- 1 Physicians' lifestyle advice on primary and secondary CVD prevention in Germany: A
- 2 comparison between the STAAB cohort study and the German subset of EUROASPIRE IV

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- 25 Parts of the results have been presented at the "Herztage" of the Autumn Conference of the
- 26 German Society of Cardiology, Berlin 2018, Germany.

# 27 Abstract

Background: We assessed prevalence and determinants on appropriate physician-led lifestyle
 advice (PLA) in a population-based sample of individuals without cardiovascular disease (CVD)
 compared to a sample of CVD patients.

Methods: PLA were assessed via questionnaire in a subsample of the population-based 31 Characteristics and Course of Heart Failure Stages A-B and Determinants of Progression (STAAB) 32 cohort free of CVD (primary prevention sample), and the German subset of the 4<sup>th</sup> EUROASPIRE 33 34 Survey (EA-IV) comprising CVD patients (secondary prevention sample). "PLA" was fulfilled if the 35 participant reported on having ever been told by a physician to: stop smoking (current/former 36 smokers), reduce weight (overweight/obese participants), increase physical activity (physically inactive participants), or keep a healthy diet (all participants). Factors associated with receiving 37 38 at least 50% of PLA were identified using logistic regression: including in the first step age, sex, education, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL) and, in a second 39 step. also lifestyle factors such as smoking, BMI >25 kg/ $m^2$ , and physical inactivity. 40

**Results:** Information on PLA was available in 665 STAAB participants (55±11; 55% females) and in 536 EA-IV patients (67±9; 18% females). Except for smoking, appropriate PLA was more frequently given in the secondary compared to the primary prevention sample. Determinants associated with appropriate PLA in primary prevention were: DM (OR 5.61; 95%CI 2.40-13.08), HPL (OR 2.92; 95%CI 2.03-4.21), and HT (OR 1.85; 95%CI 1.29-2.66); and in secondary prevention: age (OR per year 0.95; 95% CI 0.93-0.98), and DM (OR 2.43; 95%CI 1.43-4.12).

47 Conclusions: In primary prevention, PLA was mainly determined by the presence of vascular risk
 48 factors, whereas in secondary prevention the level of PLA was higher in general, but the
 49 association between CVD risk factors and PLA was less pronounced.

50 <u>Key words</u>: cardiovascular risk factors, primary prevention, secondary prevention, population 51 based, primary care, lifestyle advice

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# 53 Introduction

<sup>54</sup> Implementing and maintaining good lifestyle habits constitutes a central recommendation of guidelines <sup>55</sup> on primary and secondary prevention of cardiovascular disease (CVD).<sup>1, 2</sup> CVD prevention aims to <sup>56</sup> improve quality of life and life expectancy, both in primary and secondary care.<sup>3</sup> The strong relationship <sup>57</sup> between the risk of developing CVD and behavioural risk factors including lack of regular physical <sup>58</sup> activity, smoking, and poor diet, is well described.<sup>3</sup> Favourable adoption of lifestyle factors was shown to <sup>59</sup> significantly reduced incident and recurrent CVD events as well as CVD mortality risk.<sup>3-8</sup>

60 The EUROASPIRE (EUROpean Action on Secondary and Primary prevention In order to Reduce Events) 61 surveys iteratively report on the magnitude of and secular trends regarding lifestyle and risk factor management according to European guidelines in individuals at high CVD risk or with established CVD.<sup>6</sup> 62 For example, in EUROASPIRE IV (EA-IV), only half of coronary patients were advised to attend a CVD 63 prevention and rehabilitation program.<sup>6, 9, 10</sup> Time trends in lifestyle risk factors of the EUROASPIRE II, III 64 and IV surveys of 9 European countries over a period of 14 years showed that the prevalence of adverse 65 66 lifestyle factors such as obesity and central obesity increased by 7% and 6%, respectively, and one out of 67 five coronary patients still smoked at the time of evaluation, 6 months to three years after a cardiac event.11 68

To positively impact on cardiovascular risk, a multidisciplinary approach is advocated emphasizing lifestyle modification and risk factor management in both primary and secondary prevention.<sup>6, 12, 13</sup> The importance of the treating physician promoting a healthy lifestyle in routine care has been underscored by various reports.<sup>6, 14, 15</sup> Treating physicians play an important role in addressing good lifestyle habits and supporting patients to implement lifestyle into their everyday life using health education, health promotion, and behavioral counselling in primary and secondary prevention.<sup>13, 16, 15</sup> However, little is known about the frequency of appropriate physician-led lifestyle advices (PLA) according to recent CVD prevention guidelines as well as factors determining, which patient will receive PLA in different health care settings. Therefore, we compared the prevalence and determinants of PLA between participants from the general population without CVD (i.e. primary prevention setting) and CVD patients (i.e., secondary prevention setting).

80 Methods

#### 81 **Primary prevention**

Information regarding primary prevention sample was derived from a subset of the population-based *Characteristics and Course of Heart Failure Stages A-B and Determinants of Progression* (STAAB) cohort study. STAAB aims to examine the prevalence and natural course of early heart failure stages in a randomly selected representative sample of 5000 inhabitants of the City of Würzburg, aged 30-79 years. The study design and rationale have been published in detail previously.<sup>17</sup> For the current analysis, we excluded participants with established cardiovascular disease (CVD) defined by a self-reported history of coronary artery disease, peripheral artery disease, or stroke.

## 89 Data collection

Information on sociodemographic status (sex, age, education), smoking, recommended lifestyle advice given by physicians, and physical activity, was obtained via face-to-face interview. Weight, height, and blood pressure were obtained applying standard operative procedures. Blood pressure was measured on the dominant upper arm up to three times in sitting position. Self-reported history of CVD and cardiovascular risk factors (diabetes, high blood pressure, hyperlipidemia) were obtained by study physicians. Blood samples were collected in fasting participants. All examinations were performed according to standardized operation procedures.

#### 97 Secondary prevention setting

98 Information regarding secondary prevention sample was derived from the German subset of the 99 "hospital-arm" of the EA-IV Survey recruited from the University Hospital Würzburg and the Dept. of 100 Medicine, Klinik Kitzinger Land. Study subjects were approached six months to three years after 101 hospitalization for a coronary event (index). EA-IV was conducted between 2012 and 2013 in 24 European countries to investigate the quality of cardiovascular risk factor control and guideline 102 implementation in clinical practice.<sup>9</sup> Patients were aged between 19 and 79 years and suffered from 103 coronary heart disease (acute myocardial infarction, unstable angina, percutaneous coronary 104 105 intervention, or coronary bypass grafting). The study design and rationale of the German subset of EA-IV have been published in detail previously.<sup>18</sup> 106

## 107 Data collection

Medical records were reviewed to collect information about details of the index event. Sociodemographic status (sex, age and education), self-reported CVD risk factors (diabetes, high blood pressure, hyperlipidemia) and information on smoking were obtained in a personal patient interview 6 to 36 months after hospitalization for the index event. Weight, height, and blood pressure were assessed by physical examination. Blood pressure was measured twice on the dominant upper arm in sitting position. Provided lifestyle advice was collected by self-administered questionnaire. All examinations were performed according to EA-IV standards at the study visit.

For both prevention samples, body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Physical activity ( $\geq$ 150 min/week of moderate activity or  $\geq$ 75 min/week of strenuous activity) was operationalized by the International Physical Activity Questionnaire (IPAQ).<sup>19</sup>

118 Due to the differences in the assessment of the individual's educational level in STAAB (school leave 119 qualification) and EA-IV (vocational qualification), we harmonized the educational level as follows: no formal schooling, less than primary schooling, primary school completed, secondary school completed, high school completed, intermediate between secondary level and university (e.g. technical training) to low school-leaving qualification. College/University completed and postgraduate degree were allocated to graduate of a higher school.

#### 124 Definition of recommended lifestyle advice

125 Physician-led appropriate lifestyle advice (PLA) was defined according to recent European Guidelines on 126 CVD Prevention in Clinical Practice (version 2016)<sup>3</sup> if the study participant reported on having ever been 127 told by a physician: to stop smoking in current/former smoking participants; to reduce weight in participants with a BMI >25 kg/m<sup>2</sup>; to increase physical activity in participants with less than <150 min/ 128 129 week moderate activity; or to keep a healthy diet was recommended for all participants. The rate of 130 adequately received lifestyle advices was calculated as the percentage of lifestyle advices divided by the 131 number of all lifestyle advices a patient was potentially eligible for. For example, if a patient met criteria 132 for three, but had received only two lifestyle advices, then he was considered having received 67% of 133 adequate lifestyle advices.

### 134 Determinants for receiving lifestyle advice

A priori, we identified a set of covariables potentially related to receiving PLA including sociodemographic factors (age, sex, education), self-reported CVD risk factors (diabetes, high blood pressure, hyperlipidaemia), and lifestyle risk factors (smoking, overweight, physical inactivity).<sup>6, 20-22</sup>

## 138 Data analysis

For categorical variables, we reported proportions (%). For univariable analysis,  $\chi^2$ - test for categorical and binary variables or Fisher's exact were used, as appropriate. Percentage of PLA was calculated and determinants of receiving at least 50% of PLA in either study sample were identified. We calculated in a 142 sensitivity analysis proportions for PLA in STAAB participants at "high CVD risk" according to the recent 143 definition for EA-IV patients from the "primary care arm". This definition based on the prescription of blood pressure lowering and/or lipid-lowering medication, and/or diabetes on treatment (diet or 144 medications). <sup>23</sup> In a first multivariable logistic regression analysis we calculated odds ratios (OR) with 145 146 95% confidence intervals (CI) to assess whether sociodemographic status or self-reported CVD risk factors predicted the chance to receive ≥50% of PLA. In a second model, we adjusted also for CVD 147 148 lifestyle risk factors. P-values < 0.05 were considered statistically significant. Analyses were performed 149 with IBM SPSS Statistics 23 (IBM<sup>®</sup> SPSS<sup>®</sup> Statistics Version 23).

# 150 Ethics and data protection

For the STAAB cohort study and the EA-IV study, approvals of the Ethics Committee of the Medical Faculty of the University of Würzburg (votes 98/13 and 58/12, respectively) and the data protection officer of the University of Würzburg (J-117.605-09/13) were obtained. All participants provided written informed consent prior to study examinations.

## 155 Results

## 156 Characteristics of the study participants in primary and secondary prevention

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For the primary prevention sample, we assessed recommended lifestyle advice in a subsample of 707 participants via face-to-face interview. All 707 participants received and completed the lifestyle questionnaire. Of those, 42 (5.9%) reported a history of CVD. Therefore, 665 participants (mean age 54.9±11.4 years; 55.3% women) were included in the present analyses.

- 162 For the secondary prevention sample, recommended lifestyle advice was assessed in the entire 536
- 163 participants (mean age 67.4±8.9 years; 17.7% women) from the German subsample of the EA-IV survey.
- 164 Characteristics of both study populations are shown in Table 1.

165 In general, frequency of receiving PLA was higher in patients from the secondary compared to the 166 primary prevention sample; "keep healthy diet": EA-IV 73.1%, STAAB 43.9% (p < 0.001); "reduce weight": 167 EA-IV 69.2%, STAAB 43.8% (p <0.001); "increase physical activity": EA-IV: 71.4%, STAAB: 52.1% (p <0.01), 168 except for the advice for smoking cessation: STAAB: 44.0%, EA-IV: 36.7% (p 0.08). According to the recent definition for EA-IV patients at high CVD risk from the "primary care arm" we identified 200 169 170 (31.0%) STAAB participants at high CVD risk with higher proportions for PLA (reduce weight: 56.4%; 171 increase physical activity: 54.7%), except for smoking with 42.7% compared to the entire STAAB primary 172 prevention sample.

Significantly higher proportions for receiving ≥50% of PLA were observed in participants with selfreported hypertension (63.5%, p <0.001), high LDL-C levels (67.6%, p <0.001) and diabetes mellitus (85.4%, p <0.001) in the primary prevention sample.

176 In the secondary prevention sample, patients with self-reported diabetes mellitus (84.4%, p 0.01) more 177 frequently received  $\geq$ 50% PLA; no statistically significant differences were observed for the other risk 178 factors. Age, sex and education were not associated with receiving  $\geq$ 50% PLA in both primary and 179 secondary prevention settings (Table 1).

## 180 Determinants for receiving ≥50% appropriate lifestyle advices

In multivariable analyses, the chance for receiving  $\geq 50\%$  PLA in primary prevention was significantly higher in patients with self-reported diabetes mellitus (OR 5.61; 95%CI 2.40-13.08), hyperlipidemia (OR 2.92; 95%CI 2.03-4.21), and hypertension (OR 1.85; 95%CI 1.29-2.66). In secondary prevention setting, patients with diabetes mellitus was independently associated with a higher chance for receiving  $\geq 50\%$ PLA (OR 2.43; 95%CI 1.43-4.12), whereas a decrease of receiving  $\geq 50\%$  PLA with advancing age (OR per year 0.95; 95% CI 0.93-0.98) was observed in the total secondary prevention sample (Table 3a). Adding lifestyle risk factors as potential determinants to the multivariable models did not substantially alter these results, except for BMI >25 kg/m<sup>2</sup> in the primary prevention sample (OR 1.80, 95%CI 1.22; 2.65) [Table 3b]. A relevant number of missing values occurred in the second multivariable model (18.2% in STAAB and 28.7% in EA-IV) therefore we compared the distribution of the dependent as well as the independent variables between the total data set and the selected data set, and observed no variations. Consequently, we assume that the selected data set is representative for the whole sample and that values are missing at random (Supplement Table 3 a-b).

## 194 Discussion

195 Our study assessed the prevalence and determinants for receiving PLA recommended in current clinical 196 guidelines for CVD prevention in primary and secondary prevention settings. We observed that 197 individuals in secondary prevention setting received significantly more often PLA compared to individuals 198 without established CVD, except for smoking cessation. In the primary prevention setting, established 199 CVD risk factors such as hypertension, hyperlipidemia and diabetes mellitus were strongly related to a 200 higher chance of receiving ≥50% PLA. In secondary prevention settings, the only association between 201 CVD risk factors and PLA was found for diabetes mellitus. In addition, we observe a decrease of PLA with 202 increasing age in secondary prevention.

## 203 Prevalence of adequate lifestyle advice in primary prevention samples

A direct comparison of lifestyle risk factor management with previous studies is limited due to varying target populations as well as due to differences in the assessment of lifestyle risk factors. In addition, most of the previous studies on this topic were conducted in primary care settings in patients with high CVD risk. The "primary care arm" from the EA-IV survey included 4579 patients at high risk of CVD in 14 European countries (mean age 58.8 years, 57.8% women) observed more frequently lifestyle advice (smoking cessation: 73.5%, reduce weight: 65.2% and increase physical activity: 59.0%) compared to the

entire STAAB primary prevention sample with 44.0%, 43.8% and 52.1%, respectively.<sup>23</sup> In addition, we 210 211 observed still lower proportions in the predefined STAAB participants at high CVD risk. The higher 212 recommendation rates in EA-IV could result from the fact, that also recommendations made by other 213 healthcare professionals were considered. Another international cross-sectional observational study from the European Practice Assessment of Cardiovascular Risk Management (EPA Cardio) project<sup>24</sup> in 9 214 215 European countries including 3723 individuals at high risk of CVD (mean age 66 years, 29.5% women; 216 without established diabetes) from 268 general practices recorded lifestyle counselling by general practitioners documented within the medical records within the last 15 month.<sup>25</sup> This study also 217 observed higher proportions of advice for smoking cessation (65.5%) compared to STAAB, but lower 218 proportions for physical activity advice (38.8%) were reported.<sup>25</sup> Advice for a healthy diet was 219 comparable with our findings (EPA Cardio: 42.9%; STAAB: 43.8 %).<sup>25</sup> 220

There may be a stronger tendency of physicians to recommend lifestyle advice in patients at high CVD risk compared to individuals with lower CVD risk as were present in the healthier STAAB subsample with less comorbidity, considering that the STAAB sample with a mean age 54.9 was overall younger than patients from the EA-IV survey (mean age 58.8 years) and EPA cardio project (mean age 66).<sup>23, 25</sup>

## 225 Prevalence of adequate lifestyle advice in secondary prevention samples

The EUROASPIRE "hospital arm" from the EA-IV survey with 7998 coronary patients (mean age at interview 64.0 years [± SD 11.3], 24.4% women) observed higher rates of recommendation over all forms of advice in smoking cessation. Having received verbal advice was reported in 88.5%, written information material in 42.6% and attended to a smoking cessation clinic in 18.6% which was more frequently when compared to the German EA-IV subsample with 34.2%, 13.1% and 8.2%, respectively. Similarly, higher rates of smoking cessation advice compared to our data were observed in the New Zealand SNAPSHOT ACS study, a large prospective audit of 2299 patients (mean age 69 years [± SD 1.3], 35% women)

hospitalized with an acute coronary syndrome.<sup>26</sup> In this survey, almost two-thirds of smoking patients 233 234 received the advice to stop smoking. The higher recommendation rates regarding smoking advice in 235 current studies underlines the insufficient recommendation to stop smoking advice in our German 236 secondary prevention sample. The world-wide considerable potential of the improvement of healthy 237 lifestyle in secondary prevention is also emphasized by the Prospective Urban Rural Epidemiology (PURE) cohort study in 153,996 adults, aged 35-70 years from 628 urban and rural communities of whom 7519 238 239 individuals reported CVD or stroke. From a total of three investigated healthy lifestyle behaviours 240 (healthy eating, smoking cessation and physical activity) only 4.3% (95%CI 3.1-5.8%) of the participants had received all healthy life style behaviours.<sup>27</sup> 241

## 242 Comparison of lifestyle advice in primary and secondary prevention setting

243 We found PLA more frequently given in secondary compared to primary prevention sample, except for 244 smoking. To the best of our knowledge, no comparable data was found with regard to directly analyzing 245 recommended lifestyle advice between primary and secondary prevention settings based on comparable 246 data collection and risk factor definitions. However, there are few studies focussing on differences in 247 frequency of healthy lifestyle behaviours in patients using comparable data. A cross-sectional study by 248 Wang et al. from the PURE-China study compared healthy lifestyle behaviours in individuals with and 249 without CVD or stroke among 40,490 participants. Four healthy lifestyle habits were assessed (smoking 250 cessation in current/former smokers, physical activity, healthy diet, self-reported alcohol consumption) 251 and participants with CVD, stroke and diabetes were allocated to disease group, whereas participants 252 without report any disease were allocated to control group. Overall, they reported significantly higher 253 rates of smoking cessation, guit drinking alcoholic products in participants with disease compared to the 254 healthy control group, whereas equal proportions were found for physical activity, and dietary intake 255 was depended from income and rural vs. urban communities. Further, less than 10% had all four healthy 256 lifestyle habits and the adoption of two or more lifestyle habits, increased with the number of CVD events.<sup>28</sup> In line with the present PURE study, there is evidence, that participants with CVD might be aware of their CVD related mortality and recurrent events and, therefore, more likely to follow healthy lifestyle habits.<sup>29, 30</sup> Our result showed that also at the physician's side, lifestyle advice in secondary prevention settings are more frequently recommend compared to primary prevention. However, considering that in our primary and secondary prevention samples, still a substantial number of patients are overweight/obese or physically inactive, there is a clear demand of improvement of increasing physicians' lifestyle advice in both, primary and secondary prevention settings.

### 264 **Determinants for adequate lifestyle advice**

### 265 **Primary prevention setting**

266 CVD risk factors (self-reported blood pressure, high LDL-C levels and diabetes) were strongly associated with a higher chance of receiving  $\geq$  50% PLA. A study from the EPA cardio project focused on 267 determinants regarding recording rates of single lifestyle advice (stop smoking, diet and physical activity) 268 from medical records in participants with high cardiovascular risk.<sup>25</sup> A healthy diet was less often 269 270 recorded with increasing age, but more often recorded in women as well as the advice for increasing 271 physical activity compared to men. Furthermore, with increasing number of risk factors including CVD 272 risk factors (elevated blood pressure, high total cholesterol and raised blood glucose) such as lifestyle 273 risk factors (weight or BMI, physical activity and smoking), the documentation rates increased for all three lifestyle advice.<sup>25</sup> This is in line with our finding from the STAAB primary prevention sample, where 274 275 CVD risk factors also strongly related to receive PLA.

### 276 Secondary prevention setting

We observed a lower probability of PLA with increasing age in our study. This is in line with results from
 previous studies. The SNAPSHOT ACS study assessed optimal preventive care defined by the patients
 having received at least one of exercise or healthy diet advice or advice for smoking cessation.<sup>31</sup> The
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280 probability of receiving in-hospital lifestyle advice was significantly lower (p 0.012) in patients being older than 70 years compared to younger ones.<sup>31</sup> The Survey of Health, Ageing and Retirement in Europe 281 282 (SHARE) also showed improvable behavioural lifestyle habits in the elderly.<sup>32</sup> However, as older patients 283 benefit significantly from lifestyle interventions, the reasons for the lower frequency of adequate lifestyle recommendations by physicians in older age groups should be identified and amended. 284 Individual comorbid conditions and the ability to adopt new lifestyle habits might be specifically 285 286 considered in this patient group, e.g. by recommending light to moderate physical activities instead of reaching official recommended targets.<sup>33, 34</sup> A recent study examined the relationship between health 287 288 beliefs and behavioural changes among younger (50-69 years) and older adults (70-89 years) and 289 pointing out that compared to younger participants, older participants were more confused about healthy eating habits or how to stay healthy in general.<sup>35</sup> This highlights that lifestyle interventions 290 291 should be adapted according to the needs of older aged individuals including close guidance to avoid 292 confusion with regard to health behaviours.

Furthermore, diabetes was the only cardiovascular risk factor, associated with a higher chance for 293 294 lifestyle recommendations  $\geq$  50% in our secondary prevention sample. There is evidence, that especially 295 patients with diabetes do not achieve treatment targets for secondary prevention. In addition, health 296 care providers might specifically focus on this high-risk population because of their higher risk of all-297 cause and CVD-related mortality. For example, the EA-III survey assessed determinants for risk factor control (failing recommended targets in total cholesterol <4.5 mmol/l, blood pressure <149/90 mmHg 298 299 and non-smoking) in coronary subjects and observed a tree time higher risk for patients diagnosed with diabetes to failing secondary prevention targets compared to non-diabetics.<sup>36</sup> The National Health 300 301 Interview Survey (NHIS) examine the epidemic of diabetes in 22,305 subjects aged ≥18 years from the 302 United States. In male patients with diabetes, they observed a 1.56 times higher risk of death from all-303 cause, a 1.72 times higher risk from heart disease, a 1.48 times higher risk from cerebrovascular disease and 1.67 times risk higher from CVD than subjects without diabetes, respectively with no difference from female patients with diabetes.<sup>37</sup> Further studies reported an increased mortality especially in patients with ACS and the Health Professional Follow up study shows that an overall healthy lifestyle is significantly associated with a 27% (p <0.001) lower risk of CVD mortality in patients with type 2 diabetes.<sup>38, 39, 40, 41</sup>

#### 309 Limitations

310 There might be a selection bias of invited participants. Healthier subjects from the primary prevention 311 setting might tend to participate more frequently in the study, whereas present secondary prevention 312 setting might represent a "healthier" CVD population, which survived long enough after index event and 313 therefore able to undergo physical examinations and interviews. Therefore, our results might over-314 estimate the level of PLA. The samples were derived from our local Würzburg population, thus, our 315 results may not generalizable to other German regions due to different risk profiles, age structure, and 316 distribution of lifestyle factors. We did not assess reasons for the individual lifestyle recommendations by 317 the physician. Furthermore, the prevalence of self-reported lifestyle recommendations could be subject 318 to recall bias. Due to the different assessment of the school-leave certificate in the primary and 319 secondary sample with the resulting harmonization, a misclassification regarding this marker of 320 socioeconomic status may have occurred. Finally, the multivariable model only accounted for a number 321 of a priori defined factors leaving room for residual confounding.

## 322 Conclusion

The present study demonstrates opportunities to improve the implementation of guideline-recommend lifestyle advice, in both primary and secondary prevention settings. Whereas presence of cardiovascular risk factors was strongly associated with the probability of receiving at least 50% of adequate PLA in primary prevention, such associations were absent or less pronounced in secondary prevention. This might indicate that physicians are more focused on clinical risk factors instead of lifestyle risk factors
when recommending lifestyle advice in the general population. In our secondary prevention sample,
older patients with CVD had a lower chance of receiving PLA. Therefore, a closer guidance of lifestyle
counselling with respect to the needs and quality of life should be considered.

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## 332 Acknowledgements

<u>On behalf of the STAAB consortium</u>: S. Frantz (Dept. of Medicine I, Div. of Cardiology, University Hospital Würzburg); C. Maack (Comprehensive Heart Failure Center, University Hospital and University of Würzburg); M. Fassnacht (Dept. of Medicine I, Div. of Endocrinology, University Hospital Würzburg); C. Wanner (Dept. of Medicine I, Div. of Nephrology, University Hospital Würzburg); J. Volkmann (Dept. of Neurology, University Hospital Würzburg); J. Deckert (Dept. of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg); H. Faller (Dept. of Medical Psychology, University of Würzburg); R. Jahns (Interdisciplinary Bank of Biomaterials and Data Würzburg, University Hospital Würzburg).

333 We greatly appreciate the time of all STAAB participants and their willingness to provide data to the 334 study. We also thank the Mayor of the City of Würzburg and the local registration office for their kind 335 and sustained support of our study. Further, we thank the entire study team including F. Eichner, V. 336 Ceijka, M. Mattern, C. Morbach, M. Breunig, study nurses, technicians, data managers, and students for 337 their efforts on the STAAB study. We also thank Rudy Meijer from Meijer Medical Ultrasound, 338 Vorschooten, The Netherlands, for external training and certification in vessel ultrasound as well as M. 339 Ertl, G. Fette, F. Puppe from the CHFC DataWarehouse, Institute of Informatics VI, University of 340 Würzburg. Further, we thank the participants of the German EUROASPIRE IV survey for providing their 341 data, as well as we thank all study coordinators, physicians, nurses, assistants, and students of the 342 recruiting centers for their time and effort on data collection. We gratefully acknowledge the support of 343 A. Adamska (Dept. of Cardiovascular Medicine, National Heart and Lung Institute, Imperial College 344 London, UK) for the administrative assistance and M. Glemot and M. Konte (EURObservationalResearch 345 Programme, European Heart House, Sophia-Antipolis, France) for the data management assistance within the EUROASPIRE IV survey. EUROASPIRE survey was carried out under the hospices of European 346 347 Society of Cardiology EURObservational Research Programme.

We also thank the Divisions of Nephrology (C. Wanner) and Endocrinology (B. Allolio<sup>+</sup>, M. Fassnacht), University Hospital Würzburg, and the Interdisciplinary Bank of Biomaterials and Data Würzburg (R. Jahns), University of Würzburg. The content of this publication is within responsibility of the author.

# 351 Funding

The STAAB cohort study is supported by the German Ministry of Research and Education within the Comprehensive Heart Failure Centre Würzburg (BMBF 01EO1004 and 01EO1504).

Data collection at the German EUROASPIRE IV study center was supported by the German Ministry of Education and Research (BMBF) within the Comprehensive Heart Failure Center Würzburg (BMBF 01EO1004). This publication was funded by the German Research Foundation (DFG) and the University of Würzburg in the funding programme Open Access Publishing.

The EUROASPIRE IV survey was carried out under the auspices of the European Society of Cardiology, EURObservational Research Programme. The survey was supported through unrestricted research grants to the European Society of Cardiology from AstraZeneca, Bristol-Myers Squibb/ Emea Sarl, GlaxoSmithKline, F. Hoffman-La Roche (Gold Sponsors), Merck, Sharp & Dohme and Amgen (Bronze Sponsors). The sponsors of the EUROASPIRE surveys had no role in the design, data collection, data analysis, data interpretation, decision to publish, or writing the manuscript.

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## 366 **Declaration of conflicting interests**

367 **CMo** reports a speakers honorarium from Amgen, a travel grant from Thermo Fisher, Orion Pharma, and 368 Alnylam, and participation in Scientific Advisory and Patient Eligibility Boards sponsored by AKCEA, 369 Alnylam, and EBR Systems outside the submitted work. **SS** reports research grants from the German 370 Ministry of Education and Research, European Union, University Hospital Würzburg; participation in Data 371 Safety Monitoring and Event Adjudication Boards in trials sponsored by ROCHE and MEDTRONIC; 372 principal investigator in trials (co-)sponsored by BOEHRINGER, NOVARTIS, BAYER, LUNDBECK; speaker 373 honaria by BOEHRINGER, SERVIER, NOVARTIS, ASTRA-ZENECA, PFIZER, BAYER. PUH reports research 374 grants from the German Ministry of Research and Education, German Research Foundation, European 375 Union, Charité, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, 376 Robert-Koch-Institute, German Heart Foundation, Federal Joint Committee (G-BA) within the 377 Innovationfond, Charité–Universitätsmedizin Berlin (within MonDAFIS; supported by an unrestricted 378 research grant to the Charité from Bayer), University Göttingen (within FIND-AF-randomized; supported 379 by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), and 380 University Hospital Heidelberg (within RASUNOA-prime; supported by an unrestricted research grant to 381 the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo), outside 382 submitted work. GE reports research grants from the German Ministry of Education and Research 383 (BMBF), Lundbeck non-financial support, Bayer grants, and Novartis grants and personal fees. KK reports 384 research grants from the European Society of Cardiology related the submitted work; consultancy fees 385 from Amgen, outside the submitted work.

# 386 Authors' contributions

TT contributed to conception and design of the STAAB cohort study and drafted the manuscript. CMo contributed to data acquisition and interpretation. CM contributed to analysis. GG contributed to study conception, analysis, and interpretation. MW contributed to study conception and data acquisition. SS and PUH designed the STAAB cohort study and the German subset of EUROASPIRE IV, acquired funding and drafted the manuscript. VW, KK, DW, GE, RL and WK contributed to data acquisition of the EA-IV survey. All authors critically revised and approved the final manuscript.

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