To live alone and to be depressed, an alarming combination for the renin—angiotensin—aldosterone-system (RAAS)

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KEYWORDS
Renin—angiotensin-system; Living alone; Depressed

Summary
Introduction: The renin—angiotensin—aldosterone-system (RAAS) is one of the most important systems involved in the pathogenesis of cardiovascular diseases. Its role in stress response has been generally neglected, although the progression of cardiovascular disease is considerably increased in the presence of stress and especially in the presence of depression risk.

With the present analysis we aimed to evaluate whether the activity of the RAAS correlates with depressive symptomatology and with chronic stress. Moreover, we aimed to analyse whether stress response is altered in the presence of depressed symptomatology. We chose “living alone” to be our paradigm of chronic stress.

Methods and results: Aldosterone and renin levels were assessed in 1743 (829 men, 914 women) from the population-based KORA study (Cooperative Health Research in the Region of Augsburg). The relationship between aldosterone, renin levels and the different combinations of living alone and depressive symptomatology was examined in three different multiple linear regression models adjusted for age, sex, creatinine levels, potassium levels, body mass index (BMI) and bio-behavioural factors.

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Neither “living alone” nor depressive symptomatology alone were associated with an activation of the RAAS, but the combination of living alone and depressive symptomatology yielded a highly significant increase in the aldosterone (p < 0.01) and renin level (p = 0.03).

**Conclusion:** Our findings show that depressive symptomatology is associated with a hyperresponsiveness to chronic stress. Under the condition of chronic stress depressed individuals have an activated RAAS. Activation of the RAAS might explain the known increased risk of negative cardiovascular disease outcomes in this group.

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1. Introduction

Numerous studies support the notion that stress-related depressive symptomatology and a lack of social relations are risk factors for cardiovascular disease (CVD) (Rozanski et al., 2005; Dimsdale, 2008; Frasure-Smith and Lesperance, 2010). Particularly, the combination of social isolation and depressive symptoms is known to be a malignant bio-behavioural risk factor for cardiovascular morbidity and mortality (Mookadam and Arthur, 2004; Wang et al., 2006; Frasure-Smith and Lesperance, 2010). In patients diagnosed with depression there is evidence of stress-related activation of the hypothalamic–adrenal–pituitary axis (HPA) (Holsboer et al., 1982; Gillespie and Nemeroff, 2005; Matthews et al., 2006; Belda et al., 2008), and the sympathoadrenal–medullary system (SAMS) (Kaplan et al., 1991) as well as altered autonomic cardiac control (Ehrenthal et al., 2010), and health-related behaviour (Rozanski et al., 2005). The increased mortality in socially isolated individuals is proposed to be caused by an increased response to stress in the absence of emotional and informational resources that promote adaption to acute or chronic stressors (Cohen and Wills, 1985).

Several large studies have demonstrated the fundamental role of the renin–angiotensin–aldosterone-system (RAAS) in the development and progression of CVD. Activation of the RAAS stimulates a range of processes involved in cardiovascular injury including oxidative stress (Leopold et al., 2007; Stehr et al., 2010), inflammation (Gekle and Grossmann, 2009), and insulin resistance (Lastra et al., 2010). Therefore, the commonly used agents to attenuate the progression of cardiovascular disease are ACE-inhibitors and Angiotensin-II-type-1-receptor-blockers (Cohn, 2007).

There is a tight interaction between the HPA axis and the RAAS in stress response (Gaillard et al., 1981; Whitworth et al., 1985; Ganong, 1993; Deuschle et al., 1998; Pavlatou et al., 2008), however the RAAS has not been considered as relevant to explain the relationship between the lack of social relations, depression and cardiovascular disease until now. In fact, research on the RAAS in the context of lack of social relations and depression is scarce. Plasma levels of aldosterone have been found to be elevated in depressed patients in two clinical studies (Murck et al., 2003; Emanuele et al., 2005).

To our current knowledge, no epidemiological study has investigated aldosterone and renin levels in relation to lack of social relations and depressive symptomatology. We propose that depressive symptomatology and the lack of social relations are associated with activation of the RAAS as a part of stress response. Moreover, we hypothesize that the combination/joint effect of “living alone” and depressive symptomatology is associated with activation of the RAAS, explaining part of the high cardiovascular mortality in this group.

We, therefore, aimed to investigate whether the conditions “living alone”, depressive symptomatology and the combination of both are associated with an activated RAAS. The measure of social relationships “living alone” has been found to be a reliable predictor of cardiovascular mortality (Case et al., 1992; Lund et al., 2002; Murphy et al., 2008). To this end, we analysed data from a large population-based study in southern Germany, representing a middle European population.

2. Methods

2.1. Settings

Data are based on the KORA (Cooperative Health Research in the Region of Augsburg) F4 study (2006–2008), a follow-up study of the KORA S4 survey conducted in 1999–2001. The KORA S4 study population was recruited from the region of Augsburg and two adjacent counties in the South of Germany. Study design, sampling method and data collection have been described in detail elsewhere (Herder et al., 2005). Briefly, in the KORA S4 survey men and women aged 25–74 years were randomly selected from population registries. 4261 participated in the baseline examination in order to study the role of biomarkers in the development of CHD and type 2 diabetes. In the follow-up examination KORA F4, conducted between 2006 and 2008, 3080 participants took part. The F4 study was restricted to subjects aged 32–81 years at follow-up. Written informed consent was obtained from each study participant. The study was approved by the local ethics committee.

2.2. Study group

In order to obtain a study population without major chronic diseases conditions, individuals with a history of heart disease, kidney disease, liver disease, inflammatory bowel disease, cancer or stroke (n = 478) and regular consumers of beta-blockers, diuretics, ACE-inhibitors and angiotensin-receptor antagonists (n = 641) were excluded, leaving a data set of 1916 participants. Furthermore, participants with missing data on biomarkers and covariates (n = 245) were excluded, leaving a final data set of 1743 (829 men, 914 women).
2.3. Assessment of metabolic factors

During the physical examination, standardised measurements of height, weight, waist circumference and blood pressure were performed. Blood pressures were measured three times on the right arm of the seated participant using an oscillometric digital blood pressure monitor (HEM-705CP, OMRON Corporation, Tokyo, Japan). For statistical analyses the mean of the second and third measurements were used. Medication intake was categorized according to the Anatomical Therapeutical Chemical (ATC) classification index. Antihypertensive medication was defined following the guidelines of the German Hypertension Society.

Blood samples were taken in the mornings from the cubital vein of seated participants. Patients had fasted overnight and rested in seated position for 5–10 min, before venous blood samples were drawn.

Creatinine was determined by means of modified Jaffee method (KREA Flex, Dade Behring). Total cholesterol, HDL, and triglycerides were measured as described elsewhere (Rathmann et al., 2003). Plasma sodium and potassium were measured by indirect potentiometry (QuikLYTE, Dade Behring).

2.4. Assessment of aldosterone and renin levels

Blood samples and questionnaire-based data were collected on the same day. After collection, samples were centrifuged within 30 min and EDTA plasma was stored at –80 °C until analysis. As longer exposure to 4 °C can potentially affect active renin concentrations (croyactivation), storage at 4 °C was avoided and samples were not cooled during the 30 min before centrifugation. On the day of the respective assays (aldosterone concentration, active renin concentration), samples were thawed and analysed in parallel. Plasma aldosterone concentration (PAC) was measured with an in house immuno- fluorometric assay. Inter- and intra-assay coefficients of variation were 15.2% and 7.3% in low and 8.0% and 4.4% in high concentrations, respectively (Manolopoulou et al., 2008).

Plasma renin concentrations (PRC) were determined using the Liaison active renin assay ( Diasorin, Dietzenbach, Germany). This assay is based on monoclonal antibodies and/ or only detects active renin molecules with no interference from pro-renin. Intra- and inter-assay coefficients of variation were below 5.6% and 12.2%, respectively, and the functional sensitivity was <2.0 µU/ml.

To obtain equal units, PRC was first converted to pg/ml. The conversion factor was 1.66.

2.5. Assessment of behavioural risk factors and psychosocial factors

Information on behavioural risk factors was obtained in standardised personal interviews conducted by trained medical staff or through a self-administered questionnaire. Participants were asked to provide details on their health behaviours concerning smoking, alcohol consumption, and physical activity. High alcohol consumption was defined as daily intake ≥40 g for men and ≥20 g for women. The applied thresholds are defined by the WHO as thresholds for “hazardous drinking” (Rehm et al., 2004). Participants were classified as “physically active” if they regularly participated in sports during leisure time in summer and winter and if they were active in summer and in winter with duration of ≥1 h/week in either season. Similar assessments of physical activity have been used in other population-based studies (Verkooijen et al., 2008; Hahn et al., 2009). In addition, information regarding a participant’s housing situation was assessed.

Living alone: Living alone was assessed by asking the subject how many people lived in the household including the participant himself. Participants who chose the answer “one person” were comprised in the category “living alone”.

Depressive symptomatology was assessed by the Depression and EXhaustion subscale (DEEX scale). The scale combines eight items (fatigability, tiredness, irritability, loss of energy, difficulty in concentrating, inner tension, nervousness, anxiety) rated from 0 to 3, leading to a score of 24. Subjects in the top third of the depressive symptom distribution were considered as the index group with depressive symptomatology. Sex-specific cut-off points were applied (≥12 for women, ≥10 for men) (Ladwig et al., 2004).

2.6. Statistical analysis

Skewed variables were log-transformed to reach an approximately normal distribution. These include aldosterone, renin, triglycerides, HDL, and total cholesterol. All analyses for these variables were then based on log-transformed data. Means and proportions for baseline demographic characteristics and metabolic characteristics, behavioural risk factors and psychosomatic symptoms were computed for the categories “living together, not depressed”, “living alone, not depressed”, “living together, depressed”, “living alone, depressed”. Differences in means were tested with ANOVA. Differences in proportions were tested with χ²-test.

To investigate the association of different combinations of depressive symptomatology and living alone with the outcome renin and aldosterone, we conducted a multiple linear regression model adjusted for age, sex, creatinine and potassium levels. Ageing, sex, potassium levels and renal function are known to influence the levels of renin and aldosterone (Stowasser et al., 2010). First, a possible modification of these associations was assessed by including the interaction term: depressive symptomatology × living alone. Then, three multiple linear regression models with different adjustments were performed to compare the association between the different risk groups created by combining “living alone” with depressive symptomatology, using the reference category “living together, not depressed”. Dummy variables were used for the different combinations of living alone and depressive symptomatology. The first model was adjusted for age, sex, creatinine and potassium. The second model was adjusted for age, sex, creatinine, potassium, and behavioural risk factors (alcohol consumption, smoking, physical inactivity). These three behavioural factors have been suggested to influence the RAAS activity (Bezegh et al., 1991; Kovacs et al., 1992; Andersson et al., 1993; Fallo, 1993). Moreover, there were significant differences in smoking behaviour and physical activity between the groups under investigation. The third model was adjusted for age, sex, creatinine, potassium and BMI (since the RAAS is known to be dysregulated in obese individuals) (Sarzani et al., 2008). Adjusted means were drawn from model 1.
To test the assumption that different degrees of depressive symptomatology are the underlying cause for any effect of the combination of depressive symptomatology and the condition “living alone”, we tested for a dose–response relationship between depressive symptomatology and renin and aldosterone levels in men using Pearson’s correlation coefficient between log-transformed aldosterone and renin levels and a continuous measure of depressive symptomatology. For the dose–response analysis the sum of scores in the DEEX scale was used as a continuous measure.

SAS (V9.1) was used for statistical analysis with a significance level of \( p < 0.05 \) (SAS Institute, Carey, North Carolina).

3. Results

3.1. Descriptive analysis

Among the 1743 subjects enrolled in the present investigation, 1094 subjects lived with somebody and did not fulfil the criteria of depressive symptomatology. This subgroup was taken as the reference group for the 3 risk groups under investigation. A group of 165 subjects lived alone but did not suffer a depressive symptomatology. A group of 411 subjects fulfilled the criteria of depressive symptomatology but lived with somebody, and a group of 73 subjects lived alone and suffered from depressive symptomatology.

Clinical, metabolic, and behavioural characteristics of the 4 groups are reported in Table 1. The most striking difference was a significantly increased aldosterone level in the group of subjects who lived alone and fulfilled the criteria of depressive symptomatology. Subjects in this group were significantly older. No significant differences in clinical and metabolic characteristics between groups could be seen. With regard to behavioural risk factors the following difference could be seen: Subjects who lived alone were more likely to smoke.

3.2. Association between aldosterone and depressive symptomatology and “living alone”

In the multiple linear regression analysis, we first tested for a possible modification of the association between depressive symptomatology, living alone and aldosterone by using the interaction term depressive symptomatology \( \times \) living alone. This model was adjusted for age, sex, creatinine and potassium. The interaction term was highly significant with a \( p < 0.01 \). Results are not shown.

Then 3 models with different adjustments were calculated to test for the association between aldosterone and the different combinations of depressive symptomatology and living alone (Table 2). All 3 models were adjusted for age, sex, creatinine and potassium. The second model was additionally adjusted for behavioural factors (alcohol, smoking, physical activity). The third model was additionally adjusted for BMI. In all four models a highly significant association between aldosterone and the combination of depressive symptomatology and living alone was found \( (p < 0.01) \), whereas neither depressive symptomatology nor the condition “living alone” by themselves were associated with increased aldosterone levels.

### Table 1  Characteristics of study subjects \((n = 1743)\), data are shown for each category of combining living alone and depressed symptomatology.

<table>
<thead>
<tr>
<th>Subjects (number)</th>
<th>Living together not depressed</th>
<th>Living alone not depressed</th>
<th>Living together depressed</th>
<th>Living alone depressed</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.93 ± 0.31</td>
<td>50.01 ± 0.88</td>
<td>49.82 ± 0.45</td>
<td>53.10 ± 1.37</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.59 ± 0.13</td>
<td>26.34 ± 0.31</td>
<td>26.71 ± 0.22</td>
<td>26.25 ± 0.55</td>
<td>0.75</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>119.12 ± 0.52</td>
<td>120.09 ± 1.31</td>
<td>118.27 ± 0.76</td>
<td>115.91 ± 2.00</td>
<td>0.27</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75.59 ± 0.30</td>
<td>75.61 ± 0.71</td>
<td>75.32 ± 0.45</td>
<td>72.64 ± 1.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Heart rate</td>
<td>72.74 ± 0.29</td>
<td>72.73 ± 0.70</td>
<td>73.61 ± 0.45</td>
<td>74.62 ± 1.11</td>
<td>0.19</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.18 ± 0.29</td>
<td>4.19 ± 0.02</td>
<td>4.20 ± 0.01</td>
<td>4.20 ± 0.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>139.15 ± 0.01</td>
<td>138.87 ± 0.22</td>
<td>139.08 ± 0.12</td>
<td>138.62 ± 0.31</td>
<td>0.19</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio(^a)</td>
<td>3.82 ± 1.00</td>
<td>3.83 ± 1.01</td>
<td>3.84 ± 1.00</td>
<td>3.77 ± 1.01</td>
<td>0.31</td>
</tr>
<tr>
<td>Triglycerids/HDL ratio(^a)</td>
<td>3.15 ± 1.01</td>
<td>3.18 ± 1.07</td>
<td>3.20 ± 1.01</td>
<td>3.15 ± 1.02</td>
<td>0.54</td>
</tr>
<tr>
<td>Creatinine ((\mu)mol/l)</td>
<td>76.64 ± 0.01</td>
<td>75.76 ± 0.01</td>
<td>77.52 ± 0.01</td>
<td>74.88 ± 0.08</td>
<td>0.61</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)(^a)</td>
<td>38.78 ± 1.02</td>
<td>36.33 ± 1.06</td>
<td>37.82 ± 1.04</td>
<td>47.73 ± 1.08</td>
<td>0.03</td>
</tr>
<tr>
<td>Renin (pg/ml)(^a)</td>
<td>6.28 ± 0.61</td>
<td>6.27 ± 0.64</td>
<td>6.36 ± 0.62</td>
<td>7.12 ± 0.66</td>
<td>0.6</td>
</tr>
<tr>
<td>Ratio aldosterone/renin(^a)</td>
<td>6.18 ± 1.03</td>
<td>5.79 ± 1.07</td>
<td>5.94 ± 1.04</td>
<td>6.71 ± 1.11</td>
<td>0.78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavioural risk factors</th>
<th>Living together not depressed</th>
<th>Living alone not depressed</th>
<th>Living together depressed</th>
<th>Living alone depressed</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker (%)</td>
<td>21.9</td>
<td>31.5</td>
<td>19.2</td>
<td>32.9</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;20 g/40 g alcohol/day (%)</td>
<td>16.5</td>
<td>23.0</td>
<td>19.71</td>
<td>23.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Physically inactive (%)</td>
<td>38.6</td>
<td>39.4</td>
<td>48.2</td>
<td>49.3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are expressed as arithmetic means ± SE or as percentage, unless otherwise indicated. \( p \)-Value for comparison across the different categories using ANOVA for continuous variables and \( \chi^2 \) for categorical variables.

\(^a\) Geometric mean ± SE.
3.3. Association between renin, depressive symptomatology and living alone

In the model using renin as the outcome, the interaction term living alone x depressive symptomatology was not significant with a $p = 0.11$. Data are not shown.

In all 3 models with different adjustments (Table 2), the association between renin and the combination of living alone and being depressed was significant ($p = 0.02$ in model 1, $p = 0.04$ in model 2, $p = 0.03$ in model 3). Again, neither depressive symptomatology nor the condition “living alone” by themselves were associated with increased renin levels.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Multiple linear regression to assess the association of categories of different combinations of living alone and depressed symptomatology with aldosterone and renin.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Living alone, not depressed</td>
</tr>
<tr>
<td></td>
<td>$\beta$-Estimate</td>
</tr>
<tr>
<td>Aldosterone</td>
<td></td>
</tr>
<tr>
<td>Model 1 $^a$</td>
<td>$-0.04$</td>
</tr>
<tr>
<td>Model 2 $^b$</td>
<td>$-0.05$</td>
</tr>
<tr>
<td>Model 3 $^c$</td>
<td>$-0.06$</td>
</tr>
<tr>
<td>Renin</td>
<td></td>
</tr>
<tr>
<td>Model 1 $^a$</td>
<td>$0.01$</td>
</tr>
<tr>
<td>Model 2 $^b$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>Model 3 $^c$</td>
<td>$0.01$</td>
</tr>
</tbody>
</table>

Reference category is the category “living together, not depressed”.

$^a$ Model 1: adjusted to age, sex, creatinine, potassium.

$^b$ Model 2: adjusted to age, sex, creatinine, potassium, alcohol, smoking, physical activity.

$^c$ Model 3: adjusted to age, sex, creatinine, potassium and BMI.

3.4. Comparison of adjusted means

Adjusted means were drawn from model 1 (Fig. 1). Mean aldosterone levels in the group “living alone, depressed” were highly significantly increased ($p < 0.01$) in comparison with the reference group (“living alone, depressed”: mean: 48.13 (CI: 41.55–55.75) pg/ml, “living together, not depressed”: mean: 38.45 (CI: 36.97–39.98) pg/ml). There were no significant differences between means in the group “living alone, not depressed” (mean: 36.93 (CI: 32.96–41.37) pg/ml) and in the group “living together, depressed” (mean: 37.95 (CI: 35.60–40.46) pg/ml) in comparison with the reference group.

Mean renin levels were significantly increased in the group “living alone, depressed” (mean: 7.58 (CI: 6.40–8.97) pg/ml) in comparison with the reference group (mean: 6.20 (CI: 5.93–6.47) pg/ml). Significant differences could be seen in the groups “living alone, not depressed” (mean: 6.23 (CI: 5.46–7.12) pg/ml), “living together, depressed” (6.30 (CI: 5.89–7.43) pg/ml).

3.5. Correlation between depressive symptomatology, renin and aldosterone levels

The correlation of the continuous measure of depressive symptomatology with aldosterone and renin levels was not significant (aldosterone: $p = 0.8$, renin: $p = 0.9$). Data are not shown.

4. Discussion

To our knowledge, this is the first study conducted on an epidemiological level to show that the combination of depressive symptomatology and living alone is associated with an activated RAAS with significantly increased renin levels and highly significantly increased aldosterone levels. The association could not be explained by differences in potassium or creatinine levels. Adjustment for age, sex, BMI, and behavioural risk factors did not change the result. Individuals who lived alone and suffered depressed symptomatology were significantly older than the other groups in our
study. Interestingly, the RAAS tends to decrease with age (Bauer, 1993). Thus, it appears that the combination of living alone and depressive symptomatology reverses this trend.

Human studies on the role of the RAAS in stress and depression have been scanty. One small clinical study by Murck et al. showed significantly elevated night time aldosterone levels in 7 depressed patients (Murck et al., 2003). In a second study investigating the RAAS in depression, Emanuele and colleagues reported 2.77 times higher odds of elevated plasma levels of aldosterone in 65 depressed patients in comparison with the 65 controls (Emanuele et al., 2005) but only a slight trend in elevated renin levels. Some studies have found an association between RAAS polymorphism in humans, which have phenotypes with higher AT and angiotensin-converting-enzyme (ACE)-activity and increased incidence of depression (Arinami et al., 1996; Baghai et al., 2006).

Interestingly, RAAS activation was neither associated with depressive symptomatology alone nor with the condition “living alone” but with the combination of depressive symptomatology and the condition “living alone”. There is evidence that in depressed individuals the physiologic response to acute stress is altered in comparison with healthy individuals (Pace et al., 2006; Weinstein et al., 2010). Our results suggest that individuals suffering depressive symptomatology also react differently to the chronic stress condition “living alone”. As the combination of social isolation and depression has been shown to be particularly malignant concerning the development of CHD (Mookadam and Arthur, 2004; Wang et al., 2006; Frasure-Smith and Lesperance, 2010), our results suggest that activation of the RAAS may contribute to the pathologic effect of depression and social isolation. Aldosterone is known to promote cardiovascular injury (Connell et al., 2008) and endothelial dysfunction (Sowers et al., 2009).

Our study is an association study, giving no information on the direction or causality, but animal studies have shown that aldosterone can induce depressive-like behaviour in rats in rodents (Hlavacova et al., 2011), and angiotensin II receptor blockers are supposed to reduce stress (Gard et al., 1999; Armando et al., 2001; Baiardi et al., 2004; Saavedra et al., 2011), suggesting that the activated RAAS might not only be a consequence of increased stress in socially isolated and depressed individuals but may be causally, directly or indirectly related to depression.

The RAAS is not just one circulating hormonal system but also a so-called local RAAS with local angiotensin 2 (AT 2)-synthesis is expressed in different tissues, including the brain (Saavedra, 2005). Brain RAAS distribution of angiotensin 1 (AT 1)-receptors follows the hypothalamic—pituitary—adrenal axis (Yang et al., 1996). During stress, enhanced sympathetic activation leads to an increase in renin production and this generates increased blood levels of AT 2 (Yang et al., 1993; Yang et al., 1996). Increased circulation of AT 2 augments the stimulation of physiologically active AT 1-receptors (Timmermans, 1999) contributing to increased anterior pituitary ACTH, adrenal glucocorticoid, aldosterone and catecholamine formation and release during stress.

4.1. Strength and limitations

“Living alone” has limitations in measuring social relationships (Holt-Lunstad et al., 2010), as “living alone” does not necessarily exclude having a large supportive social network. However, there is clear evidence that although there are more sophisticated measures of social relations, “living alone” has been proven to be a reliable risk factor for increased cardiovascular mortality (Case et al., 1992; Lund et al., 2002; Murphy et al., 2008). To combine “living alone” and “depressive symptomatology” focuses on subjects who already suffer from depressive symptoms. These subjects are more likely to lack social support as a stress buffer, in comparison with subjects who live alone and are not depressed. Therefore, the combination of “living alone” and “depressive symptomatology” might be a useful tool to investigate chronic stress in combination with the stress-related “depressive symptomatology”.

Our sample was composed of Caucasians of European ancestry, so generalizations to other ethnicities cannot be made. The cross-sectional design of this study precludes conclusions with regard to causal relationships.

Unfortunately, we did not have any information on dietary sodium intake which is known to influence RAAS activity. But adjustment for plasma sodium, a weaker indicator for dietary sodium intake did not change the results. Depressed mood was assessed using the DEEX scale. The DEEX scale assesses the acute psychopathological state of depressive symptomatology and not a certain interval. Nevertheless, validity within the framework of depression-to-somatic illness concept has been proven to be highly significant. The DEEX scale with equal cutpoints has been proven as a reliable instrument to measure depressive symptoms in several publications (Ladwig et al., 2003, 2005, 2006; Hafner et al., 2011). The DEEX scale focuses on symptoms which measure “vital exhaustion” like reduced vitality and weakness. Items reflecting negative self-concepts, or feelings of guilt and distrust were not included, because the depressive symptoms depletion and tiredness rather than feelings of guilt and hopelessness have been found to be predictive for cardiovascular morbidity and mortality (Appels and Mulder, 1988; Schulz et al., 2000; Kop et al., 2005). Despite these limitations, our study has several strengths, including the large number of study participants, the population-based design and particularly the detailed and structured information on metabolic variables, behavioural risk factors and psychosocial factors of study participants.

5. Conclusion

Our results show that the combination of living alone and suffering from depressive symptomatology is a sustained stress condition in humans associated with increased activation of the RAAS. It is not unlikely that the activated RAAS is part of the underlying link between depression and cardiovascular mortality. Further studies are needed to better assess the role of the RAAS in stress and depression, with the focus on cause—effect relationships using longitudinal designs. Moreover, in longitudinal designs time effects like the duration of the depressive symptomatology and the duration of the condition “living alone” can be taken into account. Future research should elucidate the possible preventive effect of AT1-receptor blockers in the long-term development of cardiovascular disease in depressed and stressed patients. Such efforts could answer whether the activated RAAS is only a consequence of increased stress in
socially isolated and depressed individuals or might be also causally related to depression.

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Conflict of interest
All other authors declare that they have no conflicts of interest.

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