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Correlation between a positive family risk score and peripheral artery disease in one case-control and two population-based studies

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1. Introduction

Peripheral arterial disease (PAD) is one of the most common diseases with a prevalence of 10–20% in those aged over 65 years [1–3]. In addition to the impairments caused by the disease symptoms themselves these patients have also a higher prevalence and incidence of cardiovascular events such as myocardial infarctions or strokes [4–7]. In patients without symptomatic PAD, asymptomatic PAD is diagnosed by a decreased ankle-brachial-index (ABI) [8]. Although the measurement of ABI is not invasive it is not included in preventive screening for cardiovascular diseases [9].

Individual disease risk assessment, such as risk calculators, and targeted examinations for primary and secondary prevention continues to gain importance. Risk calculators for cardiovascular complications such as the Framingham Risk Score [10–14] primarily take into account personal life-style factors such as smoking or laboratory values such as total cholesterol and HDL cholesterol. Since genetic components play a crucial role in complex diseases, they should not be ignored in risk assessment. In light of growing knowledge on genetic susceptibility variants for complex diseases, one is tempted to incorporate information on single genetic loci

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into individual risk profiles. So far, however, genetic risk scores are not able to distinguish sufficiently between diseased and non-diseased subjects for most complex diseases. For myocardial infarction, for example, genetic risk scores have been shown to improve prediction only modestly in addition to traditional risk factors [15]. It has also been shown that family history outperforms genetic risk scores with regard to prediction for common diseases as myocardial infarction or Type 2 Diabetes, although a fair amount of their genetic component is already known [16]. This might be due to the fact that family history incorporates both, the genetic component as well as part of a shared environment. In comparison to a genetic risk score, for taking the family history no costly laboratory measurements are required since family history should be part of obtaining the general medical history anyway. Despite large-scale genetic association studies, knowledge on the genetic basis of PAD is very limited [17,18]. Therefore, a validated family risk score as well as a genetic risk score for PAD are still lacking.

It is known that PAD occurs more frequently in patients with other cardiovascular or metabolic diseases [19,20] or with diseased parents [21–23]. To evaluate family risk adequately, age of onset of diseased family members should be taken into account. The Family Risk Score (FamRS) proposed by Williams et al. [24] includes both, the number of diseased family members and age at onset. The effectiveness of this score has already been demonstrated for stroke and myocardial infarction (MI) [24,25]. However, this has not yet been validated for peripheral artery disease.

It was the intention of our study to evaluate family risk scores for cardiovascular (MI, stroke, PAD, hypertension) and metabolic (diabetes, obesity) diseases or risk factors on the prevalence of PAD and/or its association with ankle-brachial-index. Three studies were available for this investigation: two population-based studies (KORA F3 and KORA F4) and one age- and diabetes matched case-control study for peripheral arterial disease (CAVASIC Study). We specifically evaluated family risk scores for peripheral arterial disease itself, but also for obesity, hypertension, diabetes mellitus, stroke or myocardial infarction.

2. Methods and materials

2.1. Study participants and study design

2.1.1. KORA F3

Participants of the population-based cohort Study of the "**CO**operative Health Research in the **R**egion of **A**ugsburg" (KORA) were Inhabitants of Augsburg, Southern Germany, and two surrounding counties who were invited to the third MONICA (**Moni**toring of Trends and Determinants of **Ca**rdiovascular Diseases) Augsburg Survey in 1994/95. The age range was 25–74 years at baseline. The follow-up study KORA F3 was conducted from February 2004 until June 2005 including 3184 participants. The study methods were a standardized computer-assisted interview, a standardized self-administered questionnaire, a physical examination and a blood sampling [26]. In the questionnaire the participants were asked about the occurrence and the age at first onset of following diseases of their parents and siblings: myocardial infarction, stroke, diabetes mellitus, peripheral artery disease and obesity. The ankle-brachial-index (ABI) was measured in all subjects. Therefore, our analysis dataset in KORA F3 comprised $n = 3118$ individuals after exclusion of individuals with missing ABI and/or missing family history.

2.1.2. KORA F4

The population-based KORA F4 study was designed as a follow-up to the KORA S4 Study from 1999 to 2001 with 4261 individuals. 3080 of these subjects took part in the follow-up from 2006 to 2008. The study methods were almost the same as in KORA F3. In KORA F4, the family history of PAD was not assessed. Instead, participants were asked for family history of hypertension. The family history was assessed using a self-administered questionnaire that was given only to participants younger than 75 years. The ABI was measured from all subjects aged 53 years and above ($n = 1802$). Family history was available for 1325 of these 1802 individuals.

2.1.3. CAVASIC study

The CAVASIC (**CA**rdio**VAS**cular disease in patients with **I**ntermittent **C**laudication) Study is a case-control study that started in 2002 including 249 patients with intermittent claudication and 251 age- and sex-matched controls without peripheral arterial disease. All participants were enrolled either at the Department of Vascular Surgery at the Innsbruck Medical University, or the 3rd Medical Department of Metabolic Diseases and Nephrology, Hietzing Hospital Vienna [27–29]. Inclusion criteria for the patients were a positive history of intermittent claudication of the grades IIa or IIb according to the PAD Fontaine staging, regardless of whether they were treated (bypass surgery or intervention) in the past. Exclusion criteria were presence of acute or critical limb ischemia (Fontaine III or IV), impaired liver function, impaired kidney function with serum creatinine >133 μmol/L, malignancy, past organ transplantation, or therapy with nicotinic acid or corticosteroids. Patients with missing family history ($n = 16$) were excluded from the present analysis. As controls 251 volunteers were recruited after an invitation in a local newspaper, matched on age and the presence of type 2 diabetes mellitus. All control individuals with presence or history of PAD were excluded from the study but those with known cardiovascular diseases were allowed to participate [28]. Three individuals were excluded from the calculations due to missing family history data. Neither patients nor controls were suffering from an acute or inflammatory disease. Both patients and controls live in the same geographic region. To avoid interobserver bias, the examination and interviews at the two study centers has been executed by each one specially trained physician.

All three studies were approved by the respective institutional review boards and written informed consent was obtained from each participant.

2.2. Definition of outcome variables

2.2.1. Measurement of ankle-brachial-index (ABI)

In KORA F3 and F4, ABI was measured according to a standardized protocol. A Doppler ultrasound and a blood pressure cuff were used. Blood pressure measurements at the right arm and both ankles were done twice. In case the systolic pressure differed by more than 10 mmHg for the two measurements at each location, a third measurement was performed. Mean values were then taken for each arm and both ankles. For the ABI calculation, the lowest mean value of both legs was taken and divided by the mean value of the arm. According to literature we defined an ABI <0.9 as evidence for the presence of asymptomatic or symptomatic PAD [30,31]. In the analyses on continuous ABI we excluded participants with ABI >1.4 from the analysis. These values may indicate vascular calcification, which prohibits accurate pressure measurements in the legs [32]. ABI measurements were not used in the CAVASIC Study since they might not be additionally informative due to previous vascular interventions in subgroups of the cohort.

2.2.2. Definition of PAD

The outcome variable PAD was defined by the case-controls status in the CAVASIC Study. Thus, PAD cases were either

symptomatic as defined by the Edinburgh questionnaire [31] or had a history of symptomatic disease.

In the KORA studies various categorizations were possible due to the availability of the ABI measurements. The Edinburgh Claudication Questionnaire was used to identify the presence of symptomatic intermittent claudication [31]. In this questionnaire the subjects were asked about pain in their legs during walking standing and sitting. According to the Edinburgh Questionnaire intermittent claudication was defined as such, if the patient affirmed pain in the calf (classical PAD) or thigh/buttock (atypical PAD) during walking (but not during sitting or standing), the pain also appears during hurrying or walking uphill and the pain disappears after walking (in a sitting or standing position) in 10 min or less. Participants having either intermittent claudication or an ABI <0.9 were defined as having PAD.

2.3. Definition and calculation of Family Risk Scores

In all three cohorts, family risk scores (FamRS) were available for the following diseases or risk factors: myocardial infarction (FamRS-MI), stroke (FamRS-stroke), type 2 diabetes mellitus (FamRS-DM), and obesity (FamRS-obesity). There is an additional FamRS for PAD (FamRS-PAD) in KORA F3 and CAVASIC and a FamRS for hypertension (FamRS-HT) in KORA F4 and CAVASIC.

The FamRS was derived by means of an algorithm based on a standardized interview (KORA F3 and CAVASIC) or a self-administered questionnaire (KORA F4). The following question was asked for each 1st grade relative for all diseases/risk factors of interest: “Does/did your father (mother/brother/sister) suffer from the following disease?” “If yes, was it before the age of 60, at 60 years or later or was the age not known.” According to the age of onset, weights were assigned to each participant (2 if age of onset <60; 1 if age of onset ≥60; 1.5 if age not known).

The FamRS for each disease is calculated using the numbers of observed (O) and expected (E) values in each participant according to the following formula proposed by Williams et al. [24]:

$$\text{FamRS} = \frac{|O-E| - 0.5}{\sqrt{E}} \cdot \frac{|O-E|}{O-E}.$$

The observed scores for each disease for each participant were derived as the sum of the weights for all first grade relatives.

Since KORA F3 and F4 are population-based studies, the reference values to calculate expected values are derived from these studies themselves: for each 10 year age group, mean values of the weights for father, mother, sisters and brothers are calculated. For each participant, these age-group and study-specific reference values are multiplied with the number of first grade relatives, for whom information on the diseases is available. Thus, the expected values for each participant take into account the number of siblings and the age of the participants.

In all three studies, participants were asked about the diseases of each sibling individually. In KORA F3 and CAVASIC, the gender of each sibling was taken into account. Therefore, expected values could be derived specifically for brothers and sisters. This was not possible in KORA F4, where no distinction was made between brothers and sisters. In CAVASIC, controls were matched for age and diabetes and therefore their distribution does not reflect the general population. Therefore, expected scores for CAVASIC were derived from male participants of KORA F4 for FamRS-HT and male participants for KORA F3 for all other FamRS.

According to Roger R. Williams and colleagues [24], we categorized the continuous FamRS-values into the following groups: FamRS <0.5 (“average family history”), FamRS ≥0.5−0.99 (“positive family history”), FamRS ≥1.0 (“strong family history”). Since there were too few subjects with values ≥2.0, we did not further stratify values ≥1.0 into a “very strong family history” group.

Finally, we constructed a combined Family Risk Score derived from all categorized family risk score values of the cardiovascular or metabolic diseases/risk factors, which showed at least a trend in the single association analysis. This combined score was positive, if there was at least one strong family history in one of the included FamRS or two positive family histories.

A schematic presentation of the FamRS algorithm is given in Fig. S1. Furthermore, an online FamRS calculator is provided at http://www3.i-med.ac.at/genepi/FamRS/, calculating each single FamRS together with their respective categorizations as well as the combined Family Risk Score.

3. Statistical methods

The statistical calculations were performed by using SPSS Statistics 20 and R 3.0.1. Since we evaluated the FamRS for six different diseases/risk factors on PAD and ABI, we accounted for the resulting multiple testing situation in all analyses besides the analysis on the combined score by setting the value for a significant p-value to ≤0.008 (0.05/6) to reduce the risk for false-positive findings. p-values <0.05 are denoted as nominally significant, which indicates a trend, but no formal statistical significance.

Descriptive statistics included mean values and standard deviations for all relevant parameters in all three studies and absolute numbers and frequencies of PAD cases for different family risk categorizations. Mean values of continuous FamRS scores with 95% confidence intervals (95%CI) are graphically displayed for participants with and without PAD in all three studies.

For regression models, the categorized FamRS was used instead of the continuous score due to its highly skewed distribution. Odds ratios and 95% confidence intervals refer to the category “positive family risk” compared to “average family risk” and “strong positive family risk” compared to “average family risk”, which serves as the reference category. The reported p-value assumes a linear trend of the FamRS categories.

Since continuous ABI measurements were available in both KORA studies, linear regression analyses were performed for the categorized FamRS on ABI. Logistic regression models were performed on the outcome variable PAD (yes/no) in all three studies. The categorized FamRS was used for all diseases. Additionally to the univariate models, multivariate adjusted models were performed including classical risk factors according to the Framingham Risk Score (current smokers, systolic blood pressure, HDL-cholesterol, total cholesterol, age and sex) [12,14].

As a sensitivity analysis, we also evaluated the parents' case history, defined by “at least one parent diseased” (yes/no) on PAD.

The combined risk score including all family risk scores, which show at least a trend in the association with PAD, was analyzed in logistic regression models in all three studies on the presence of PAD (univariate, as well as multivariate). This analysis was also performed excluding the FamRS of PAD to evaluate the risk for PAD considering family risks of other cardiovascular and metabolic diseases.

For all analyses, a combined effect over all available studies was obtained using a logistic mixed effects model (using package lme4 in R), resulting in a common odds ratio over all three studies. Differences between random slopes and random intercepts models were tested using an ANOVA. In the case of no difference between models, random intercepts models were used to increase power. For some analyses, random slopes models were superior, indicating heterogeneity of results between studies.

4. Results

4.1. Descriptive statistics

The main characteristics of the participants of the two population-based KORA studies and the CAVASIC case-control study are shown in Table 1.

In Table 2, the categorical distribution of the FamRS for each disease is provided. The frequencies of PAD cases generally increased for increasing FamRS categories. For example, the frequencies of participants with PAD increased from 6.1% in KORA F3 and 5.4% in KORA F4 for the average family risk group for FamRS-MI to up to 8.8% in KORA F3 and 12.6% in KORA F4 in the strong positive family risk group. Comparable increases were observed for FamRS-stroke, FamRS-DM and FamRS-PAD in KORA F3, FamRS-DM, FamRS-obesity, FamRS-HT in KORA F4 and the FamRS for all diseases except FamRS-obesity in CAVASIC. In CAVASIC, there was no single person with a FamRS-PAD >1.0 in the control group which might be explained by the fact that symptomatic PAD in the controls was an exclusion criterion.

Fig. 1 shows mean values for all FamRS in groups of participants with PAD versus participants without PAD for each of the three studies. In KORA F3 an increase of the risk was observed for all disease risk scores. Similar observations were made for KORA F4 except for FamRS-stroke. In KORA F4, the increase was obviously strongest for FamRS-obesity and FamRS-HT. In CAVASIC all FamRS increased in cases when compared to controls except FamRS-obesity. Since mean values are susceptible for outliers and extremely skewed distributions, subsequent regression models were based on categorized FamRS levels.

4.2. Association of single FamRS with PAD

Table 3 shows the results of the logistic regression on PAD in all three studies. We observed in KORA F3 in the univariate model a significant association for FamRS-stroke ($p = 0.003$), which was primarily triggered by the "strong positive family history" group compared to the reference group. This finding, however, was no longer significant after adjusting for classical risk factors according to the Framingham Risk Score. A similar pattern was observed for the strong positive family history of PAD (univariate model: OR [95%CI] = 2.520 [1.268–5.011], adjusted model: OR [95%CI] = 1.671 [0.765–3.649]). In KORA F4, none of the evaluated FamRS showed significant associations with PAD, although a remarkable Odds Ratio could be found for "strong positive family history" of MI (adjusted model: OR [95%CI] = 3.020 [1.328–6.867]).

The associations were markedly stronger in the CAVASIC Study and we found significant associations for FamRS-HT ($p = 0.005$) and FamRS-PAD ($p = 5.4 \times 10^{-6}$). The latter was also significant even after adjusting for Framingham Risk Score factors ($p = 2.9 \times 10^{-4}$). There was no single person in the CAVASIC control group with a strong positive family history for PAD (FamRS-PAD ≥1). Therefore, risk estimates are overinflated in that group with infinitive confidence intervals. Even for a positive family history of PAD (FamRS-PAD ≥0.5 and <1), the chance of being a case is ~6 times higher than for average family history in the univariate model and ~4.5 times higher in the multivariate adjusted model. A comparable Odds Ratio could be observed for the strong positive family history of DM (adjusted model: OR [95%CI] = 4.693 [1.387–15.881]). The overall association with FamRS-DM, however, was not significant ($p = 0.185$) since the category of a "positive family history" of DM did not contribute at all.

In the combined analysis of all three studies, family history of MI and hypertension remained significantly associated with PAD even after adjusting for classical risk factors ($p = 0.003$ and $p = 0.005$, respectively).

4.3. Association of a combined score with PAD

As described above and in Table 3, for many family risk scores we only saw a slightly increased risk in terms of OR for the second risk category ("positive family history" or FamRS between 0.5 and

Table 1
Descriptive statistics of the three studies considered in the analysis.

Mean (SD) or *n* (%)	KORA F3 $n = 3118$	KORA F4 $n = 1325$	CAVASIC	
			Controls $n = 248$	Cases $n = 233$
Age (years)	57.2 ± 12.8	61.3 ± 5.8	57.0 ± 9.4	58.4 ± 6.3
Women (%)	1614 (51.8)	679 (51.2)	0 (0)	0 (0)
Body mass index (kg/m)	27.6 ± 4.6	28.4 ± 4.8	26.6 ± 3.9	26.9 ± 4.0
Current smoker (%)	501 (16.1)	166 (12.5)	29 (11.7)	118 (50.6)
HDL cholesterol (mg/dl)	58.8 ± 17.1	56.3 ± 14.6	59.4 ± 16.6	49.4 ± 13.7
LDL cholesterol (mg/dl)	128 ± 32	143 ± 35	136 ± 33	131 ± 37
Total cholesterol (mg/dl)	218 ± 40	225 ± 39	208 ± 35	203 ± 41
Triglycerides (mg/dl)	165 ± 126	136 ± 89	131 ± 76	166 ± 105
Diabetes (%)	246 (7.9)	115 (8.7)	41 (16.5)	38 (16.3)
RR systolic (mmHg)	130.7 ± 20.0	125.6 ± 18.0	139.5 ± 16.8	149.5 ± 19.9
RR diastolic (mmHg)	81.9 ± 10.8	76.8 ± 9.9	82.3 ± 8.6	83.1 ± 9.9
Ankle-brachial-index	1.13 ± 0.15	1.16 ± 0.14	1.08 ± 0.13	0.74 ± 0.25
ABI < 0.9 & claudication (%)	33 (1.1)	11 (0.8)	n.a.	n.a.
Claudication & ABI ≥ 0.9 (%)	71 (2.3)	26 (2.0)	n.a.	n.a.
ABI < 0.9 & no claudication (%)	94 (3.0)	38 (2.9)	n.a.	n.a.
PAD outcome variable (%)[a]	198 (6.4)	75 (5.7)	n.a.	n.a.

[a] Intermittent claudication or an ABI < 0.9.

Table 2
Number of PAD cases in the FamRS categories in all three studies for different FamRS categories (in parenthesis are the proportion of participants with PAD or PAD cases in % of all participants in this FamRS category).

	Family history	FamRS value	KORA F3	KORA F4	CAVASIC
			# (% PAD)	# (% PAD)	# (% cases)
Myocardial infarction	Average	<0.50	162 (6.1)	59 (5.4)	179 (45.9)
	Positive	0.50 – 0.99	26 (7.9)	8 (5.5)	35 (60.3)
	Strong positive	≥1.00	10 (8.8)	8 (12.6)	18 (58.6)
Stroke	Average	<0.50	166 (6.0)	68 (5.8)	208 (46.9)
	Positive	0.50 – 0.99	16 (6.2)	6 (7.1)	19 (65.5)
	Strong positive	≥1.00	16 (15.2)	1 (2.0)	6 (66.7)
Diabetes Mellitus	Average	<0.50	159 (6.0)	61 (5.5)	201 (47.8)
	Positive	0.50 – 0.99	21 (6.9)	7 (6.0)	17 (40.5)
	Strong positive	≥1.00	18 (9.9)	6 (7.3)	15 (78.9)
PAD	Average	<0.50	171 (6.2)	n.a.	193 (44.5)
	Positive	0.50 – 0.99	14 (5.1)	n.a.	34 (82.9)
	Strong positive	≥1.00	10 (14.2)	n.a.	6 (100)
Obesity	Average	<0.50	153 (6.3)	52 (5.2)	199 (48.8)
	Positive	0.50 – 0.99	29 (6.7)	7 (4.5)	27 (47.4)
	Strong positive	≥1.00	16 (6.6)	15 (9.8)	7 (43.8)
Hypertension	Average	<0.50	n.a.	51 (5.1)	191 (47.0)
	Positive	0.50 – 0.99	n.a.	6 (5.1)	20 (52.6)
	Strong positive	≥1.00	n.a.	15 (8.8)	22 (75.8)

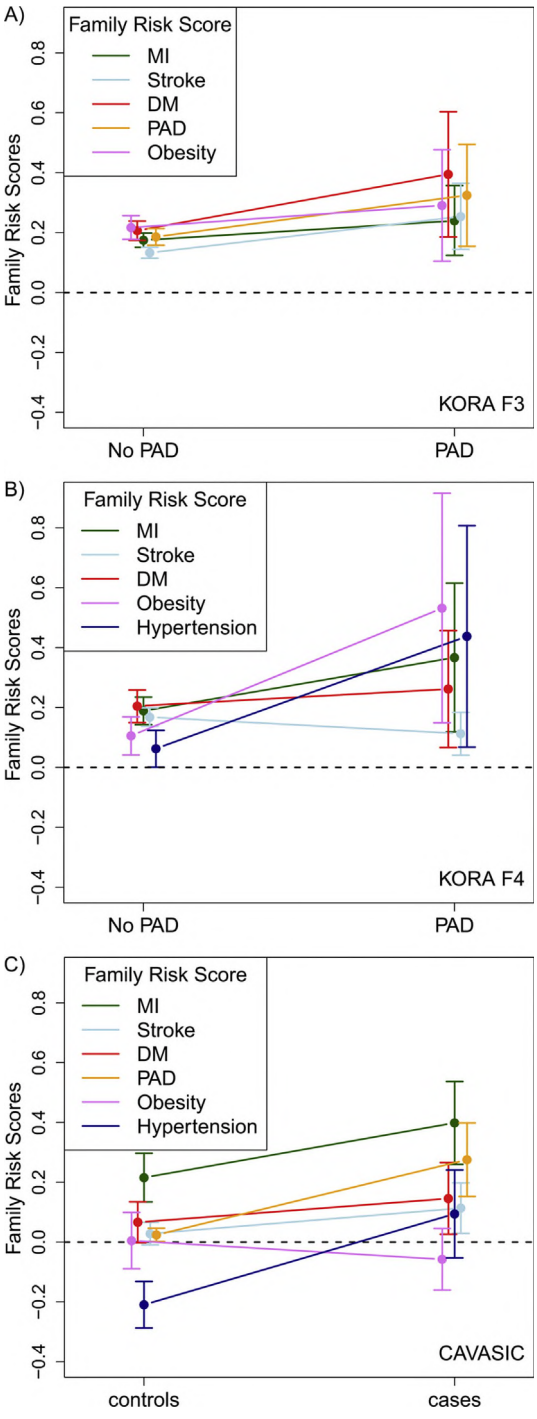

Fig. 1. Mean values of the continuous Family Risk Scores ± 95% confidence intervals for participants with PAD (cases) and no PAD (controls) in KORA F3 (A), KORA F4 (B) and CAVASIC Study (C). These results demonstrate that the family risk scores were with few exceptions higher in subjects with compared to those without PAD.

1) compared to the reference, but a clearly increased risk for the highest category ("strong family history" or FamRS ≥ 1). It seems that the accumulation of more than one of the evaluated diseases or risk factors with a "positive family history" in the family or the presence of at least one "strong positive family history" in the family contribute to an increased PAD risk. We therefore created a combined risk score that was positive, if there was at least one strong positive family history in one of the calculated FamRS or two positive family histories (Table 4). FamRS obesity was excluded from this combined score, since it was not associated with PAD in either one of single studies or in the combined analysis. The combined score was significantly associated with PAD in KORA F3 (OR = 1.818, $p = 3.6 \times 10^{-4}$) and CAVASIC (OR = 2.695, $p = 3.2 \times 10^{-5}$). The result in KORA F4 (OR = 1.519, $p = 0.103$), although not significant, support the overall combined analysis using a mixed-effects model, yielding a highly significant OR of 1.932 for all three studies ($p = 2.6 \times 10^{-8}$). When the data were adjusted for classical risk factors of the investigated patients (according to the Framingham Risk Score) the presence of an increased family risk was still highly significant (OR = 1.741, $p = 1.5 \times 10^{-5}$).

Table 4 provides also the result of the same analysis when the FamRS for PAD is excluded for the categorization of the combined risk score. The odds ratios were only slightly attenuated by this exclusion. The combined effects were significant in both, the univariate (OR = 1.798, $p = 2.4 \times 10^{-6}$) and multivariate model (OR = 1.636, $p = 2.5 \times 10^{-4}$).

4.4. Association of parents disease status with PAD

We also evaluated the parents' case history, defined by "at least one parent diseased" (yes/no) on PAD. The corresponding results can be found in Table S1. In the CAVASIC study, the presence of at least one parent with PAD or hypertension was significantly associated with prevalent PAD, which remained significant for parental PAD in the multivariate adjusted model. In the combined analysis including the results of all three studies and using a mixed effects model, no significant association with prevalent PAD could be found. In general, the direction of the effects was the same as with FamRS, but a distinction between positive and strong positive family risk was not possible.

4.5. Association of single FamRS with ABI

There was no association between any singular FamRS category and ABI in both KORA F3 and KORA F4 studies, nor the combination of both using a mixed effects model (Table S2). A slight trend was observed for increasing ABI with increasing obesity family risk in KORA F3. Since even unadjusted models did not result in significant effects, multivariate adjusted models were omitted for linear regression on ABI.

5. Discussion

We demonstrated in three independent studies that a positive family history of cardiovascular (MI, stroke, PAD, hypertension) or metabolic diseases (obesity or DM) correlates with the presence of a peripheral arterial disease. The presence of at least one strong positive family history in one of the calculated FamRS or two positive family histories was shown to increase the probability for prevalent PAD by 93%. This association was still present if data were adjusted for classical risk factors (smoking, systolic blood pressure, HDL-cholesterol, total cholesterol, age and sex), which demonstrates that some substantial information is still "buried" in the family history beyond the individual risk factors of the participants. If we excluded the family history of PAD itself that is supposed to be the most important familiar disease for the calculations in this context, the association remained stable.

Previous studies have already shown that the risk for PAD is increased in individuals with a positive family history of PAD: Valentine et al. [33] have observed that siblings of patients with premature PAD have an increased probability for having PAD, while Wassel et al. [22] described the association of family history in first degree relatives as well as diseased parents with PAD risk. A positive history of parental claudication has also been shown to be

Table 3
Results of logistic regression for single studies and logistic mixed model assuming random slopes for the combined analysis from specific FamRS on PAD.

FamRS	FamRS value[b]	KORA F3			KORA F4			CAVASIC			Combined analysis		
		OR	CI (95%)	p^{***}	OR	CI (95%)	p^{***}	OR	CI (95%)	p^{***}	OR	CI (95%)	p^{***}
Univariate model													
MI	0.5 – 0.99	1.321	[0.858 – 2.032]	0.098	1.033	[0.483 – 2.208]	0.052	1.793	[1.022 – 3.147]	0.038	1.388	[1.023 – 1.883]	**0.002**
	≥1.0	1.504	[0.771 – 2.935]		2.554	[1.163 – 5.609]		1.632	[0.778 – 3.424]		1.773	[1.148 – 2.738]	
Stroke	0.5 – 0.99	**1.034**	**[0.609 – 1.757]**	**0.003**	1.257	[0.529 – 2.987]	0.488	2.147	[0.976 – 4.721]	0.039	1.285	[0.815 – 2.027]	0.033
	≥1.0	**2.801**	**[1.608 – 4.878]**		0.327	[0.044 – 2.401]		2.259	[0.559 – 9.138]		2.213	[1.079 – 4.538]	
DM	0.5 – 0.99	1.162	[0.725 – 1.862]	0.043	1.109	[0.495 – 2.484]	0.479	0.741	[0.389 – 1.412]	0.110	1.009	[0.699 – 1.458]	0.009
	≥1.0	1.717	[1.028 – 2.866]		1.363	[0.571 – 3.254]		4.088	[1.335 – 12.518]		1.929	[1.259 – 2.954]	
PAD	0.5 – 0.99	0.811	[0.464 – 1.419]	0.146	n.a.	n.a.	n.a.	**6.068**	**[2.633 – 13.985]**	$\mathbf{5.4 \times 10^{-6}}$	2.222	[0.505 – 9.784]	0.080
	≥1.0	2.520	[1.268 – 5.011]		n.a.	n.a.		**$\sim 10^{10}$**	**[0.000 – ∞]**		19.013	[1.04 – 347.49]	
Obesity	0.5 – 0.99	1.078	[0.715 – 1.625]	0.730	0.868	[0.387 – 1.946]	0.054	0.946	[0.543 – 1.647]	0.679	0.998	[0.722 – 1.379]	0.586
	≥1.0	1.060	[0.622 – 1.806]		1.994	[1.093 – 3.639]		0.817	[0.298 – 2.238]		1.177	[0.763 – 1.814]	
HT	0.5 – 0.99	n.a.	n.a.	n.a.	1.007	[0.422 – 2.400]	0.076	**1.251**	**[0.642 – 2.436]**	**0.005**	1.106	[0.621 – 1.969]	**0.008**
	≥1.0	n.a.	n.a.		1.791	[0.983 – 3.264]		**3.536**	**[1.478 – 8.459]**		2.472	[1.275 – 4.792]	
Adjusted for classical risk factors[a]													
MI	0.5 – 0.99	1.520	[0.959 – 2.409]	0.092	1.024	[0.472 – 2.222]	0.031	1.525	[0.765 – 3.040]	0.231	1.447	[1.04 – 2.013]	**0.003**
	≥1.0	1.380	[0.686 – 2.777]		3.020	[1.328 – 6.867]		1.405	[0.564 – 3.502]		1.697	[1.073 – 2.685]	
Stroke	0.5 – 0.99	0.993	[0.552 – 1.786]	0.090	1.305	[0.539 – 3.158]	0.519	1.498	[0.587 – 3.822]	0.356	1.241	[0.802 – 1.921]	0.0767
	≥1.0	1.945	[1.033 – 3.660]		0.327	[0.043 – 2.482]		1.514	[0.305 – 7.525]		1.688	[0.906 – 3.145]	
DM	0.5 – 0.99	1.344	[0.808 – 2.234]	0.171	1.095	[0.479 – 2.506]	0.738	0.576	[0.268 – 1.240]	0.185	1.052	[0.708 – 1.563]	0.0721
	≥1.0	1.354	[0.757 – 2.420]		1.137	[0.465 – 2.778]		4.693	[1.387 – 15.881]		1.611	[1.01 – 2.572]	
PAD	0.5 – 0.99	0.545	[0.271 – 1.096]	0.945	n.a.	n.a.	n.a.	**4.504**	**[1.707 – 11.884]**	$\mathbf{2.9 \times 10^{-4}}$	1.612	[0.32 – 8.107]	0.1732
	≥1.0	1.671	[0.765 – 3.649]		n.a.	n.a.		**$\sim 10^{10}$**	**[0.000 – ∞]**		16.046	[0.689 – 373.73]	
Obesity	0.5 – 0.99	1.255	[0.805 – 1.957]	0.603	0.851	[0.374 – 1.936]	0.058	0.580	[0.296 – 1.136]	0.050	0.952	[0.623 – 1.454]	0.945
	≥1.0	1.024	[0.570 – 1.839]		2.038	[1.091 – 3.808]		0.442	[0.132 – 1.476]		1.073	[0.55 – 2.093]	
HT	0.5 – 0.99	n.a.	n.a.	n.a.	0.912	[0.377 – 2210]	0.051	1.119	[0.506 – 2.474]	0.032	1.069	[0.594 – 1.925]	**0.005**
	≥1.0	n.a.	n.a.		2.003	[1.073 – 3739]		3.184	[1.188 – 8.532]		2.446	[1.347 – 4.441]	

$^{***}p$-value for trend of the categories.
Bold font: Significant after Bonferroni correcting for number of FamRS tested (p-value <0.05/6 = 0.008).
[a] Risk factors (according to the Framingham Risk Score): Current Smokers. Systolic Blood Pressure. HDL-Cholesterol. Total Cholesterol. Age and Sex (adjustment for Sex only in the KORA studies).
[b] Reference category: FamRS value <0.5 (average family history).

associated with the occurrence of claudication in the next generation [21]. Most studies evaluating family history have in common that they only look at a positive family history (yes/no) that is defined by diseased parents. Therefore, we recalculated our analysis also based on this sparse definition (i.e. at least one parent diseased). Overall, results are comparable at least in the CAVASIC Study with positive significant associations if PAD or hypertension was present in parents. However, the Family Risk Score has the advantage that family history can be stratified into severity categories: for most FamRS, even if they are not significantly associated overall, a substantial risk increase can be observed from the "positive" to the "strong positive" family history group: while individuals in the positive family history group have only a small risk increase or even none, the strong positive family history group is distinctly more often affected (Tables 2 and 3). Thus, high-risk individuals seem to be detectable more effectively by calculating the FamRS as compared to the simple assessment of diseased parents. In the CAVASIC Study, for example, there is no association of parental diabetes mellitus with PAD (OR = 0.995). In contrast, when calculating FamRS-DM according to Williams et al., it can be observed that the chance of being a case is ~4–5 times higher for persons with strong positive family history of DM compared to average family history. This might also reflect a change in risk factor profiles over generations considering that parents of currently

Table 4
Results of the logistic regression analysis of the combined FamRS on PAD for KORA F3, F4 and CAVASIC separately as well as the mixed logistic regression model assuming random intercepts results from all three studies.

	Study	Combined family risk sore (including FamRS MI, stroke, DM, PAD, HT)				Combined family risk score (including FamRS MI, stroke, DM, HT)			
		n (%)[a]	OR	CI (95%)	p-value	n (%)[a]	OR	CI (95%)	p-value
Univariate model	KORA F3	559 (18.0)	1.818	[1.309 – 2.524]	$\mathbf{3.6 \times 10^{-4}}$	459 (14.8)	1.775	[1.253 – 2.515]	**0.014**
	KORA F4[b]	335 (26.4)	1.519	[0.919 – 2.509]	0.103	335 (26.4)	1.519	[0.919 – 2.509]	0.103
	CAVASIC	100 (21.2)	2.695	[1.689 – 4.301]	$\mathbf{3.2 \times 10^{-5}}$	85 (18.0)	2.175	[1.336 – 3.543]	**0.002**
	Combined Analysis	994 (20.6)	1.932	[1.532 – 2.435]	$\mathbf{2.6 \times 10^{-8}}$	879 (18.1)	1.798	[1.409 – 2.294]	$\mathbf{2.4 \times 10^{-6}}$
Adjusted for classical risk factors[c]	KORA F3	559 (18.0)	1.486	[1.034 – 2.134]	**0.032**	459 (14.8)	1.477	[1.005 – 2.169]	**0.047**
	KORA F4[b]	335 (26.4)	1.637	[0.979 – 2.739]	0.060	335 (26.4)	1.637	[0.979 – 2.739]	0.06048
	CAVASIC	100 (21.2)	2.566	[1.474 – 4.466]	$\mathbf{8.6 \times 10^{-4}}$	85 (18.0)	1.974	[1.105 – 3.527]	**0.022**
	Combined Analysis	994 (20.6)	1.741	[1.355 – 1.741]	$\mathbf{1.5 \times 10^{-5}}$	879 (18.1)	1.636	[1.257 – 2.129]	$\mathbf{2.5 \times 10^{-4}}$

Bold specifies p-value <0.05.
[a] Number (%) of subjects that are positive in combined risk score (from all, who have all relevant family risk scores available).
[b] Combined risk score in KORA F4 does not include FamRS PAD, leading to the same results in both analyses.
[c] Risk factors (According to the Framingham Risk Score): Current Smokers. Systolic Blood Pressure. HDL-Cholesterol. Total Cholesterol. Age and Sex (no adjustment for sex in the CAVASIC Study).

middle-aged PAD patients might have been exposed less frequently to diabetes-inducing lifestyles. Nowadays, diabetes in the siblings of PAD patients is likely to be more frequent and starts even at an earlier age [34].

From our findings we conclude, that it does not seem to be sufficient to consider only the parents' disease status. Would it be sufficient, though, if we knew the number of diseased first grade relatives? This approach would give more information than the simple "parent's diseased (yes/no)", but would still be much easier than the calculation of the FamRS. Wassel et al. [22] could not show a superiority of this analysis as compared to a positive PAD family history or diseased parents' analysis. Since the number of diseased relatives is highly dependent on the number of relatives at all, the total number does not seem to be relevant. The bigger a family, the more diseased persons would be expected. The family risk score considers the family size by relating the number of observed diseased family members to the number of family members, which are expected to be diseased. This number takes into account the number of known parents and siblings as well as the age of the participant. A young individual is more likely to have younger and therefore healthier relatives than an older individual. Implicitly, a diseased relative of a young study participant is weighted higher in the calculation of the FamRS as a diseased relative of an older participant. Thus, taking the number of family members and also age into account is a major advantage of the FamRS and distinguishes it from other ways of assessing family history.

The cardiovascular and metabolic diseases and risk factors, for which family risk scores were derived, are known to be not independent from each other. For example, the presence of hypertension or obesity is frequently a common risk factor for sequelae such as a MI or stroke [35,36]. Moreover, it has been shown that patients with PAD have increased cardiovascular complications [5]. A correlation between all studied family risk scores should therefore be assumed. Thus, an independent evaluation of all these family risks might be questioned. Furthermore, we observed an increased risk for several different family risk scores (see Table 3). Besides PAD itself, the most important singular family risk score could not be identified, but there seems to be a slight contribution not only by more than one disease risk scores but also in different combinations. Therefore, we derived a combined score from individual family risk scores of MI, stroke, DM, PAD and hypertension. This combined score categorizes a patient as "at risk", if there is at least one FamRS with "strong positive family history" or at least two FamRS with "positive family risk". For example, one person who has a strong positive family history for a FamRS-MI would fall in this "at risk" group of the combined score. Another person who has a positive family history for two or more diseases is likely to have a rather normal or slightly increased risk, when looking at all FamRS individually. However, risks might accumulate due to the correlations between the investigated diseases. Such a person is identified as "at risk" in the combined score. This risk group derived from the combined score has an about 70–90% higher risk for the presence of PAD (Table 4), even after adjustment for classical risk factors. Since we also found significant associations in the combined risk score excluding FamRS-PAD, knowledge on PAD in the family is desirable but does not seem to be necessary to define a positive combined family risk for PAD.

Our finding is important, since family history and/or the derivation of a family risk score relies on the common knowledge of diseases in general and of the occurrence of these diseases within the family. Rather hard events like stroke or MI are more impressive and might be kept in mind more easily. Therefore, the presence of PAD or hypertension might be underestimated [37]. This might be especially true in population-based studies as KORA F3 and F4. It can be assumed that PAD is not very well-known in the general population in comparison to the cases in the CAVASIC Study, which are affected themselves. Besides the difference in disease severity, this potential recall-bias might contribute to the effect-differences between the FamRS-PAD in KORA F3 and in CAVASIC. In light of this reasoning it is reassuring to find associations not only with PAD family history, but even with a risk score not involving PAD at all.

It is the strength of this investigation that we evaluated positive family risk in population-based studies as well as one PAD case-control study. Risk estimates are higher in the case-control study but similar results can also be seen in the population-based studies, which reflect the risk in the general population. An additional explanation for the smaller estimates in the general population can be found in the definition of PAD in these studies: CAVASIC includes symptomatic patients searching the treatment in a hospital. Cases in the KORA study are mostly in earlier stages since these two studies do not only include symptomatic cases according to the Edinburgh questionnaire but also asymptomatic cases according to an ABI <0.90. This is also in line with the observation that we did not find an association of cardiovascular or metabolic family risk scores with continuous ABI values. Since about 96% of participants in KORA F3 and F4 have ABI values in the normal range (ABI ≥ 0.9), these findings might just indicate that there is no linear association of family risk within normal ranges of ABI.

Our study is limited by including only Caucasian individuals from geographically close regions. Therefore, our findings cannot be generalized to other ethnicities. Furthermore, not all metabolic and/or cardiovascular risk factors that are likely to be clustered within families are recorded in the three included studies (e.g. hypercholesterolemia). It has also to be noted that the question on obesity is rather subjective. Most persons do not know exact "measurements of obesity" such as BMI or waist circumference of their relatives. Therefore, the question, if a relative is obese or not, might be judged differently by different individuals. This circumstance might contribute to the non-significant finding of FamRS-obesity in our evaluation. Finally, in KORA F4 the FRS was only obtained from those participants younger than 75 years and ABI was only measured in participants older than 53 years. Therefore, the number of participants is considerably lower in KORA F4 with low numbers in especially the "high risk" groups with an FRS ≥ 1 and p-values are far away from being significant. In most cases, however, the results in KORA F4 support the results obtained in KORAF3 and CAVASIC.

Our findings support our initial hypothesis that the presence of cardiovascular and/or metabolic diseases or risk factors in the family history indicates an increased probability for the presence of PAD. Therefore, a positive family history not only of PAD but also for other correlated cardiovascular or metabolic diseases should be added to the list of individual risk factors for PAD (as smoking and hypertension). Since calculation of a family risk score as in our investigation is complicated, a programmed online interface is required for establishing the FamRS-calculation in practice. We implemented such an online-tool that can be found at http://www3.i-med.ac.at/genepi/FamRS/.

6. Conclusion

In conclusion, taking a comprehensive family history might be essential for risk evaluation and possible diagnosis of PAD. In cases with a positive family history of various cardiovascular and metabolic risk factors, physicians should take the presence of PAD as well as other common diseases into consideration. They should perform examinations such as the ABI to exclude complications at an early stage and to prevent progression of the disease before invasive interventions are mandatory. From a patient's standpoint it could improve the awareness for controlling cardiovascular

complications. Counseling a so far healthy individual could include that the familial genetic burden cannot be altered but that the control of lifestyle factors might counteract the development and progression of the disease.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.08.032.

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