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

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

Depression is a leading cause of disability worldwide affecting more than 264 million people1. Depression is also an independent risk factor for cardiovascular disease (CVD)2,3, which continues to cause the greatest disease burden worldwide1. The mechanisms underlying the relationship between depression and CVD are not yet elucidated. Pathophysiological pathways involving increased blood pressure (BP) have been the focus of proposed explanations linking depression and CVD2,4. Given the heavy burden these conditions cause globally, it is of great public health relevance to investigate the potential causal role of depression in the course of BP to provide greater insight into the potential of depression control in reducing CVD risk and the global disease burden.

Several studies propose mechanisms mediating the relationship between depression and CVD2,4, and focus on shared pathways with high BP. Firstly, depression and BP are linked by lifestyle. Depression is associated with an increased risk for unhealthy behaviours such as smoking, physical inactivity, increased alcohol consumption, poor nutrition, and poor sleep5–11, all of which are known risk factors for raised BP. Secondly, biological mechanisms such as autonomic nervous system dysfunction are associated with depression, resulting in decreased heart rate variability and increased heart rate12, which in turn lead to an increase in BP. Thirdly, there is evidence that antidepressant treatments themselves may independently increase BP13,14.

The evidence on the prospective associations between depression and BP is currently mixed. Longitudinal studies have concentrated on the predictive association between depression and incident hypertension13,15–17. A...
A meta-analysis of 9 prospective studies revealed that depression increased the risk of incident hypertension (RR 1.42, 95% CI 1.09 to 1.86). Although some studies detected hypertension with BP measurements alone or in combination with hypertension diagnosis or antihypertensive medication use, several others relied solely on physician-diagnosed hypertension and the use of antihypertension medication to assess the presence of hypertension. However, many people remain unaware that they have high BP, especially if they do not experience symptoms and fail to get a diagnosis. Depression is associated with higher healthcare utilization, thus people living with depression might be more likely to have underlying hypertension diagnosed than those without depression.

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

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

Methods

Participants. We used longitudinal data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) which began in 1991 (SAPALDIA1) with 9651 randomly selected participants aged 18 to 60 from eight representative Swiss areas. SAPALDIA1 focused on air pollution and respiratory health and expanded into cardio-metabolic outcomes and wellbeing thereafter (SAPALDIA2 (2001–2003), SAPALDIA3 (2009–2011), SAPALDIA4 (2016–2018)). The current study used data collected from SAPALDIA2, SAPALDIA3 and SAPALDIA4 for longitudinal analyses. At each of these follow-ups, participants completed a...
health examination and questionnaire covering their lifestyle and health status including information on physician diagnosis, and medication use for depression and hypertension. While all participants at SAPALDIA2 and SAPALDIA3 were subjected to a health assessment, the health examination in SAPALDIA4 was restricted to participants aged 55 years and older at the time (SAPALDIA4 55+). Details of the SAPALDIA study protocols are provided elsewhere32–34. The overall participation rate at SAPALDIA1 (n = 9651) was 59.3% of the sample frame34, with a retention rate of 83% from SAPALDIA1 to SAPALDIA2 (n = 8047), 76% from SAPALDIA2 to SAPALDIA3 (n = 6088), and 85% from SAPALDIA3 to SAPALDIA4 (n = 5149). Of the 5149 SAPALDIA4 participants, 2179 were eligible for the 55+ health exam of whom 1746 underwent it33. For our longitudinal analyses, we pooled data from two waves, SAPALDIA2 to SAPALDIA3 (wave 2) and SAPALDIA3 to SAPALDIA4 55+ (wave 3). Participants were included if they met the following criteria within a wave: (1) had complete data on systolic and diastolic BP at first (termed: “baseline”) and second time point (termed “follow-up”) of each wave; (2) had complete baseline data on depression, potential confounders and mediators, (3) did not report a physician diagnosis of hypertension or CVD at baseline, (4) had no history of antihypertension treatment at baseline, and (5) were normotensive (systolic BP < 140 mmHg and diastolic BP < 90 mmHg) at baseline (n = 3214). A flow diagram for the inclusion of study participants is depicted in Fig. 2. The number of participants meeting these criteria was n = 2467 for wave 2 only, n = 171 for wave 3 only, and n = 576 for both waves. Data use from wave 1 was impeded due to the lack of BP data at the SAPALDIA1 survey.

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

Depression. The presence or absence of depression at baseline (first time point of each wave) was deduced from the following information provided by the participants: First, participants responded to questions about having physician-diagnosed depression and provided a medication list from which antidepressant medication use was derived. Second, participants completed the Medical Outcomes Study Short Form 36 questionnaire (version 1)35. The Mental Health domain (SF-36 MH) scores ranged from 0 to 100 and a score below 50 was found to be an appropriate cut-off to screen for depressive disorders36. We therefore defined depression as self-reported physician-diagnosed depression or a history of antidepressant use (ATC codes starting with N06A) or an SF-36 MH score < 50. We considered also depression disaggregated by any antidepressant use, and by antidepressant class (N06AA—Non-selective monoamine reuptake inhibitors; N06AB—Selective serotonin reuptake inhibi-
Depression and incident hypertension diagnosis. The prospective association between baseline depression and incident hypertension diagnosis was assessed with a logistic regression model. We included the same set of covariates as the fully adjusted models for change in BP, and additionally the baseline systolic and diastolic BP, and the follow-up duration of the wave. Effect modification by sex was assessed by introducing the appropriate interaction term. All analyses used clustered robust standard errors to account for repeat measurements of participants. Analyses were performed with Stata statistical software, release 16.
Results

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

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

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

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

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

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

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

Discussion

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

Predictive association between baseline depression and change in blood pressure. Main effect. To the best of our knowledge, our study is the first to report the predictive association between depression and change in BP as a continuous variable among normotensive people and incident hypertension diagnosis in the same study sample. While BP tends to increase with age, we found that systolic BP increased less among people with depression compared to those without depression at baseline. This association did not vary by sex in our study, although there is evidence of effect modification by sex in another study which included both normotensive and hypertensive people and found that a higher depression symptoms score (continuous) was predictive of attenuated BP after 11 years of follow-up, as was depression as a binary exposure, albeit with less confidence. A second study,
|                                    | Wave 2 (SAPALDIA2 to SAPALDIA3) (n = 2467) | Depressed at wave 2 (criteria iv) (n = 262) | Wave 3 (SAPALDIA3 to SAPALDIA55+) (n = 747) | Depressed at wave 3 (criteria iv) (n = 101) |
|------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| **Depression, frequency (%)**      |                                          |                                          |                                          |                                          |
| i. Depression diagnosis            | 113 (4.6)                                | 73 (9.8)                                 |                                          |                                          |
| ii. Depressive symptoms (SF-36 MH < 50) | 149 (6.0)                               | 31 (4.2)                                 |                                          |                                          |
| iii. History of antidepressant use | 83 (3.4)                                 | 38 (5.1)                                 |                                          |                                          |
| iv. Presence of depression<sup>b</sup> (any of i, ii, or iii) | 262 (10.6)                              | 101 (13.5)                               |                                          |                                          |
| **Age, mean (SD)**                 | 48.0 (10.5)                              | 49.1 (11.0)                               | 58.7 (7.4)                               | 58.5 (7.3)                               |
| **Sex, frequency (%)**             |                                          |                                          |                                          |                                          |
| Male                               | 1103 (44.7)                              | 85 (32.4)                                | 311 (41.6)                               | 30 (29.7)                                |
| Female                             | 1364 (55.3)                              | 436 (58.4)                               | 71 (70.3)                                |                                          |
| **Education level, freq (%)**      |                                          |                                          |                                          |                                          |
| Primary school                     | 87 (3.5)                                 | 21 (8.0)                                 | 20 (2.7)                                 | 7 (6.9)                                  |
| Secondary school                   | 1556 (63.1)                              | 165 (63.0)                               | 456 (61.0)                               | 61 (60.4)                                |
| Technical College or University    | 824 (33.4)                               | 76 (29.0)                                | 271 (36.3)                               | 33 (32.7)                                |
| **Employment, frequency (%)**      |                                          |                                          |                                          |                                          |
| Employed                           | 1968 (79.8)                              | 187 (71.4)                               | 501 (67.1)                               | 60 (59.4)                                |
| House person                       | 302 (12.2)                               | 45 (17.2)                                | 52 (7.0)                                 | 11 (10.9)                                |
| In training/military service       | 31 (1.3)                                 | 4 (1.5)                                  | 5 (0.7)                                  | 0 (0)                                    |
| Not working                        | 25 (1.0)                                 | 13 (5.0)                                 | 5 (0.7)                                  | 3 (3.0)                                  |
| Pensioner                          | 141 (5.7)                                | 13 (5.0)                                 | 184 (24.6)                               | 27 (26.7)                                |
| **Area, frequency (%)**            |                                          |                                          |                                          |                                          |
| Basel                              | 299 (12.1)                               | 25 (9.5)                                 | 93 (12.5)                                | 10 (9.9)                                 |
| Wald                               | 494 (20.0)                               | 33 (12.6)                                | 105 (14.1)                               | 12 (11.9)                                |
| Lugano                             | 196 (7.9)                                | 13 (5.0)                                 | 80 (10.7)                                | 6 (6.0)                                  |
| Montana                            | 265 (10.7)                               | 29 (11.1)                                | 106 (14.2)                               | 11 (10.9)                                |
| Payern                             | 287 (11.6)                               | 47 (17.9)                                | 79 (10.6)                                | 21 (20.8)                                |
| Aarau                              | 289 (11.7)                               | 43 (16.4)                                | 96 (12.9)                                | 17 (16.8)                                |
| Geneva                             | 406 (16.5)                               | 38 (14.5)                                | 103 (13.8)                               | 10 (9.9)                                 |
| Swiss Socioeconomic Position, mean (SD) | 64.4 (9.6)                        | 62.5 (9.8)                               | 65.0 (9.2)                               | 63.5 (9.4)                                |
| **Smoking status, frequency (%)**  |                                          |                                          |                                          |                                          |
| Never                              | 1211 (49.1)                              | 115 (43.9)                               | 387 (51.8)                               | 50 (49.5)                                |
| Former                             | 660 (26.8)                               | 59 (22.5)                                | 235 (31.5)                               | 31 (30.7)                                |
| Smoker                             | 596 (24.2)                               | 88 (33.6)                                | 125 (16.7)                               | 20 (19.8)                                |
| **Physical activity, frequency (%)** |                                          |                                          |                                          |                                          |
| Insufficiently active<sup>c</sup>  | 615 (24.9)                               | 76 (29.0)                                | 151 (20.2)                               | 26 (25.7)                                |
| Sufficiently active<sup>d</sup>     | 1852 (75.1)                              | 186 (71.0)                               | 596 (79.8)                               | 75 (74.3)                                |
| **Vegetable consumption, frequency (%)** |                                          |                                          |                                          |                                          |
| Not daily                          | 1913 (77.5)                              | 196 (74.8)                               | 552 (73.9)                               | 73 (72.3)                                |
| Daily                              | 594 (22.5)                               | 66 (25.2)                                | 195 (26.1)                               | 28 (27.7)                                |
| **Fruit consumption, frequency (%)** |                                          |                                          |                                          |                                          |
| Not daily                          | 2212 (85.6)                              | 224 (85.5)                               | 638 (85.4)                               | 73 (72.3)                                |
| Daily                              | 355 (14.4)                               | 38 (14.5)                                | 109 (14.6)                               | 28 (27.7)                                |
| **Alcohol**                        |                                          |                                          |                                          |                                          |
| Less than several times a week     | 1587 (64.3)                              | 168 (64.1)                               | 444 (59.4)                               | 69 (68.3)                                |
| Several times per week             | 880 (35.7)                               | 94 (35.9)                                | 303 (40.6)                               | 32 (31.7)                                |
| Sleepiness<sup>e</sup>, mean (SD)  | 1.8 (0.4)                                | 1.8 (0.5)                                | 1.8 (0.5)                                | 1.8 (0.5)                                |
| Body mass index (kg/m²), mean (SD) | 24.6 (3.6)                                | 24.4 (3.8)                               | 24.6 (3.7)                               | 24.6 (4.0)                                |
| Pulse (beats per minute), mean (SD)| 69.4 (9.8)                                | 69.5 (10.3)                              | 67.8 (9.5)                               | 69.9 (10.0)                               |
| Systolic BP (mmHg), mean (SD)      | 116.6 (12.4)                              | 115.0 (12.5)                             | 121.5 (10.2)                             | 119.6 (9.4)                               |

<sup>a</sup> Wave 2: (SAPALDIA2 to SAPALDIA3) (n = 2467); Wave 3: (SAPALDIA3 to SAPALDIA55+) (n = 747)

<sup>b</sup> Presence of depression (any of i, ii, or iii)

<sup>c</sup> Insufficiently active

<sup>d</sup> Sufficiently active

<sup>e</sup> Sleepiness
Table 1. Baseline participant characteristics (total n = 3214) by wave for the analysis of the prospective association between depression and change in blood pressure as well as incident hypertension diagnosis.

| Wave 2 (SAPALDIA2 to SAPALDIA3) (n = 2467) | Wave 3 (SAPALDIA3 to SAPALDIA55+) (n = 747) |
|------------------------------------------|------------------------------------------|
| Diastolic BP (mmHg), mean (SD)           | Diastolic BP (mmHg), mean (SD)           |
| 74.8 (7.7)                               | 74.2 (7.1)                               |
| Incident hypertension diagnosis          | Incident hypertension diagnosis          |
| 286 (11.6)                               | 96 (17.6)                                |

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

which was restricted to persons with hypertension, did not find that depression at case-level was predictive of change in BP (β = − 1.3, 95% CI − 5.3 to 2.7)39; however when they stratified depression by severity, they found that moderate major depressive disorder (but not mild or severe) predicted lower BP (systolic BP (β = − 7.5, 95% CI − 13.2 to − 1.9) and diastolic BP (β = − 4.5, 95% CI − 7.8 to − 1.3))30. Studies with contrasting evidence to our findings did not assess BP change over time31 or were restricted to women17.
irrelevant given the high prevalence of both depression and hypertension. Furthermore, our findings have important implications on cardiovascular epidemiology. Hypertension as a potential mechanism linking depression and CVD is in the literature spotlight. However, our findings suggest that the association between depression and CVD is not mediated through hypertension. Therefore epidemiological studies investigating other potential mechanisms are warranted.

**Effect modification antidepressant use.** In addition to assessing depression as a binary exposure, we also stratified depression by antidepressant use. When compared to persons without depression, we observed that participants reporting depression with a history of antidepressant treatment may have a greater attenuation in systolic and diastolic BP change than did participants reporting depression without a history of antidepressant treatment. This statistically non-significant finding was unexpected in light of the fact that antidepressants increase monoamines in the brain to improve depressive symptoms. Also other researchers did not find effect modification by general antidepressant use in longitudinal studies, however they were not restricted to normotensive persons\(^2\).\(^3\).\(^4\). We further conducted an analysis disaggregating depression by antidepressant class and found suggestive, but not statistically significant, evidence that attenuation of BP course may be strongest for N06AA class of antidepressants. This is in contrast to one cross-sectional study which found that certain subclasses of antidepressants (tricyclic antidepressants as well as noradrenergic and serotonergic acting antidepressants) increased BP\(^1\). In addition, a meta-analysis of Randomized Controlled Trials found that although the N06AB class of antidepressants did not change BP, N06AA led to a modest increase in systolic and diastolic BP when compared to N06AB\(^4\). The reporting of these suggestive results arising from a small study sample is meant to stimulate further investigation in the context of larger cohorts.

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

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

| Table 3. Prospective association between baseline depression (binary, disaggregated by antidepressant use, and disaggregated by antidepressant class) and incident hypertension diagnosis (self-reported physician diagnosis or antihypertensive treatment use at follow-up) among normotensives at baseline (n = 3214). A total of 357 incidences of hypertension diagnosis (11.1%) were observed. Logistic regression models with adjustment for age, sex, education, employment, Swiss SEP, area, wave, BMI, pulse, daytime sleepiness, physical activity, fruit consumption, vegetable consumption, alcohol, smoking, baseline systolic and diastolic BP, and years of follow-up. \(^1\)First time point of each wave is defined as baseline. \(^2\)N06AA—Non-selective monoamine reuptake inhibitors. \(^3\)N06AB—Selective serotonin reuptake inhibitor.

| Depression | Incident hypertension diagnosis | Odds ratio | 95% CI |
|------------|---------------------------------|------------|--------|
| No depression (n = 2851) (Reference) | | | |
| Depressed (n = 363) | | 1.86 | (1.33, 2.60) |
| Depression | | | |
| No depression (n = 2851) (Reference) | | | |
| Depression, not medicated (n = 242) | | 2.23 | (1.53, 3.27) |
| Depression, medicated (n = 121) | | 1.21 | (0.66, 2.24) |
| Depression | | | |
| No depression (n = 2851) (Reference) | | | |
| Depression, not medicated (n = 242) | | 2.22 | (1.52, 3.26) |
| Depressed, on N06AA\(^2\) (n = 16) | | 0.55 | (0.06, 4.93) |
| Depressed, on N06AB\(^3\) (n = 55) | | 0.85 | (0.32, 2.25) |
| Depressed, on other or multiple antidepressants (n = 46) | | 2.02 | (0.88, 4.64) |
mediators were measured at the same time. Future studies seeking to elucidate the mechanisms linking depression and BP should ideally be based on longitudinal designs with more frequent follow-ups.

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

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

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

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

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

**Conclusion**

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

**Data availability**

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

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**References**

1. James, S. L. *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1789–1858 (2018).
2. Gan, Y. *et al.* Depression and the risk of coronary heart disease: A meta-analysis of prospective cohort studies. *BMC Psychiatry* **14**, 11 (2014).
3. der Kooy, K. V. *et al.* Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *Int. J. Geriatr. Psychiatry* **22**, 613–626 (2007).
4. Roth, G. A. et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J. Am. Coll. Cardiol. 76, 2982–3021 (2020).
5. De Hert, M., Detraux, J. & Vancampfort, D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin. Neurosci. 20, 31–40 (2018).
6. Lippi, G., Montagnana, M., Favaloro, E. J. & Franchini, M. Mental depression and cardiovascular disease: A multifaceted, bidirectional association. Semin. Thromb. Hemost 35, 325–336 (2009).
7. Musselman, D. L., Evans, D. L. & Nemeroff, C. B. The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. Arch Gen Psychiatry 55, 580–592 (1998).
8. Penninx, B. W. J. H. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. Neurosci. Biobehav. Rev. 74, 277–286 (2017).
9. Bonnet, F. et al. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis 178, 339–344 (2005).
10. Gangwisch, J. E. et al. Insomnia and sleep duration as mediators of the relationship between depression and hypertension incidence. Am. J. Hypertens. 23, 62–69 (2010).
11. Hartik, E. et al. A meta-analysis of depressive symptomatology and alcohol consumption over time*. Br. J. Addict. 86, 1283–1289 (1991).
12. Koschke, M. et al. Autonomy of autonomic dysfunction in major depression. Psychosom. Med. 71, 852–860 (2009).
13. Crookes, D. M., Demmer, R. T., Keyes, K. M., Koenen, K. C. & Suglia, S. F. Depressive symptoms, antidepressant use, and hypertension in young adulthood. Epidemiology 29, 547–555 (2018).
14. Licht, C. M. M. et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension 53, 631–638 (2009).
15. Ginty, A. T., Carroll, D., Roseboom, T. J., Phillips, A. C. & de Rooy, S. B. Depression and anxiety are associated with a diagnosis of hypertension 5 years later in a cohort of late middle-aged men and women. J. Hum. Hypertens. 27, 187–190 (2013).
16. Pantell, M. S., Prather, A. A., Downing, J. M., Gordon, N. P. & Adler, N. E. Association of social and behavioral risk factors with earlier onset of adult hypertension and diabetes. JAMA Netw. Open 2, 10 (2019).
17. Räikkönen, K., Matthews, K. A. & Kuller, L. H. Trajectory of psychological risk and incident hypertension in middle-aged women. Hypertension 38, 798–802 (2001).
18. Meng, L., Chen, D., Yang, Y., Zheng, Y. & Hui, R. Depression increases the risk of hypertension incidence: A meta-analysis of prospective cohort studies. J. Hypertens. 30, 842 (2012).
19. Gromova, H. A., Gafarov, V. V. & Gagulin, I. V. Depression and risk of cardiovascular diseases among males aged 25–64 (WHO MONICA–psychosocial). Alaska Med. 49, 255–258 (2007).
20. Shinn, E. H. et al. Blood pressure and symptoms of depression and anxiety: A prospective study. Am. J. Hypertens. 14, 660–664 (2001).
21. Delaney, J. A. C. et al. Baseline depressive symptoms are not associated with clinically important levels of incident hypertension during two years of follow-up: The Multi-Ethnic Study of Atherosclerosis. Hypertension 55, 408 (2010).
22. Everson, S. A., Kaplan, G. A., Goldberg, D. E. & Salonen, J. T. Hypertension incidence is predicted by high levels of hopelessness in Finnish men. Hypertension 35, 561–567 (2000).
23. Jonas, B. S., Franks, P. & Ingram, D. D. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Am. Fam. Med. 6, 43–49 (1997).
24. Yan, L. L. et al. Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. JAMA 290, 2138–2148 (2003).
25. Meyer, C. M., Armenian, H. K., Eaton, W. W. & Ford, D. E. Incident hypertension associated with depression in the Baltimore Epidemiologic Catchment area follow-up study. J. Affect. Disord. 83, 127–133 (2004).
26. Patten, S. et al. Major depression as a risk factor for high blood pressure: epidemiologic evidence from a National Longitudinal Study. Psychosom. Med. 71, 273–279 (2009).
27. Vogt, T., Pope, C., Mullolooy, J. & Hollis, J. Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. Am. J. Public Health 84, 227–231 (1994).
28. Tusa, N. et al. The profiles of health care utilization among a non-depressed population and patients with depressive symptoms with and without clinical depression. Scand. J. Prim. Health Care 37, 312–318 (2019).
29. Hildrum, B., Romild, U. & Holmen, J. Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. BMC Public Health 11, 601 (2011).
30. Spierer, S. F. et al. 12-year changes in cardiovascular risk factors in people with major depressive or bipolar disorder: A prospective cohort analysis in Germany. Eur. Arch. Psychiatry Clin. Neurosci. https://doi.org/10.1007/s00406-018-0923-1 (2018).
31. Shah, M. T., Zonderman, A. B. & Waldstein, S. R. Sex and age differences in the relation of depressive symptoms with blood pressure during two years of follow-up: The Multi-Ethnic Study of Atherosclerosis. Hypertension 35, 631–638 (2009).
32. Arni, L. J. et al. Patterns of cross-sectional and predictive physical activity in Swiss adults aged 52+: results from the SAPALDIA cohort. Swiss Med. Weekly 150, 2020 (2020).
33. Martin, B. W. et al. SAPALDIA: Methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991–2003: Methods and characterization of participants. Soz. Praventivmed. 50, 245–263 (2005).
34. Arni, L. J. et al. Patterns of cross-sectional and predictive physical activity in Swiss adults aged 52+: results from the SAPALDIA cohort. Swiss Med. Weekly 150, 20 (2020).
35. Ware, J. et al. SF-36 Physical and Mental Health Summary Scales: A Users’ Manual (The Health Institute, 1994).
36. Martin, B. W. et al. Patterns of cross-sectional and predictive physical activity in Swiss adults aged 52+: results from the SAPALDIA cohort. Swiss Med. Weekly 150, 20 (2020).
37. Stahl, S. M. Blue genes and the monoamine hypothesis of depression. J. Clin. Psychiatry 61, 77–78 (2000).
38. Zhong, Z. et al. A meta-analysis of effects of selective serotonin reuptake inhibitors on blood pressure in depression treatment: outcomes from placebo and serotonin and noradrenaline reuptake inhibitor controlled trials. Neuropsychiatr Dis. Treat. 13, 2781–2796 (2017).
39. Davidson, J. R. T. Major depressive disorder treatment guidelines in America and Europe. J Clin Psychiatry 71 Suppl E1, e04 (2010).
40. Baune, B. T. et al. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. Transl. Psychiatry 2, e92–e92 (2012).
47. Rantanen, A. T., Korkeila, J. I. A., Kautiainen, H. & Korhonen, P. E. Non-melancholic depressive symptoms increase risk for incident cardiovascular disease: A prospective study in a primary care population at risk for cardiovascular disease and type 2 diabetes. J. Psychosomatic Res. 129, 109887 (2020).
48. Ford, C. D. et al. Psychosocial factors are associated with blood pressure progression among african americans in the Jackson heart study. Am. J. Hypertens. 29, 913–924 (2016).
49. Jeon, S. W. & Kim, Y.-K. Cognitive dimensions of depression: Assessment, neurobiology, and treatment. In Understanding Depression: Volume 2. Clinical Manifestations, Diagnosis and Treatment (ed. Kim, Y.-K.) 151–160 (Springer, 2018).
50. Cole, S. R. et al. Illustrating bias due to conditioning on a collider. Int. J. Epidemiol. 39, 417–420 (2010).

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

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Competing interests
The authors declare no competing interests.

Additional information
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