
44			
45	686	WHO	World Health Organization
46			

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58 857 **SUPPLEMENTARY FILE**  
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858 **Figure 1**

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3 859 Title: Hypothesized associations between variables under study  
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7 860 Legend: The hypothesized associations between outcome variables on the right, predictor  
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9 861 variables on the left and mediating variables in the middle are represented in the figure.  
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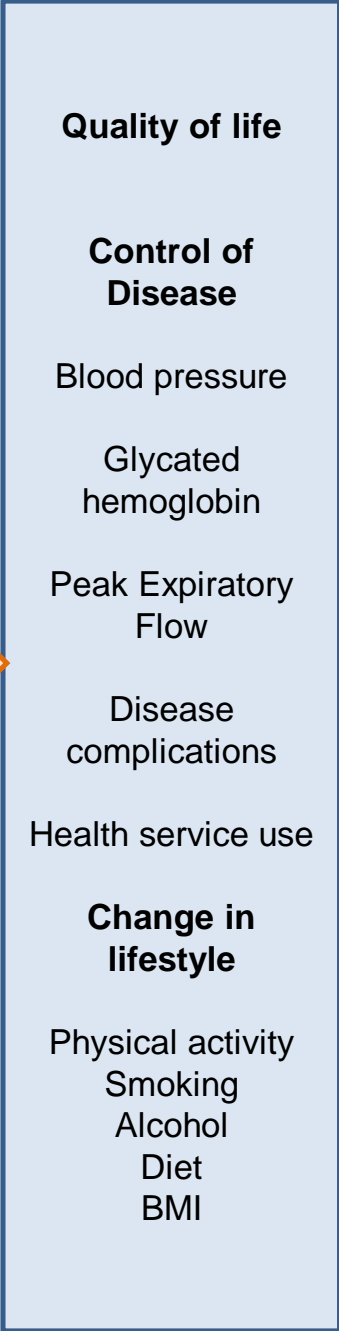
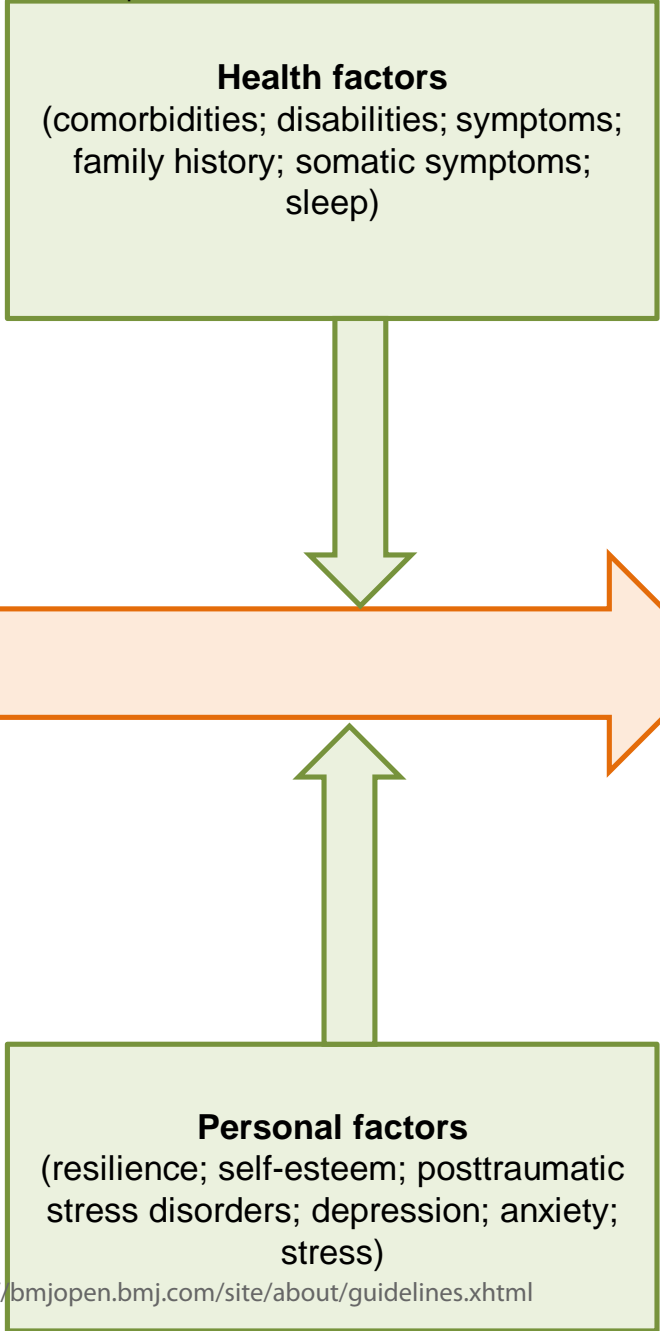
11 862 Sociodemographic factors, social and environmental factors, health literacy and self-care, as  
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14 863 well as health system factors are thought to impact the outcome of quality of life, the control  
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16 864 of chronic diseases and lifestyle change, and mediated by personal and health factors.  
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# BMJ Open

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

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

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## 30 **ABSTRACT 248/300**

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

37 **Methods and Analysis:** Primary healthcare users aged 40 years and above were recruited consecutively  
38 between March and October 2019 from 12 Main Family Medicine Centers across Kosovo. The data  
39 collected through interviews and health examinations included: socio-demographic characteristics,  
40 social and environmental factors, comorbidities, health system, lifestyle, psychological factors, and  
41 clinical attributes (blood pressure, height, weight, waist/hip/neck circumferences, peak expiratory flow  
42 and HbA1c measurements). Cohort data were collected annually in two phases, approximately 6 months  
43 apart, with an expected total follow-up time of 5 years.

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

50 **Registration:** not applicable

## 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 52 • As the first prospective cohort covering different areas of Kosovo, the study will provide  
53 important evidence on the course of non-communicable diseases in a country with limited  
54 epidemiological evidence.
- 55 • The longitudinal study design will allow us to observe changes in non-communicable diseases  
56 and their determinants over time in individuals and analyze the temporal sequence of changes,  
57 thus providing stronger evidence in investigating causal relationships, for example between  
58 depression and hypertension. Further, annual follow-ups during a 5 year cohort allows for  
59 potential mediation analysis.
- 60 • This study will evaluate the longitudinal association between non-experimental primary  
61 healthcare interventions and the course of non-communicable diseases. Study results can be

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62 immediately applied in designing or adapting existing targeted behaviour change interventions  
63 by healthcare stakeholders.

- 64 • This study is not population-based due to the recruitment scheme in primary healthcare  
65 facilities, which limits its generalizability and may overestimate the prevalence of health  
66 conditions, however healthy persons are included in the study because primary healthcare  
67 patients visit centers for an array of conditions including general check-ups.

## 68 INTRODUCTION

### 69 Burden of non-communicable diseases in Kosovo

70 The burden of disease in the Balkan region falls heaviest on Kosovo, suggested by a life expectancy of  
71 72 [1], which is lower than neighbouring countries such as Albania (78 years), Montenegro (77 years),  
72 Macedonia (76 years), and Serbia (76 years) [1]. It is a challenge, however, to get a better understanding  
73 of the main culprits of Kosovo's disease burden due in part to limited epidemiological evidence given  
74 the country's health information system is still in its initial developmental phase [2].

75 Although it is well known that non-communicable diseases (NCDs) are the greatest contributor to health  
76 loss in the world, accounting for 61% (or 1.5 billion) of Disability Adjusted Life-Years (DALY), only  
77 a few estimates on NCDs in Kosovo are available. A national population-based study conducted in 2010  
78 in Kosovo of adults over the age of 65 (n=1890) indicated that the most common self-reported NCDs  
79 were cardiovascular diseases (CVDs), with a prevalence of 63%, followed by stomach and liver disease  
80 (21%), then diabetes mellitus (DM) (18%) [3].

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

88 Although CVDs are the principal causes of death worldwide, mental disorders are now among the  
89 leading causes of disability [4]. Among mental disorders, depression is the most common with over 300  
90 million prevalent cases worldwide (4.4% global prevalence) [6]. Depression results from a complex  
91 interaction of social, psychological and biological factors and is characterized by persistent sadness, loss  
92 of interest in activities a person normally enjoys, and inability to carry out daily activities. People who  
93 have gone through adverse life events (unemployment, bereavement, psychological trauma) are more  
94 likely to develop depression as well as post-traumatic stress disorder (PTSD). PTSD differs from



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95 depression in that the person must have experienced a traumatic event and experiences intense,  
96 disturbing thoughts and feelings related to their trauma that last long after the event has ended.

97 Depression and PTSD in Kosovo have been studied more extensively in the past two decades as a result  
98 of the scientific interest to study psychological effects following the war in the late 1990s. One nationally  
99 representative study (n=1161) of persons aged 15 years or older found that 41.7% had moderate to severe  
100 depressive symptoms and 41.6% had severe anxiety, measured by the Hopkins Symptoms Checklist  
101 (HSCL) [7]. PTSD was present in 22% of respondents, measured by the Harvard Trauma Questionnaire,  
102 and was predictive of suicidal ideation which was measured with a suicidal ideation index created using  
103 items from the General Health Questionnaire and HSCL [7]. Other studies, which focused on specific  
104 regions of the country or specific subgroups, found a prevalence of depression which ranged from 29.7%  
105 to 66.5% [8–11]. It is clear that depression is common in Kosovo, far exceeding the global average.  
106 Some interpret the high rates of depression as an aftermath to the stressful conditions following the war  
107 [12].

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

#### 110 **NCD prevention and control in Kosovo**

111 Primary Healthcare (PHC) plays a key role in the prevention and control of CVDs and other NCDs [13].  
112 Primary prevention includes interventions which avert the occurrence of disease, whereas secondary  
113 prevention includes interventions which stop or slow the progression of disease once it has started [14].  
114 Many PHC interventions aim to reduce common risk factors of NCDs, such as smoking, physical  
115 inactivity, and poor diet, in both healthy people and patients with NCDs. In Kosovo, the PHC system is  
116 divided into three tiers: Each municipality has one Main Family Medicine Center (MFMC), several  
117 Family Medicine Centers (FMC) and several Family Medicine Ambulantas (FMA). MFMCs, which  
118 formed the basis for the recruitment of the study participants, are the largest facilities at the highest level  
119 of PHC, which offer more services, staff, and medical equipment and therefore have a higher patient  
120 flow compared to the second level FMCs and third level FMAs.

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

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129 population improves its health literacy and is empowered to demand the right to quality services and  
130 better access to care.

131 Health systems strengthening interventions implemented by the AQH project in Kosovo are broad and  
132 complex. One of the AQH interventions for improvement of PHC services is the implementation of  
133 service packages (SPs). This intervention aims to improve the quality of care by setting standards that  
134 should be provided at PHC facilities, based on the World Health Organization (WHO) ‘Packages of  
135 Essential Non-Communicable Disease (PEN) Protocols,’ [15] which have been adapted to the Kosovo  
136 context by national experts. The SPs ensure a continuum of care with the family physician in a  
137 gatekeeper role, where patients who are at risk of developing diabetes or hypertension, or those who  
138 have already been diagnosed are referred to a health educator for one-to-one motivational counselling  
139 sessions to facilitate behaviour change. Behaviour change is facilitated through lifestyle medicine,  
140 which is “evidence based practice of assisting individuals and families to adopt and sustain behaviors  
141 that can improve health and quality of life (QoL). Healthy behaviours could greatly influence future  
142 health and well-being, especially among patients with NCDs” [16]. In the long run, improving the health  
143 of populations means that individuals, communities and organizations need to change their behaviour  
144 to become healthier [17]. The principal modifiable risk factors for CVDs and other NCDs include:  
145 tobacco use, an unhealthy diet and physical inactivity (which together result in obesity), hypertension,  
146 dyslipidemia and diabetes [18]. Prevention, management, or reversal of the modifiable risk factors can  
147 be achieved through leading a healthier lifestyle [19].

148 When considering the reduction of CVDs, the most damaging risk factor in terms of attributable DALYs  
149 is hypertension [4]. Hypertension is defined as blood pressure of above 140/90mmHg according to the  
150 European Society of Cardiology [20]. The prevalence of hypertension is available in a few Kosovar  
151 studies, but no data on hypertension control is yet available. One cross-sectional study (n=423, mean  
152 age 51 years) of two rural predominantly ethnic-Serb communities in Kosovo found a hypertension  
153 prevalence of 42% [21]. Another cross-sectional study of primary healthcare users (n=1793, mean age  
154 51 years) in the capital city of Pristina found a prevalence of hypertension at 33.6% (39% in men and  
155 29% in women) [22]. A third cross sectional study in 20 villages with a mixture of ethnic-Serbs and  
156 ethnic-Albanians found a hypertension prevalence of 30.6% (mean age men =62 years, women=49  
157 years) [23].

158 The state of other risk factors for CVDs in Kosovo is even less well known. Although one study showed  
159 that 18% of older adults self-reported a diagnosis of diabetes mellitus (DM) [3], it is suspected that DM  
160 is highly underdiagnosed in Kosovo, indicating a large diagnostic gap. For example, another population  
161 study (n=423) conducted in 2006 assessing the prevalence of kidney disease (a positive family history  
162 for Balkan Endemic Nephropathy (BEN), mild proteinuria, alpha 1-microglobulinuria,  
163 eGFR<60mL/min/1.73m<sup>2</sup>, anemia, low specific gravity of urine, and reduced kidney length) in adults

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3 164 aged 18 years and older living in 2 Serbian settlements in the municipality of Rahovec found that 13%  
4 165 of participants had a previous diagnosis of diabetes but 21% (n=89) still had a pathological glycaemia  
5 166 finding (fasting blood glucose >6.1mmol/L) [24]. Although all residents aged 18 years and above in the  
6 167 2 settlements were eligible to participate in the study, the methodology in recruitment was not specified.  
7  
8 168 Some studies on physical activity are available on Kosovar adolescents [25], but no evidence is available  
9 169 for adults. Similarly, evidence on tobacco use in Kosovo has been focused on schoolchildren and  
10 170 adolescents. However, a recent publication on the WHO Stepwise approach to surveillance (STEPS)  
11 171 survey of persons aged 15 to 64 years conducted in 2010 (n= 6400) showed that 37% of men and 20%  
12 172 of women in Kosovo smoke [26]. The prevalence increased with age until it dropped at age 45. The  
13 173 results from the same STEPS survey on physical activity, diet and cholesterol have not yet been  
14 174 published. The AQH project conducted a population-based study in 12 municipalities, with the aim to  
15 175 collect primary data on project indicators for a baseline against which the impact of the project activities  
16 176 will be measured. The study found that 20.6% of respondents smoked, 15% had ever consumed alcohol,  
17 177 and 46% did not meet WHO recommendations on physical activity [27].

18  
19 178 In summary, more information is needed about NCD risk factors in the context of Kosovo and the impact  
20 179 of current interventions aimed at their reduction for a better understanding of where to target PHC  
21 180 services.

### 22 181 **Mental disorders and their relationship with hypertension**

23 182 CVDs and mental disorders are among the most burdensome NCDs to global health. It is furthermore  
24 183 disconcerting that there is a well established bidirectional relationship between CVDs such as coronary  
25 184 artery disease and mental disorders like depression [28]. In PHC, the prevention of CVDs is a high  
26 185 priority. Thus the relationship between depression and risk factors of CVDs such as hypertension is of  
27 186 great relevance for the public health sector. According to a meta-analysis of 41 cross-sectional studies  
28 187 [29], the prevalence of depression in patients with hypertension was much higher than in the general  
29 188 population (26.8% compared to 4.4%), suggesting that the two are strongly connected.

30 189 *Potential mechanisms linking depression and hypertension.* Some mechanisms have been proposed to  
31 190 explain how depression is linked to hypertension. Firstly, people living with depression tend to have  
32 191 unhealthy lifestyles which include habits such as smoking, alcohol abuse and physical inactivity [30],  
33 192 all of which are risk factors for hypertension and CVDs. Secondly, depression can cause autonomic  
34 193 nervous system dysfunctions which activates sympathetic activities [31] thereby elevating blood  
35 194 pressure. Insomnia and short sleep duration, which are typical symptoms of some forms of depression,  
36 195 have been found to significantly increase the risk of hypertension incidence [32,33]. Little sleep can  
37 196 activate the hypothalamic–pituitary–adrenal axis, which raises blood pressure in the short term, and can  
38 197 lead to long term structural adaptation that gradually reset the cardiovascular system to operate at an  
39 198 elevated pressure equilibrium. Finally, beyond its role in the etiology of hypertension and CVDs, the

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199 presence of depression may also affect the treatment of hypertension. It was found that physicians were  
200 more cautious with augmenting antihypertensive treatment in people with depression [34] because some  
201 antihypertensive medications have been found to cause or worsen depression [35]. This means that  
202 depressed persons may be less likely to receive adequate treatment from their physician for their blood  
203 pressure. In another sense, depression is a risk factor for poor adherence to antihypertensive medication  
204 [36].

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

209 *Evidence on depression and hypertension incidence.* The goal of primary prevention in PHC in terms of  
210 blood pressure is to prevent people from developing hypertension. According to a meta-analysis of  
211 longitudinal studies, depression significantly increased the risk of incident hypertension (RR, 1.42; 95%  
212 CI, 1.09-1.86) [37]. However, authors cautioned that the limited number of longitudinal studies available  
213 may have impacted conclusions. It should also be noted that definitions of hypertension differed among  
214 studies, which included either high blood pressure measurement (with differing cut-offs such as  
215  $\geq 140/90$ mmHg or  $\geq 165/95$ mmHg), prescribed antihypertensive medication, physician diagnosis, self-  
216 reported hypertension, or a combination of these. The inverse relationship (hypertension as a risk factor  
217 for incident depression) was assessed in another meta-analysis, which did not find a significant  
218 association [38]. One possible explanation is that hypertension is often asymptomatic, having less  
219 impact on quality of life and thus depression when compared to more advance stages of CVDs.

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

231 *Evidence on depression and the course of blood pressure.* Looking at blood pressure on a continuous  
232 scale is also of interest to better understand the magnitude depression can impact blood pressure. One  
233 cross-sectional study (n=2981) found that depressed subjects had lower mean systolic blood pressure

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3 234 than controls, and tricyclic antidepressant users had higher mean systolic and diastolic blood pressure  
4 235 [42]. A recent longitudinal study in Germany (n=1887) also found that after 12 years of follow-up, a  
5 236 history of moderate major depressive disorder (MDD) was associated with a decrease in both systolic  
6 237 and diastolic blood pressure [43]. Since depressive symptoms vary over time, this study was limited by  
7 238 its definition of depression (a lifetime history of depression) because conclusions about the relative  
8 239 effect of short and long-term depressive symptoms could not be made. The importance of evaluating  
9 240 depressive symptoms in parallel to blood pressure over time was noted in another longitudinal study in  
10 241 Norway [44], which also found that baseline depression predicted lower blood pressure at year 22, but  
11 242 further found that a high symptom level of depression and anxiety at baseline and year 11 was more  
12 243 strongly associated with a decrease in blood pressure at year 22, and associated with an even stronger  
13 244 decrease in blood pressure if there were high levels of symptoms at all three examinations.

14 245 Other emotional states such as anxiety and stress have overlapping symptomology with depression but  
15 246 are distinct negative emotional states. The independent associations between anxiety and stress with  
16 247 hypertension have been studied.

17 248 *Evidence on anxiety and hypertension.* According to the Depression Anxiety Stress Scale (DASS),  
18 249 which differentiates the three emotional states, symptoms of anxiety include autonomic arousal (heart  
19 250 rate increase, mouth dryness, etc.), skeletal muscle effects (trembling), feelings of panic, faintness or  
20 251 being terrified for no good reason [45]. A meta-analysis which pooled 13 cross-sectional studies with  
21 252 151 389 subjects found a significant positive association between anxiety and hypertension (OR 1.40,  
22 253 95% CI 1.20-1.62) [46]. Although significant publication bias was detected, the OR remained significant  
23 254 after trim and fill analysis (OR 1.18, 95% CO 1.02-1.37). In the same meta-analysis, eight prospective  
24 255 studies on baseline anxiety and incident hypertension were pooled (n=80 146) and presented a hazard  
25 256 ratio by random effect model of 1.55 (95% CI 1.24-1.94) with strong heterogeneity ( $p<.001$ ,  $I^2=84.6\%$ )  
26 257 but no publication bias was detected ( $p=.663$ ). Although there are clear relationships, the mechanisms  
27 258 for them are not yet well understood.

28 259 *Evidence on stress and hypertension.* Symptoms of stress included in the DASS are difficulty relaxing,  
29 260 nervous arousal, getting easily upset or agitated, irritable/over-reactive, and impatience [45]. In a recent  
30 261 meta-analysis (n=5696) of 11 studies, domains of mental stress were defined as psychological stress,  
31 262 anxiety/depression or work stress [47]. Two studies (n=622) looked at the association of mental stress  
32 263 on the risk of hypertension (OR 2.40, 95%CI 1.65-3.49,  $I^2=0\%$ ,  $p =0.33$ ) and the other 9 studies looked  
33 264 at the association of hypertension on the risk of mental stress (OR=2.69, 95%CI 2.32-3.11). The  
34 265 limitation of studies on stress and hypertension, as seen in the meta-analysis, are that they are few in  
35 266 numbers and have varying definitions of stress, which in some cases include depression and anxiety.  
36 267 Therefore, more studies are needed on the relationship between stress and hypertension, with a clear  
37 268 definition of stress as a distinct emotional state.

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269 *Mental health care in Kosovo.* Supporting persons with mental illness in Kosovo is a challenge. This is  
270 because mental health services are only available upon referral to a specialist, which may deter persons  
271 with mental illness from seeking care as it remains highly stigmatized in the country. Seeking  
272 professional support to address mental health problems is associated with “tremendous shame” in the  
273 country, thus support is rarely requested or is kept within the family circle [48]. Indeed, only 15% of  
274 people who stated they needed help actually sought the help from a psychologist or psychiatrist due to  
275 fear of being stigmatized [11]. If help for mental illness is sought outside the home, families often consult  
276 with traditional healers or local religious persons instead of mental health professionals [48].

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

#### 284 **Objectives of the KOSCO study**

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

- 288 1. To assess the prevalence and temporal change of NCDs such as hypertension, depression,  
289 diabetes, and COPD, as well as the prevalence and temporal change of etiologic risk factors,  
290 disease control, and underdiagnosis of these NCDs among PHC users.
- 291 2. To evaluate the longitudinal relationship of PHC non-experimental interventions such as  
292 motivational counselling sessions with adherence to healthy lifestyles (physical activity,  
293 nutrition, smoking, alcohol consumption), clinical measurements (blood pressure, BMI and  
294 HbA1c), and the stage of health behavior change.
- 295 3. To assess the predictive association between depression and the course of blood pressure in  
296 adult primary healthcare users living in Kosovo, as well as the mediators of the association.

#### 297 **METHODS AND ANALYSIS**

##### 298 **Study design**

299 This prospective 5-year longitudinal study of primary healthcare users in Kosovo conducted follow-ups  
300 annually in 2 phases, spaced by approximately 6 months. Part 1 included an in-person interview and  
301 health examination, while part 2 included a telephone interview. Part 1 of baseline data collection began

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302 in March 2019 and part 2 began in October 2019. The second follow-up started in March 2020. Annual  
303 follow-ups during a 5 year cohort allows for potential mediation analysis.

### 304 **Setting**

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

313 The study was embedded within the AQH project and the selection of municipalities was based on the  
314 project's established stakeholder collaboration. The AQH project engaged with these municipalities  
315 based on 9 indicators: RAE population as percentage of total population, per capita public expenditure,  
316 per capita total primary healthcare financing, social welfare beneficiaries per 100 inhabitants, female  
317 lone parent as percentage of female population, doctors per 1000 inhabitants, nurses per 1000  
318 inhabitants, total PHC visits per capita, diarrhea per 1000 inhabitants, and applying a convenience  
319 sample to ensure geographic clustering and representation of ethnic-Serbs.

### 320 **Participants**

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

### 332 **Incentive**

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

### 336 **Study preparation**

337 Four research nurses were hired to conduct the data collection. They participated in a 3-day training  
338 certified by the Kosovo Nursing Chamber which covered standard operating procedures to perform  
339 interviews and health assessments. One week prior to recruitment, research nurses and the field research  
340 coordinator visited all sites to meet and inform relevant staff about the study and ensure necessary on-  
341 site equipment was ready for use. A plan of the recruitment schedule, which rotated between study sites,  
342 was provided to all directors.

### 343 **Patient and Public Involvement**

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

352 *Patient involvement in piloting the interview guide.* The interview guide was piloted on a convenience  
353 sample of 9 PHC patients from the MFMC in Obiliq. The questions were adapted according to patient  
354 feedback (for example some questions were repetitive or not culturally appropriate, therefore removed).  
355 The first follow-up questionnaire was piloted on 42 cohort participants and the questionnaire was again  
356 modified based on feedback.

### 357 **Variables and data collection**

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



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

Theme	Variables	Part 1: In-person interview	Part 2: Telephone interview
Socio-demographic 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 utilization, patient satisfaction with services	x	Repeat only: provider adherence to protocol, healthcare utilization
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	

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366 *Data collection was divided into two parts: in-person interviews with health examination (part 1) and*  
 367 *telephone interviews (part 2). Variables assessed are grouped by theme, and inclusion in part 1 and/or*  
 368 *2 is indicated with an “x” or with comments.*

369 **Table 2.** Overview of validated instruments used in interviews

Theme	Questionnaire	Description
Socio-demographic factors	None	
Social and environmental factors	Modified Medical Outcome Survey Social Support Scale (mMOS-SSS)	The modified Medical Outcome Study-Social Support Scale (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 [50].
Health factors, part I	self-report generated Charlson Comorbidity Index (SRG-CCI)	The self-report generated Charlson Comorbidity Index (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 [51]. 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)	Rose Angina Questionnaire (RAQ) was developed to detect ischemic heart pain (angina pectoris and myocardial infarction) for epidemiological field-surveys [52]. 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 European Community Respiratory Health Survey II (ECRHS II) Main questionnaire was included to assess respiratory symptoms. Items assess presence of wheezing, tightness in chest, shortness of breath, cough and phlegm with binary responses [53].
	Medical Research Council (MRC) Dyspnea Scale	The Medical Research Council (MRC) Dyspnea Scale was developed to categorize the level of disability in Chronic Obstructive Pulmonary Disease (COPD) [54]. The scale has one item with 5 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)	Patient Health Questionnaire (PHQ 15) is a 15-item somatic symptom scale which measures the severity of somatization in patients [55]. 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

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		summary score ranges 0 to 30 and classified as minimal (0-4); mild (5-9); moderate (10-14) and high (15-30) severity of somatic symptoms.
Health system factors	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 co-operation, and accessibility [56]. All items are aggregated into two dimensions: clinical behaviour (items 1-16) and organization of care (items 17-23). Responses are rated on a 5 point Likert scale 1 (poor) to 5 (excellent).
Lifestyle behaviour, part I	None	
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 5 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 [57].
	Smoking Abstinence Self-Efficacy Questionnaire (SASEQ)	Smoking Abstinence Self-Efficacy Questionnaire (SASEQ) has 6 items with statements of various situations where a one might be tempted to smoke and asks for the participant's confidence level that they will not smoke [58]. Response options are on a 5-point Likert scale ranging from certainly (4) to certainly not (0).
	Health-Specific Self-Efficacy Scales (HSSES)	The Health-Specific Self-Efficacy Scales (HSSES) assesses a person's optimistic self-belief about being capable to resist temptations and to adopt a healthy lifestyle [59]. 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 (5 items), physical exercise (5 items) and alcohol consumption (3 items). Response options range on a 4-point Likert scale from (1) very uncertain to (4) very certain.
	Short Form Health Survey version 2 (SF12)	The Short Form Health Survey version 2 (SF12) is a 12-item questionnaire which measures health-related quality of life. 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 4 through 7 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 through 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 (PCS & MCS) using a norm based method and transformed to each have a mean of 50. The total score ranges from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health [60].

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Psychological factors, part I	Depression, Anxiety, Stress Scale (DASS-21)	Depression, anxiety and stress were measured using the Depression, Anxiety Stress Scale-21 (DASS-21) [61,62], a 21-item questionnaire consisting of three subscales, each containing 7 items scored on a four-point Likert scale ranging from 0 (did not apply to me at all) to 3 (applied to me very much), and multiplied by two. The scores are classified as; depression 0-9 (normal), 10-13 (mild), 14-20 (moderate), 21-27 (severe), $\geq 28$ (very severe); anxiety 0-7 (normal), 8-9 (mild), 10-14 (moderate), 15-19 (severe) $\geq 20$ (very severe); stress 0-14 (normal); 15-18 (mild), 19-25 (moderate), 26-33 (severe), $\geq 34$ (very severe).
	Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)	Primary Care PTSD Screen for DSM-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; $\leq 2$ (improbable PTSD) and $\geq 3$ (probably PTSD) [63].
	Resilience Scale (RS-14)	Resilience Scale (RS-14) is a 14-item questionnaire that assesses individual resilience in a general population [64]. Items are scored on a 7 point Likert scale from 1 (strongly disagree) to 7 (strongly agree). Scores are categorized 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)	Self-esteem (SE) is a 1-item scale developed as an alternative to the Rosenberg self-esteem scale [65]. 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	

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

373 *Physical examination.* Immediately following the in-person interview, the research nurse performed a  
 374 brief health examination of about 10 minutes.

- 375 • *Height (cm) and weight (kg)* were measured using stadiometers and scales which were available  
 376 at the MFMCs (various brands). The precision of scales were assessed regularly with a weight  
 377 of 10 kilograms. Circumferences of the waist, hip and neck were measured using the SECA 201  
 378 measuring tape (Seca GmbH & Co. KG., Switzerland).
- 379 • *Peak expiratory flow (PEF) (L/min)* was measured 3 times with 30 seconds pause between  
 380 attempts, using the OMRON Peak Flow Meter PFM20 (Omron Healthcare, Switzerland). PEF

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3 381 predicted (%) was calculated as follows: Estimated (measured) PEF / Expected PEF. The  
4 382 expected PEF values were derived based on age, gender and height using the regression equation  
5 383 developed by Hankinson et al. [66]  
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8 384 • *Systolic and diastolic blood pressure (in mmHg)* were measured three times, at least 3 minutes  
9 385 apart, after sitting quietly for about 10 minutes, using an M3 model Omron blood pressure  
10 386 monitor (Omron Healthcare, Switzerland). The research nurses placed the blood pressure cuff  
11 387 2 centimeters above the elbow on the bare left upper arm (in the case of arteriovenous fistula,  
12 388 radiotherapy or removal of lymph nodes in the armpit of the left arm, the right arm was used)  
13 389 of the seated participant and elevated the arm on the table to the level of the fourth intercostal  
14 390 space.  
15  
16 391 • Towards the end of the battery of tests, the research nurse accompanied participants to the  
17 392 laboratory of the MFMC for a finger-prick (non-invasive) *glycated haemoglobin test (HbA1c,*  
18 393 *%)*. The HbA1c test was performed by a MFMC staffed laboratory technician who received  
19 394 training by the supplier on how to use the SUPER ID clinchem device (Dr. Müller Gerätebau  
20 395 GmbH, Germany).  
21  
22 396 • Participants were given a ‘self-care passport’ at baseline, which was developed by local experts  
23 397 in collaboration with the AQH project. The research nurses transcribed the participants’ health  
24 398 examination results in the passport which also had additional space for participants to write  
25 399 blood pressure or blood glucose measurements taken at home. Participants were instructed that  
26 400 they will be re-contacted in 6 months for a telephone interview.

#### 401 **Definitions of main variables by objective:**

##### 402 *Objective 1*

- 403 • *Depression* was defined as self-reported depression diagnosis by a healthcare professional  
404 and/or prescribed antidepressant medications and/or a DASS depression score of >13 (moderate  
405 to very severe depressive symptoms). *Uncontrolled depression* was defined as being diagnosed  
406 with depression and/or taking antidepressant medication yet having a DASS depression score  
407 of >13. *Undiagnosed depression* was defined as not being diagnosed with depression nor taking  
408 antidepressant medication yet having a DASS depression score of >13  
409 • *Hypertension* was defined as a self-reported hypertension diagnosis by a healthcare professional  
410 and/or prescribed antihypertensive medications and/or a blood pressure measurement  
411  $\geq 140/90$ mmHg. *Uncontrolled hypertension* was defined as being diagnosed with hypertension  
412 and/or taking antihypertensive medication yet having a blood pressure measurement  
413  $\geq 140/90$ mmHg. *Undiagnosed hypertension* was defined as not being diagnosed with  
414 hypertension nor taking antihypertensive medication yet having a blood pressure measurement  
415  $\geq 140/90$ mmHg.

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3 416 • *Diabetes* was defined as a self-reported diabetes diagnosis by a healthcare professional and/or  
4 417 prescribed antidiabetic medications and/or an HbA1c measurement  $\geq 6.5\%$ . *Uncontrolled*  
5 418 *diabetes* was defined as being diagnosed with diabetes and/or taking antidiabetic medication yet  
6 419 having an HbA1c measurement  $\geq 6.5\%$ . *Undiagnosed diabetes* was defined as not being  
7 420 diagnosed with diabetes nor taking antidiabetic medication yet having an HbA1c measurement  
8 421  $\geq 6.5\%$ .
- 9  
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11 422 • *COPD* was defined as a self-reported COPD diagnosis by a healthcare professional and/or a  
12 423 PEF  $< 80\%$  predicted with breathlessness and/or cough symptoms for greater than 6 months.  
13 424 *Uncontrolled COPD* was defined as being diagnosed with COPD yet having a PEF  $< 80\%$   
14 425 predicted. *Undiagnosed COPD* was defined as not being diagnosed with COPD yet having a  
15 426 PEF  $< 80\%$  predicted with breathlessness and/or cough symptoms for greater than 6 months. A  
16 427 PEF  $< 80\%$  predicted with respiratory symptoms (breathlessness or cough for greater than 6  
17 428 months) was found to be an appropriate cut-off to detect COPD in the absence of spirometry  
18 429 [67].
- 19 430 • *Lifestyle factors included*: smoking (current smoker, ex-smoker, never smoker), meeting WHO  
20 431 recommendations for physical activity (at least 150 minutes of moderate-intensity physical  
21 432 activity throughout the week, or at least 75 minutes of vigorous-intensity physical activity  
22 433 throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity  
23 434 [68]), meeting WHO recommendations for fruit and vegetable intake (at least 5 portions (400g)  
24 435 of fruits and vegetables per day [69]), binge drinking (consumption of  $\geq 60$  grams of pure  
25 436 alcohol (6 or more standard drinks) on at least one single occasion at least once in a month  
26 437 ([70])), and BMI: weight (kg) / height (m<sup>2</sup>).

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39 438 *Objective 2*

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41 439 • *Motivational counselling sessions*: are a non-experimental community intervention, where all  
42 440 patients being treated at a MFMC, FMC or FMA aged 40 or older with diabetes, hypertension  
43 441 or at risk for developing diabetes and/or hypertension are eligible to be referred by a doctor or  
44 442 nurse to the nearest Health Resource Center. There, the nurse provides one-on-one motivational  
45 443 counselling sessions on lifestyle changes based on the patient's needs. Prior to rolling out this  
46 444 intervention, several preparatory steps were undertaken by the AQH project. First, Health  
47 445 Resource Centers were established within MFMCs as a new location for nurses to provide  
48 446 motivational counselling sessions and other preventive services for management of NCDs.  
49 447 Furthermore, nurses from MFMCs completed several training sessions on motivational  
50 448 counselling. At the time of baseline, motivational counseling was offered in 5 of the 12 study  
51 449 sites (Fushë Kosovë, Gjakovë, Malishevë, Mitrovicë, and Vushtrri), and a staggered  
52 450 introduction of the intervention to other study sites is anticipated. Attending a motivational  
53 451 counselling session was the main exposure, a dichotomous variable where participants answered

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3 452           yes or no to the question: “Have you ever participated in a motivational counselling session /  
4 453           health education session with a nurse in a health resource center?”  
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6 454           • *Lifestyle factors* were among the main outcomes, described under ‘Objective 1’.  
7  
8 455           • *Clinical measurements* were among the main outcomes, which were continuous variables that  
9 456           included blood pressure, BMI and HbA1c described under ‘physical examination’.  
10  
11 457           • *Stage of behavioural change* was one of the main outcomes, an ordinal variable assessed using  
12 458           the Stages of Change Survey. For each lifestyle (smoking, nutrition, physical activity and  
13 459           alcohol consumption) participants were categorized into one of the following stages of change  
14 460           based on their responses: Maintenance, Action, Preparation, Contemplation and Pre-  
15 461           contemplation.  
16 462           • *Patient satisfaction* and *quality of care* were predictors included in the secondary analysis.  
17 463           *Patient satisfaction* was a binary variable defined as an average EUROPEP score per item of  $\geq$   
18 464           4. *Quality of care* was a continuous variable defined as the number of patient-reported  
19 465           healthcare provider actions completed from the list of recommendations in the PEN protocol  
20 466           during the participant’s last visit in a PHC center.

### 28 467 *Objective 3*

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31 468           • *Depression* was the main exposure, a dichotomous variable defined under ‘Objective 1’.  
32 469           • *Change in blood pressure* was the main outcome, which was the blood pressure (described  
33 470           under ‘physical examination’) from baseline subtracted from blood pressure at follow-up.  
34 471           • *Hypertension incidence, uncontrolled hypertension and underdiagnosed hypertension* are  
35 472           secondary binary outcomes described under ‘Objective 1’.

### 39 473 **Non-participants**

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42 474   Non-participants (patients approached who declined to participate or who did not meet inclusion  
43 475   criteria) were asked 9 optional questions with the purpose to understand if participants differ from non-  
44 476   participants. The optional questions provided information on sex, age, education level, diagnosis of  
45 477   diabetes, lung disease, cardiovascular disease, smoking status, weight, level of satisfaction with PHC  
46 478   services and reason for non-participation.

### 50 479 **Data Management**

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53 480   Data from in-person and telephone interviews were collected using Open Data Kit (ODK) software.  
54 481   Results from health examinations were also entered into ODK. Data quality was assured through (1)  
55 482   formulation of standard operating procedures for all aspects of the study, (2) extensive and careful  
56 483   training of the study team according to the standard operating procedures, (3) onsite supervision of field  
57 484   activities ensuring adherence to protocol, and (4) regular monitoring and internal evaluation of data  
58 485   entry during the field visits. The ODK and STATA programs kept track of all changes made to the data.

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486 All data was merged into a single database at the end of data entry using STATA version 15.1 (STATA  
487 Corporation).

#### 488 **Power calculation**

##### 489 *Power calculation without local effects*

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

##### 500 *Power in the presence of clustering*

501 To take into account the potential local variation in the effect of depression on blood pressure, we  
502 performed explicit simulations to make sure that the study has sufficient power under a range of  
503 plausible scenarios. Specifically, we posited that the mean blood pressure can vary between the 12  
504 municipalities (random effect with variance  $\sigma^2$ ), and also that the effect of depression on blood  
505 pressure can be different in each municipality (random effect with variance  $\rho^2$ ). The magnitudes  
506  $\sigma$  and  $\rho$  of these local effects were tunable parameters of the simulation, as was the overall effect  
507 size  $\tau$ . Preliminary analyses showed that the power of the study is driven by the relationship of  $\tau$   
508 and  $\rho$ , and is not sensitive to  $\sigma$ ; this is because the municipality-level effect affects depressed and  
509 non-depressed people equally. Thus we fixed  $\sigma=\tau$  in what follows.

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

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



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519 **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%

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521 **Statistical Analysis Plan**

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

524 **Figure 1.** Hypothesized associations between variables525 *Objective 1*

526 The descriptive statistics of depression, hypertension, diabetes, COPD as well as the control and  
527 underdiagnoses of these diseases will be presented as follows: categorical variables will be presented as  
528 numbers and percentages. Normally distributed quantitative variables will be presented as mean and  
529 standard deviation. Other quantitative variables will be presented as medians and interquartile ranges.  
530 Chi-squared tests, t-tests and Wilcoxon rank-sum tests will be used for bivariate analysis where  
531 appropriate, such as to assess differences by age, gender or socioeconomic status.

532 *Objective 2*

533 The main exposure of interest was attendance in motivational counselling sessions (non-experimental  
534 PHC intervention). In light of the absence of pure controls for this non-experimental intervention,  
535 comparisons will be made between those who chose to participate in the invention and those who did  
536 not within the same center. The first outcome variable was stage of behaviour change, which was ordinal  
537 (Maintenance, Action, Preparation, Contemplation and Pre-contemplation). Two approaches will be  
538 used: Initially, the analysis will be done using ordinal regression, then the outcome variable will be split  
539 into two categories: a) High motivation (Maintenance, Action, Preparation) and b) Low motivation  
540 (Contemplation and Pre-contemplation) and logistic regression will be applied. The second outcome  
541 was adherence to the following aspects of healthy lifestyles: nutrition, physical activity, alcohol  
542 consumption, and smoking. Logistic regression analysis will be conducted for each lifestyle. For the  
543 third outcome (clinical measurements), a mixed linear regression model will be constructed for each  
544 outcome of interest: blood pressure, BMI and HbA1c. Comorbidities, physical ability, SES, living status,

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545 and employment status are potential confounders and will be controlled for during data analysis. The  
546 intrinsic municipality and participant effects will be modelled with random effects. Potential effect  
547 modifiers include sex, age, and social support. Self-efficacy will be considered as a potential mediator.  
548 Secondary analyses with predictors of patient satisfaction and quality of care will be conducted with  
549 logistic regression models.

### 550 *Objective 3*

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

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

- 561 1. Predictive perspective: A regression model will be constructed with the outcome of change in  
562 blood pressure from baseline (continuous). Baseline blood pressure will be adjusted for by  
563 including it as a covariate in the model. This model will allow predicting the future course of  
564 blood pressure, based on a set of variables observed at baseline. This model is of value for a  
565 provider perspective: based on what the provider observes at a specific point in time, what is  
566 the predicted course of blood pressure?
- 567 2. Change perspective: The effect of change in depression (predictor) on change in blood pressure  
568 (outcome) will be assessed with a repeated measures model. This model will allow assessing  
569 the parallel change in depression and blood pressure and in that sense takes cross-sectional  
570 short-term associations at baseline and follow-up into consideration.

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

### 575 **STRENGTHS AND LIMITATIONS**

576 Given the limited evidence on NCDs in Kosovo, the cohort is of great benefit for healthcare decision  
577 makers which rely on health data. Results from this cohort study will provide an overall insight into the

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3 578 relationship between NCDs and their determinants through study objective 1. Considering that this study  
4 579 is assessing the longitudinal association of PHC interventions (such as delivery of motivational  
5 580 counselling sessions for behavior change) in study objective 2, the scientific findings of this study can  
6 581 be applied in designing targeted behaviour change interventions. Behaviours affect morbidity, and  
7 582 extremely unhealthy behaviours may lead to mortality, therefore understanding what causes patients to  
8 583 do certain behaviours and what motivates them to change, provides information which could be useful  
9 584 for populations with similar characteristics [14]. Further, understanding potential mutual influences  
10 585 between depression and hypertension could indicate the need for integrated mental health services in  
11 586 primary healthcare for more effective control of both conditions [46], and will be addressed through  
12 587 objective 3.

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20 588 Having embedded this cohort in an existing local implementation project, namely AQH which builds  
21 589 on strong partnerships with local stakeholders, greatly increased the ease of implementation and  
22 590 acceptability of this study. For example, the study population lives in mostly rural areas, with high levels  
23 591 of poverty and low levels of education which meant that there was little awareness of research and their  
24 592 benefits. Being embedded within the AQH project, which had established trust with municipalities,  
25 593 helped in the recruitment process. Further, given that the healthcare system is decentralized, getting  
26 594 directors of MFMCs from multiple municipalities on board to participate in the cohort study would  
27 595 normally be a long and complicated process, but was simplified since the directors had a longstanding  
28 596 relationship with the AQH project.

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35 597 A pilot of the questionnaire with 9 primary healthcare users aged 40 years and above conducted in March  
36 598 2019 and in the MFMC of Obiliq and again in October 2019 with 42 cohort participants from various  
37 599 municipalities served to identify the understanding and flow of questions. Some questions were  
38 600 identified as inappropriate or irrelevant in the cultural context and were omitted. For example, the  
39 601 original PC-PTSD-5 questionnaire listed sexual abuse as an example of a traumatic event and this was  
40 602 considered offensive by one person in the pilot survey. Thus the example was removed. One question  
41 603 asked if the participant had ever been diagnosed with a mental disorder by a physician. Local research  
42 604 nurses unanimously stated that this question was not culturally acceptable since it was not perceived  
43 605 well by the participants therefore it was removed from part 1 of the baseline data collection (initial  
44 606 contact with participants) and moved to part 2 to allow participants time to grow trust with research  
45 607 nurses. The PHQ asks questions about menstruation pain during intercourse, which were also culturally  
46 608 unacceptable and considered unpleasant to ask in an interview and a disclaimer statement was added  
47 609 before the items to preface the question. A question in the EUROPEP which assesses satisfaction with  
48 610 “getting through to the practice on telephone” was removed as it is not common practice in Kosovo.  
49 611 Given that the average level of education in Kosovo’s older population is of primary school or lower,  
50 612 some instruments’ questions were abstract and difficult to understand by participants. In particular,  
51 613 respondents of the pilot survey noted that multiple questions in the Resilience Survey (RS-14) were

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3 614 difficult to understand, such as “I am friends with myself” which was considered a Western ideal and “I  
4 615 keep interested in things” often yielded participant questions like “what things?” A debriefing with  
5 616 research nurses ensured that these questions were clarified with participants in a uniform way. It was  
6 617 confirmed through the pilot that the questionnaire was too lengthy, demonstrated by participants asking  
7 618 to end the interview before the end. It was decided to separate questions into two parts, asked with an  
8 619 interval of 6 months.

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13 620 During the preparation period which involved site visits before the launch of recruitment, the first author  
14 621 learned that lab hours were shorter than anticipated, which limited the amount of hours of recruitment  
15 622 (from 7:00 to 13:00). This meant that the original estimated recruitment timeline was extended from 3  
16 623 months to 8 months. Further, participation rates were low, which extended recruitment time.

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20 624 Due to the recruitment scheme in PHC facilities, the study is not population-based. Thus the study is  
21 625 limited in its generalizability as well as it may overestimate the prevalence of health conditions.  
22 626 However, patients visit MFMCs for an array of conditions as well as for general check-ups, thus healthy  
23 627 persons are also included in the study. Providing participants incentives with free health consultations  
24 628 may bias towards participation of persons with chronic conditions, and thus may also overestimate the  
25 629 prevalence of NCDs and their determinants. The relevance of the study, in the absence of being entirely  
26 630 representative for Kosovo as a whole, lies in the longitudinal design; furthermore it evaluates care and  
27 631 its perception and utilization in a large number of relevant health service infrastructures. The findings  
28 632 will therefore be relevant and guiding for other similar structures in the country.

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32 633 The non-randomized nature of PHC interventions mentioned in this study is a limitation in the  
33 634 interpretation of results regarding the effectiveness of interventions. But randomization of interventions  
34 635 was not possible: centers offering the interventions were selected based on feasibility and interest of the  
35 636 MFMC staff to increase success of the pilot health centers, and the intervention is offered to all patients  
36 637 therefore exposure is self-selected.

## 37 638 **ETHICS AND DISSEMINATION**

### 38 639 **Ethics approval and Consent to Participate**

39 640 Ethical approvals for the study were obtained from Ethics Committee Northwest and Central  
40 641 Switzerland (Reference number 2018-00994) obtained 11 December 2018 and the Kosovo Doctors  
41 642 Chamber (Reference number 11/2019) obtained on 30 January 2019 and expiring on 31 December 2023.  
42 643 Before any data was collected, participants were asked for their verbal and written consent. To obtain  
43 644 consent, participants were informed that a) their participation was voluntary, b) they could withdraw  
44 645 from participation at any time, and c) non-participation would not have any negative effects. The  
45 646 participants were asked for additional consent whether, in the case a previously unrecognised medical  
46 647 problem was detected, they approve that qualified staff or the research team would inform them of the

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648 results and provide advice on what the participant should do next. Standard Operating Procedures (SOP)  
649 developed by the study team and approved by MFMC directors (who are physicians), were provided to  
650 research nurses to guide them in referring participants to appropriate care. Severe findings (systolic  
651 blood pressure  $\geq 180$ mmHg and diastolic blood pressure  $\geq 110$ ) were referred immediately to emergency  
652 services in the MFMC. Participants were informed how the data will be used and that confidentiality is  
653 ensured as their data is coded. Potential risks and benefits of participation were also discussed with  
654 participants, and ample time was given to ask questions. Once consent was obtained, the research nurse  
655 proceeded to data collection.

#### 656 **Data Protection**

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

#### 666 **Data sharing**

667 The datasets will be available from the corresponding author on reasonable request.

#### 668 **Collaboration**

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

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

#### 674 **DECLARATIONS**

##### 675 **Competing Interests**

676 KO, ABK, and QR report personal fees from Swiss Agency for Development and Cooperation (SDC)  
677 during the conduct of the study;

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678 ABK reports grants from the Swiss Confederation during the conduct of the study.

679 The remaining authors declare that they have no competing interests.

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684 Department of Foreign Affairs, whom are responsible for coordinating Swiss international development  
685 projects in Eastern Europe. They are the core funders of the AQH implementation project in which the  
686 cohort is embedded. Local SDC representatives were responsible for approving the cohort budget and  
687 the study proposal. SDC contributed to the direction of study objectives.

688 The Swiss Tropical and Public Health Institute (Swiss TPH) has internally funded the salary of KO in  
689 the second and third years of the doctoral studies. Co-authors associated with Swiss TPH include KO,  
690 JG, ABK, MZ and NPH and contributed to the study in various capacities, specified in authors'  
691 contributions declaration.

692 The Swiss Government Excellence Scholarship for Foreign Scholars and Artists was awarded to ABK  
693 for the time period of 2019-2022 (Reference number 2019.0234), which will fund her doctoral studies  
694 salary.

### 695 **Authors' contributions**

696 **KO** –co-developed and implemented the study protocol, coordinated and supervised data collection,  
697 will analyze and interpret data.

698 **NJ** contributed to study objectives related to non-communicable diseases in Kosovo

699 **SS** contributed to study objectives related to mental health in Kosovo

700 **MK** conducted statistical power calculations and will supervise data analysis

701 **MZ, QR, ABK, and JG** contributed to the study objectives related to the evaluation of health service  
702 provision and to the integration of the study protocol within the AQH framework.

703 **NPH** developed the KOSCO cohort concept, study objectives, and protocol, directed the  
704 implementation, data analysis and result interpretation.

705 All authors read and approved the final protocol.

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 715 Igrishta, Selvete Zyberaj, Shqipe Agushi and Alma Stojanović.

#### 716 **List of Abbreviations**

717	AQH	Accessible Quality Healthcare Project
718	BEN	Balkan Endemic Nephropathy
719	CVDs	Cardiovascular Diseases
720	DALY	Disability Adjusted Life-Years
721	DASS	Depression Anxiety Stress Syndrome
722	DM	Diabetes Mellitus
723	FMA	Family Medicine Ambulantas
724	FMC	Family Medicine Center
725	HbA1c	glycosylated haemoglobin
726	HSCL	Hopkins Symptoms Checklist
727	KOSCO	Kosovo Non-Communicable Disease Cohort
728	MDD	Major Depressive Disorder
729	MFMC	Main Family Medicine Center
730	NCD	Non-communicable diseases
731	NIPH	National Institute of Public Health
732	ODK	Open Data Kit
733	PEN	Packages of Essential Non-Communicable Disease Protocols
734	PHC	Primary Healthcare
735	PTSD	Post-Traumatic Stress Disorder
736	QoL	Quality of Life

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3	737	RAE	Roma, Ashkali, Egyptian ethnicity
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5	738	SDC	Swiss Agency for Development and Cooperation
6			
7	739	SOP	Standard Operating Procedures
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9	740	SPs	Service Packages
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11	741	STEPS	Stepwise approach to surveillance survey
12			
13	742	Swiss TPH	Swiss Topical and Public Health Institute
14			
15	743	UP	University of Prishtina
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17	744	WHO	World Health Organization
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3 **941 Figure 1**  
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6 **942** Title: Hypothesized associations between variables under study  
7

8 **943** Legend: The hypothesized associations between outcome variables on the right, predictor variables on  
9 **944** the left and mediating variables in the middle are represented in the figure. Sociodemographic factors,  
10 **945** social and environmental factors, health literacy and self-care, as well as health system factors are  
11 **946** thought to impact the outcome of quality of life, the incidence and control of chronic diseases and  
12 **947** lifestyle change, and mediated by personal and health factors.  
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**Socio-demographic factors**  
 (age, gender, marital status, residence, ethnicity, education level, occupation, household composition, income level, pension, health insurance)

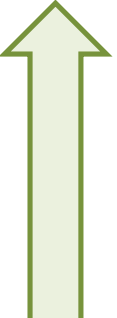
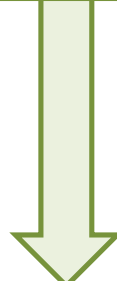
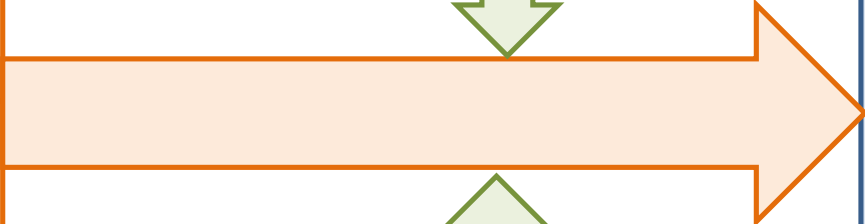
**Social and Environmental factors**  
 (Social support, proximity to health services)

**Health Literacy, Self Care, Health-specific self-efficacy**

**Medical System**  
 (motivational counselling sessions, provider adherence to treatment protocol; availability and access to medication; patient satisfaction)

**Health factors**  
 (comorbidities; disabilities; symptoms; family history; somatic symptoms; sleep)

**Personal factors**  
 (resilience; self-esteem; post-traumatic stress disorders; depression; anxiety; stress)



**Quality of life**  
**Incidence, control, underdiagnosis of NCDs**  
 Blood pressure  
 Glycated hemoglobin  
 Peak Expiratory Flow  
 Disease complications  
 Health service use  
**Change in lifestyle**  
 Physical activity  
 Smoking  
 Alcohol  
 Diet  
 BMI  
**Stage of behavioural change**