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DISSERTATION

Adipose tissue as an endocrine organ – The role of omentin-1 in cardiovascular diseases and bone health

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1. Abstract

Introduction: Adipose tissue was traditionally considered as an energy depot. Over the last decades this view considerably changed. Nowadays it is well recognized as endocrine organ, capable of synthesizing several biologically active adipokines that regulate metabolic homeostasis. Omentin-1 is one novel adipokine, suggested to be involved in multiple physiological processes including cardiovascular function and bone metabolism.

Methods: All three publications were conducted in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, using different study designs. Publication 1 aimed to investigate the applicability of a single omentin-1 measurement as a biomarker in epidemiological studies. Therefore the reproducibility of omentin-1 was estimated by intraclass correlation coefficient (ICC). A multivariable-adjusted analysis of covariance (ANCOVA) was performed to investigate the cross-sectional associations between omentin-1 concentrations and several cardiovascular risk factors (Publication 2). Prentice modified Cox regression adjusted for established cardiovascular risk factors was used to estimate longitudinal associations between omentin-1 and risk of developing myocardial infarction (MI) and stroke during 8.2 ± 1.6 years of follow-up (Publication 2). Multivariable-adjusted ANCOVA was used to investigate the relationship between omentin-1 and bone health, assessed by broadband ultrasound attenuation (BUA). Further, a mediation analysis assessed the mediating effect of osteoprotegerin on the association of BUA and omentin-1 (Publication 3).

Results: The ICC for repeated omentin-1 measurements was 0.83 (95%-CI 0.78-0.87), indicating excellent reliability. Cross-sectional analysis across quartiles of omentin-1 showed significant positive associations with age, physical activity, history of diabetes, HDL-cholesterol, adiponectin, and alcohol consumption, significant inverse association was observed with waist circumference. Omentin-1 was not significantly associated with risk of MI (HR per doubling omentin-1:1.17; 95%-CI 0.79-1.72; p=0.43), but with higher risk of stroke (HR per doubling omentin-1:2.22; 95%-CI 1.52-3.22; p<0.0001). In subgroup analyses, associations of omentin-1 with risk of stroke were in particular stronger in participants with normal waist circumference, low levels of triglyceride and hsCRP, high adiponectin levels or absence of metabolic syndrome.

Publication 3 provides evidence for an inverse association between circulating omentin-1 and BUA levels in postmenopausal women (p for trend=0.02). However, the present findings do not support a mediating effect of osteoprotegerin in the adipose tissue-bone pathway.

Conclusion: In conclusion, the present thesis, suggests that a single measurement of omentin-1 may be sufficient for risk assessment in epidemiological studies. Moreover, omentin-1 has been considered to be involved in multiple physiological processes, showing associations to both the cardiovascular system and to the bone metabolisms.

2. Zusammenfassung

Einleitung: Neue Erkenntnisse in der Wissenschaft verändern kontinuierlich Ansichten über Funktionen verschiedener Gewebe und Organe im menschlichen Organismus. So stellt das Fettgewebe in seiner klassischen Funktion nicht nur einen Energiespeicher dar, sondern wird heute auch als ein endokrines Organ angesehen. Es sezerniert eine Vielzahl biologisch aktiver Adipokine, die an vielen peripheren und zentralen physiologischen Prozessen beteiligt sind. Ein neu entdecktes Adipokin ist Omentin-1, das eine Rolle in kardiovaskulären und knochenmetabolischen Funktionen spielen könnte.

Methoden: Die vorliegende Dissertation besteht aus drei Publikationen, wobei Daten der Potsdamer EPIC (European Prospective Investigation into Cancer and Nutrition)-Kohortenstudie, unter Anwendung verschiedener Studiendesigns, genutzt wurden. Zunächst wurde mittels Reliabilitätsbestimmung untersucht, ob Omentin-1 als Biomarker in epidemiologischen Studien geeignet ist (Publikation 1). Dazu wurde die Reliabilität durch die Berechnung des Intra-Class-Korrelationskoeffizienten (ICC) bestimmt. Eine adjustierte Kovarianzanalyse untersuchte im Querschnitt den Zusammenhang zwischen Omentin-1 und einer Vielzahl von kardiovaskulären Risikofaktoren (Publikation 2). In einer prospektiven Analyse, unter Anwendung von adjustierten Cox-Regressionsmodellen modifiziert nach Prentice, wurde der Zusammenhang zwischen Omentin-1 und dem Risiko für das Auftreten von zukünftigen Myokardinfarkten und Schlaganfällen untersucht. Das Einfügen von Interaktionstermen in das volladjustierte Model diente der Untersuchung von Interaktionen von Omentin-1 mit verschiedenen kardiovaskulären Risikofaktoren (Publikation 2). Eine adjustierte

Kovarianzanalyse untersuchte den Zusammenhang zwischen Omentin-1 und der Knochengesundheit, gemessen durch Ultraschallabschwächung (BUA). Darüber hinaus wurde durch eine Mediationsanalyse untersucht, ob Osteoprotegerin als möglicher Mediator diese Beziehung fungiert (Publikation 3).

Ergebnisse: Publikation 1 zeigte eine exzellente Reliabilität wiederholter Omentin-1-Messungen, aufgezeigt durch einen Intra-Class-Korrelationskoeffizient von 0.83 (95%-KI 0.78-0.87). Die Querschnittanalyse über Omentin-1-quartile zeigte signifikante positive Assoziationen zwischen Omentin-1 und Alter, sportlicher Aktivität, prävalenter Diabetes, HDL-Cholesterin, Adiponektin, und Alkoholkonsum. Außerdem wurde eine signifikante inverse Assoziation mit dem Taillenumfang beobachtet. Omentin-1 war nicht mit dem Risiko zukünftiger Myokardinfarkt assoziiert (HR pro Verdopplung Omentin-1:1.17; 95%-KI 0.79-1.72; p=0.43), jedoch mit dem erhöhten Risiko von Schlaganfällen (HR pro Verdopplung Omentin-1:2.22; 95%-KI 1.52-3.22; p<0.0001). Subgruppenanalysen zeigten vor allem ein erhöhtes Schlaganfallrisiko in Teilnehmern mit normalem Taillenumfang, niedrigen Triglycerid- und hsCRP-Konzentrationen, hohen Adiponektinlevel und keinem Vorliegen eines metabolischen Syndroms. Publikation 3 zeigte eine inverse Assoziation zwischen Omentin-1 und BUA-Werten in postmenopausalen Frauen (p für Trend=0.02), die Mediationsanalyse konnte eine mögliche Mediation durch Osteoprotegerin jedoch nicht bestätigten.

Schlussfolgerung: Es zeigte sich, dass Omentin-1 als stabiler Biomarker in epidemiologischen Studien genutzt werden kann. Weiterhin unterstützt die vorliegende Arbeit die Hypothese, dass Omentin-1 an einer Vielzahl physiologischer Prozesse beteiligt sein könnte. So zeigten sich Assoziationen zur kardiovaskulären Gesundheit und zum Knochenmetabolismus.

3. Introduction and objectives

3.1. Omentin-1

There has been a paradigm shift from the notion of adipose tissue as a passive energy depot to a dynamic endocrine organ, able to produce and secrete a wide variety of factors called adipokines [1]. The discovery of adipokines identified adipose tissue as an important key factor in the organ crosstalk network, which could act either locally autocrine or paracrine on adipocytes or other cell types localized in adipose tissue or endocrine by entering the circulation and affecting peripheral tissues [1].

Omentin-1 is a novel adipokine, discovered as fat depot-specific secretory protein from a human omental fat cDNA library [2]. Omentin-1 has been shown to be mainly expressed in visceral adipose tissue [3, 4]. Recent studies have shown that omentin-1 is inversely related to body mass index (BMI) and waist circumference [3]. Moreover, beneficial associations with adiponectin and high density lipoprotein (HDL)-cholesterol were reported [3]. The present thesis aimed to provide additional evidence for cross-sectional associations of omentin-1 with lifestyle factors, blood lipids and other biomarkers (part of publication 2).

In observational studies assessment of biomarker concentrations often relies on one blood sample from a single time point [5]. The interpretability of such single measurements with regard to biological differences between participants depends on variations of the biomarker concentrations within individuals [5]. Thus, first publication aimed to investigate the reproducibility of omentin-1 measurements to prove omentin-1 as stable biomarker over time for further investigations.

3.1.1. Omentin-1 and cardiovascular diseases

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity globally [6]. CVDs are responsible for estimated 17.5 million deaths worldwide and projected to increase to 22.2 million in 2030 [7]. CVD also represents a major economic burden on health care systems due to hospitalizations, rehabilitation services or medication [6].

Based on reported metabolic actions of omentin-1, potential cardio-protective properties of omentin-1 in the pathogenesis of atherosclerosis and risk of CVD have been hypothesized [8]. However, so far, the relationship between omentin-1 and different

cardiovascular endpoints have been mainly investigated in patients with preexisting diseases, using cross-sectional study designs. In particular, Liu et al. showed that omentin-1 levels were negatively correlated with carotid artery intima-media thickness in patients with metabolic syndrome (MetS) [4]. Greulich et al. showed that decreased omentin-1 levels could contribute to cardiovascular dysfunction in patients with type 2 diabetes [9].

Prospective studies investigating the relationship between omentin-1 and incidence of CVD in apparently healthy participants are still missing. Therefore, the second publication aimed to investigate the longitudinal association of omentin-1 levels and future risk of myocardial infarction (MI) and stroke in apparently healthy humans.

3.1.2. Omentin-1 and bone health

Osteoporosis is a systemic skeletal disease with increasing prevalence worldwide [10]. The disease is characterized by reduced bone mass and micro-architectural deterioration of bone tissue with increased bone fragility, susceptibility to fractures and reduced quality of life [11, 12]. In women, an accelerated bone loss occurs after menopause, many factors have been discussed to contribute to this bone loss [12], including low BMI [13], decreased physical activity [14] or smoking [15]. Interestingly, it has been suggested that adipocyte-dependent hormonal factors may play an important role in bone health [12, 16, 17]. Until now, only few cross-sectional studies investigated the association between omentin-1 and bone mineral density (BMD) in healthy participants, showing inconsistent results [18-21]. Interestingly, in an experimental study high omentin-1 concentrations restored BMD, via inhibition of the receptor activator for nuclear factor κB ligand (RANKL) and stimulation of osteoprotegerin (OPG) [22], both synthesized by bone forming osteoblasts. OPG acts as a decoy receptor, binding to RANKL, thus preventing the activation of bone resorbing precursor cells, and thereby inhibiting bone resorption [23]. Otherwise RANKL, binds its receptor (RANK) settled on osteoclast precursor, leading to osteoclast differentiation and bone resorption [23].

The third publication aimed to investigate the relationship between omentin-1 and bone health in peri-/premenopausal and postmenopausal women. Bone health was assessed by broadband ultrasound attenuation (BUA). Furthermore, this publication examined whether the association between omentin-1 and BUA was mediated by OPG.

4. Methods

All three publications were conducted in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. The EPIC-Potsdam study is part of a multicenter prospective cohort study conducted in ten European countries, focusing on the relation between nutrition and several chronic diseases [24].

Between 1994 and 1998, 10 904 men and 16 644 women mainly aged 35–64 years were randomly selected from the general population of Potsdam and surrounding communities [25, 26]. The recruitment process was based on residents´ registration offices, and the study participants were invited by mail to participate [25, 26]. Study instruments of the baseline examination included computer-based interviews on lifestyle and medical history, self-administered questionnaires on nutrition and lifestyle and physical examinations [25, 26]. During follow-up, approximately every two years, information on vital status, incident diseases, changes in dietary habits and other lifestyle factors, addresses of treating physicians or hospitals, and application of medication during the previous four weeks were collected [27]. The Ethical Committee of the Federal State of Brandenburg, Germany, approved the study. All participants gave their written informed consents to their inclusion in the study. P value < 0.05 was considered to be statistically significant, for interaction terms p value < 0.1 was considered as nominally significant. All statistical analyses were performed using SAS software, version 9.4 (SAS institute, Cary, N.C., USA).

4.1. Assessment of exposure - Omentin-1 measurement

A total of 30 ml of venous blood was collected at baseline from participants at the Potsdam study center; blood was fractionated into serum, plasma, buffy coat, and erythrocytes, and stored in the vapor phase of liquid nitrogen (-196°C) or in freezers (-80°C) for conservation until time of analysis [25].

In 2014 plasma concentrations of omentin-1 were measured in commercially available enzyme linked radioimmuno assays by Biovendor (Brno, Czech Republic) at the Institute of Clinical Chemistry, University Magdeburg, with intra-assay coefficients of variation between 3.2% and 4.1%, inter-assay coefficients of variation between 4.4% and 4.8%, and a limit of detection of 0.5 ng/ml according to the manufacturer’s instructions [5, 8, 12].

4.2. Publication 1: *Reproducibility of Retinol Binding Protein 4 and Omentin-1 Measurements over a Four Months Period: A Reliability Study in a Cohort of 207 Apparently Healthy Participants*

4.2.1. Study design and study population

The study population consisted of 207 apparently healthy EPIC-Potsdam participants. All participants were aged below 64 years, had no prevalent cardiovascular events, no impaired mobility, and systolic and diastolic blood pressure below 180 mmHg and 110 mmHg, respectively. All participants provided two blood samples, approximately four months apart (median 119 days) [5].

4.2.2. Statistical Analysis

Analysis of variance (ANOVA) was used to estimate the variance components explained by within person and between person differences, with omentin-1 concentration as dependent variable and study participant as explanatory factor [5]. Coefficient of variation (CV) was calculated by the root of the mean square error of residuals from the ANOVA [5]. The intraclass correlation coefficient (ICC) was calculated by subtracting within person variance from between person variance and dividing the result by the total variance [5]. CV below 20% [28] has been considered as desirable and ICC above 0.75 indicate excellent reliability [29]. Differences between repeated measurements within a person were plotted against the individual means as proposed by Bland and Altman [5]. The reliability parameters were evaluated according to sex, age, BMI, blood pressure, and time-interval between measurements to test robustness of the results [5].

4.3. Publication 2: *Omentin-1 and risk of myocardial infarction and stroke: Results from the EPIC-Potsdam case-cohort study*

4.3.1. Study design and study population

A case-cohort design was applied, using a randomly drawn subcohort comprising 2500 individuals from the EPIC-Potsdam study providing blood and all incident cases of MI and stroke [8]. After exclusion of participants with prevalent stroke or MI, missing follow-up data, inappropriate blood samples, missing and implausible covariates, and

unreliable omentin-1 measurements, the final study population consisted of a subcohort of 2084 individuals, including 50 MI and stroke cases, and 350 external incident MI and stroke that occurred during 8.2 ± 1.6 years of follow-up (Figure 1) [8].

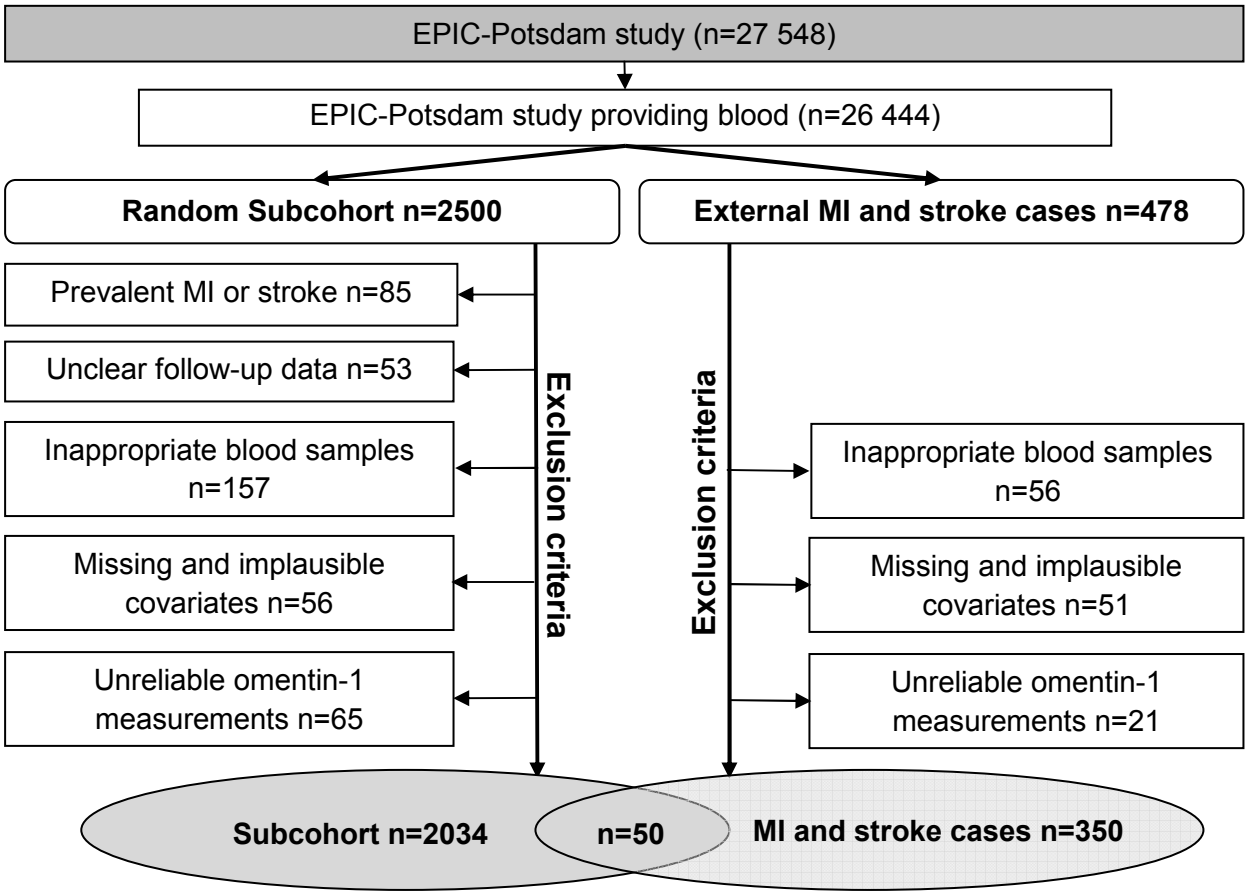

Figure 1: Flow diagram for the exclusion criteria indicating the number of subjects excluded and those remaining for the main analysis in publication 2. [8] MI: Myocardial infarction.

4.3.2. Assessment of outcome - MI and stroke cases

To identify potential MI and stroke cases several sources were used: self-report, death certificate, linkage with hospital information system and additional questionnaires about stroke symptoms [8, 30]. All identified potential MI or stroke events were validated by a study physician, in cooperation with the patients' attending physicians and hospitals, who provided a detailed medical verification of self-reports and death certificates by clinical records according to the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease criteria [8, 31]. According to the International Statistical Classification of Diseases, 10th Revision (ICD-10), cases were classified as incident MI (ICD-10 I21), ischemic stroke (ICD-10 I63.0 to I63.9), hemorrhagic stroke (ICD-10 I60.0 to I61.9) or undetermined stroke (ICD-10 I64.0-I64.9) [8, 32].

4.3.3. Statistical Analysis

A multivariable-adjusted analysis of covariance (ANCOVA) was performed to investigate cross-sectional associations between omentin-1 levels and several cardiovascular risk factors, across quartiles of omentin-1 within the subcohort [8]. Cox proportional-hazards regression modified by Prentice was used to estimate the associations between omentin-1 and risk of MI, stroke or its subtypes, ischemic and hemorrhagic stroke. Hazard ratios (HR) were adjusted for age and sex (Model 1), waist circumference, smoking status, physical activity, educational level, alcohol consumption, prevalent hypertension, prevalent diabetes, HDL-cholesterol, total cholesterol, triglycerides, high-sensitivity C-reactive protein (hsCRP) (Model 2), and adiponectin (Model 3) [8]. The risk of MI and stroke was evaluated on a continuous scale of omentin-1 and according to quartiles of omentin-1 using the first quartile as reference [8]. Effect modifications between selected CVD risk factors and omentin-1 were tested with cross-product terms in the fully adjusted model 3 [8]. Stratified analyses were performed according to established cutoff points of waist circumference, HDL-cholesterol, triglycerides and hsCRP [8]. For adiponectin the sex-specific median from the subcohort was used [8]. Metabolic syndrome was defined by the American Heart Association / National Heart, Lung and Blood Institute criteria [8, 33]. Possible nonlinear relationships between omentin-1 and MI / stroke were examined with restricted cubic splines with five knots at the 5th, 35th, 50th (reference), 65th and 95th percentile of omentin-1 [8].

4.4. Publication 3: *Association between omentin-1, adiponectin and bone health under consideration of osteoprotegerin as possible mediator*

4.4.1. Study design and study population

From 1996 until the end of the recruitment phase, BUA measurement was part of the baseline examination in women (n=9711) only [12]. Omentin-1 and OPG concentrations were measured in a random subsample of 929 out of the 9711 women with already measured BUA levels [12]. Participants were excluded due to: age below 35 years (n=12), undefined menopausal status (n=232), surgical menopause (n=38), postmenopausal women taking oral contraceptives (n=2) or missing covariates data (n=8) [12]. The final study population consisted of 388 peri-/premenopausal women and 249 postmenopausal women [12].

4.4.2. Assessment of outcome – bone health

BUA was used as one parameter reflecting bone health [12]. The measurement was performed on the right os calcis using Achilles Plus Ultrasound Densitometer (Lunar Corporation) by trained personnel [12]. Briefly, BUA was measured, when the foot is submerged in a water tank with a pair of transducers. One ultrasound transducers emits an ultrasound wave, the amplitude of the ultrasound wave is changed during the passage through the heel, which is detected by the second transducer (Figure 2).

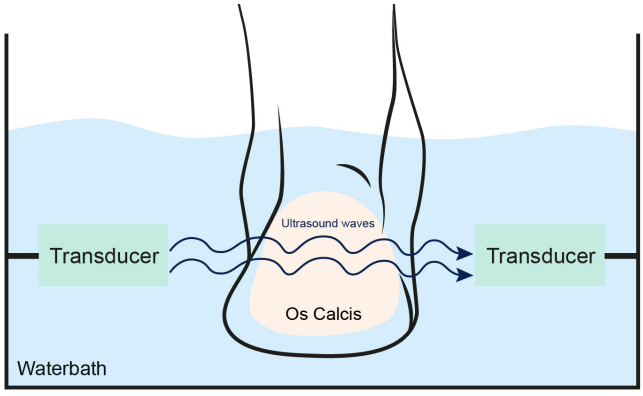

Figure 2: Schematically ultrasonic measurement with transmitting transducer, a posterior view of the os calcis and the receiving transducer in the water bath.

4.4.3. Statistical Analysis

All analyses were performed for peri-/premenopausal (n=388) and postmenopausal (n=249) women, respectively [12]. Multivariable adjusted ANCOVA was used to assess the relationship between omentin-1 and BUA according to menopausal status-specific quartiles of omentin-1, adjusted for age, BMI, waist circumference, smoking status, educational level, physical activity, adiponectin and hormone use respectively, for peri-/premenopausal and postmenopausal women [12].

To examine whether the association between omentin-1 and BUA was mediated by OPG, three fully adjusted linear regressions models were fitted based on the conventional steps of mediation analysis outlined by Baron and Kenny [12, 34]. Statistical significance and size of the indirect effect was estimated, using a bootstrapping analysis (1000 bootstrap samples, sampling rate 80%), established by Preacher and Hayes [12, 35]. The variance accounted for (VAF) determines the size of indirect effect in relation to the total effect, determined as VAF>80%: full Mediation; 80%>VAF>20%: partial Mediation; VAF<20%: no mediation [12, 36] .

5. Results

5.1. Reliability of omentin-1 measurements

As shown in publication 1 the CV for intraindividual measurement variation between repeated measurements was 13% for omentin-1 [5]. The ICC for repeated omentin-1 measurements was 0.83 (95%-confidence level (95%-CI) 0.78-0.87) suggesting an excellent reliability [5]. The agreement between repeated omentin-1 measurements within individuals in relation to individual means is visualized in figure 3 (Bland-Altman-Plot) [5]. These results were robust across strata according to sex, age, BMI, blood pressure (diastolic and systolic), and time interval between measurement time points [5].

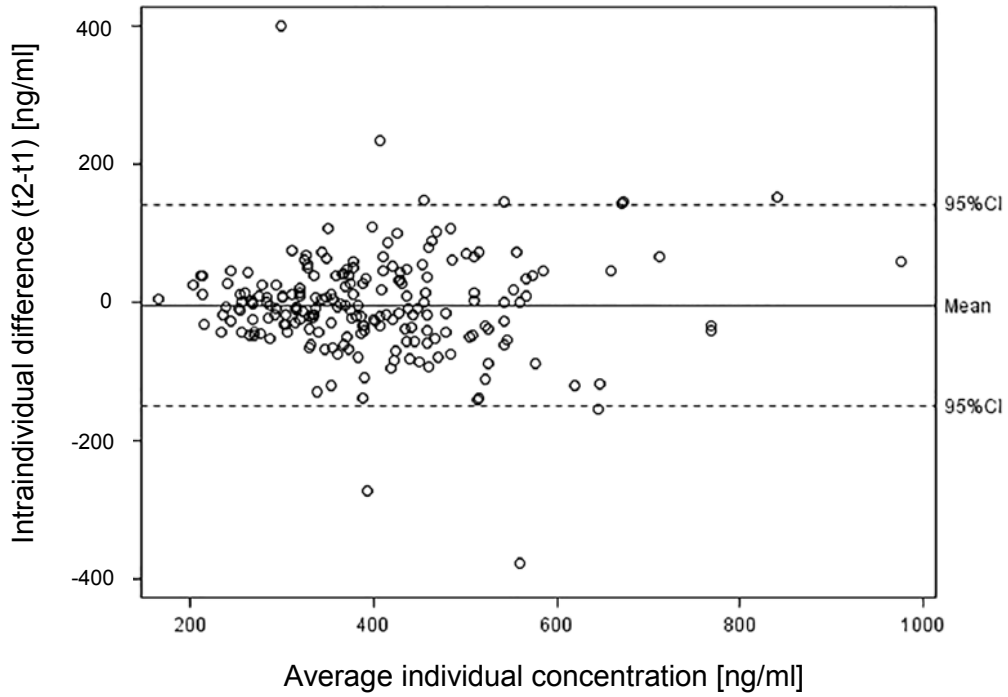

Figure 3: Agreement of repeated omentin-1 measurements in individuals in relation to the overall variability of measurements; agreement was calculated as difference in plasma-concentrations between the two blood-sampling occasions (t2-t1) within individuals; range of agreement was defined as mean ± 1.96 standard deviation and is marked by the dashed lines. [5]

5.2. Cross-sectional association between omentin-1 and lifestyle factors, blood lipids and other biomarkers

As shown in publication 2, a cross-sectional multivariable adjusted ANCOVA across quartiles of omentin-1 noticed significant positive associations with age, physical activity, history of diabetes, HDL-cholesterol, adiponectin, and alcohol consumption. A significant inverse association was observed with waist circumference (Table 1) [8].

Table 1: Characteristics of subcohort according to omentin-1 quartiles. [8]

Characteristics [a]	**Q1 (n=519)**	**Q2 (n=525)**	**Q3 (n=519)**	**Q4 (n=521)**	p linear trend [d]
Omentin-1 [ng/ml] [b]	286.5 (250.6-308.6)	363.1 (343.4-380.3)	439.6 (420.0-462.8)	569.6 (517.4-642.6)	
Men [%] [c]	41.2	36.6	37.7	33.5	0.1
Age [years] [c]	47.4 (46.6-48.1)	48.8 (48.1-49.5)	51.9 (51.1-52.6)	53.9 (53.2-54.6)	<0.0001
Waist circumference [cm]	89.8 (88.8-90.7)	84.4 (86.5-88.3)	86.6 (85.7-87.5)	85.1 (84.2-86.0)	<0.0001
Physical activity, [h/week]	0.88 (0.73-1.03)	0.91 (0.76-1.05)	0.98 (0.83-1.13)	1.26 (1.11-1.41)	0.01
Smoking *(condensed)* [%]					0.5
Non-smoker	43.1	43.3	40.7	46.9	
Smoker	23.3	23.0	22.1	19.4	
Education *(condensed)* [%]					0.4
Unskilled or skilled	35.4	35.0	35.2	35.4	
University degree	42.2	41.5	41.2	43.3	
Prevalent diabetes [%]	3.7	3.8	4.6	5.9	0.0004
Prevalent hypertension [%]	50.7	48.7	47.4	49.6	0.06
Total cholesterol [mmol/l]	5.24 (5.15-5.33)	5.26 (5.17-5.36)	5.26 (5.17-5.35)	5.37 (5.27-5.46)	0.4
HDL-cholesterol [mmol/l]	1.36 (1.32-1.39)	1.39 (1.36-1.42)	1.41 (1.38-1.44)	1.53 (1.50-1.56)	0.03
Triglyceride [mmol/l]	1.64 (1.55-1.73)	1.53 (1.44-1.62)	1.66 (1.57-1.75)	1.47 (1.37-1.56)	0.7
hsCRP [mg/l]	2.57 (2.26-2.89)	1.67 (1.37-1.97)	1.89 (1.59-2.20)	1.64 (1.33-1.95)	0.06
Adiponectin [µg/ml]	6.99 (6.67-7.32)	7.78 (7.46-8.10)	8.23 (7.90-8.55)	9.30 (8.97-9.63)	<0.0001
Alcohol [g/d]	14.6 (12.9-16.3)	16.5 (14.8-18.2)	16.6 (14.9-18.2)	19.4 (17.7-21.1)	0.0004

[a] All variables were adjusted for sex and age, expressed as adjusted percentage or mean (95%-CI). [b] Unadjusted variables, expressed as median (IQR). [c] Adjusted for sex or age; according to examined variable. [d] Mutually adjusted for sex, age, waist circumference, physical activity, education, smoking, alcohol consumption, prevalent hypertension and diabetes, HDL-cholesterol, total cholesterol, triglycerides, hsCRP and adiponectin according to examined variable.

5.3. Association between omentin-1 and the future-risk of stroke and MI

After adjustment for age and sex, individuals in the highest quartile of omentin-1 levels had significantly increased risk of stroke (Model 1, HR: 2.39; 95%-CI 1.50–3.82) compared with participants in the lowest quartile (p for trend < 0.0001) (Table 2) [8]. This association remains stable after additional adjustment for waist circumference, physical activity, education, smoking, alcohol consumption, prevalent hypertension, prevalent diabetes, total cholesterol, HDL-cholesterol, triglycerides, hsCRP, and adiponectin (Model 3, HR: 2.29; 95%-CI 1.38–3.79; p for trend = 0.0003) (Table 2) [8]. Strong positive associations were also observed when omentin-1 was modelled on a continuous scale (HR per doubling of omentin-1: 2.22; 95%-CI 1.52–3.22; p < 0.0001) [8]. Stratified analyses according to stroke subtypes showed increased risk of both ischemic (HR per doubling of omentin-1: 2.02; 95%-CI 1.34–3.05; p = 0.0008) and hemorrhagic stroke (HR per doubling of omentin-1: 2.80; 95%-CI 1.39–5.62; p = 0.004) [8]. However, no relationship was observed between omentin-1 and risk of MI (Model 3, HR: 1.13; 95%-CI 0.71–1.79; p for trend = 0.48) (Table 2) in the highest versus the lowest quartile of omentin-1 [8].

Table 2: Hazard ratios of MI and stroke according to quartiles of omentin-1 levels. [8]

	Quartiles of omentin-1 levels [a]				
	Q1	**Q2**	**Q3**	**Q4**	**p for trend**
MI (n=2267)					
Cases (n)	43	45	54	60	
Model 1 [b]	Ref.	0.99 (0.63-1.54)	0.91 (0.60-1.39)	0.95 (0.62-1.45)	0.80
Model 2 [c]	Ref.	0.90 (0.56-1.44)	0.97 (0.62-1.51)	1.16 (0.73-1.83)	0.42
Model 3 [d]	Ref.	0.89 (0.56-1.42)	0.96 (0.61-1.50)	1.13 (0.71-1.79)	0.48
Stroke (n=2251)					
Cases (n)	24	34	55	85	
Model 1 [b]	Ref.	1.29 (0.75-2.23)	1.73 (1.05-2.84)	2.39 (1.50-3.82)	<0.0001
Model 2 [c]	Ref.	1.26 (0.72-2.20)	1.63 (0.97-2.73)	2.42 (1.47-3.98)	0.0001
Model 3 [d]	Ref.	1.24 (0.71-2.16)	1.58 (0.94-2.66)	2.29 (1.38-3.79)	0.0003

Hazard ratios and 95%-CI were derived from Cox proportional-hazard regression. [a] Quartiles are based on the distribution of omentin-1 within the subcohort. [b] Sex and age adjusted. [c] Additionally adjusted for waist circumference, physical activity, education, smoking, alcohol consumption, prevalent hypertension and diabetes, HDL-cholesterol, total cholesterol, triglycerides and hsCRP. [d] Additionally adjusted for adiponectin levels.

The linearity of the shape of the associations was assessed with restricted cubic spline regression (Figure 4), there was no evidence of departure from linearity for the relation between omentin-1 and stroke risk (p for non-linearity ≥ 0.8) [8]. Also restricted cubic spline regression depicted no relationship between omentin-1 and risk of MI [8].

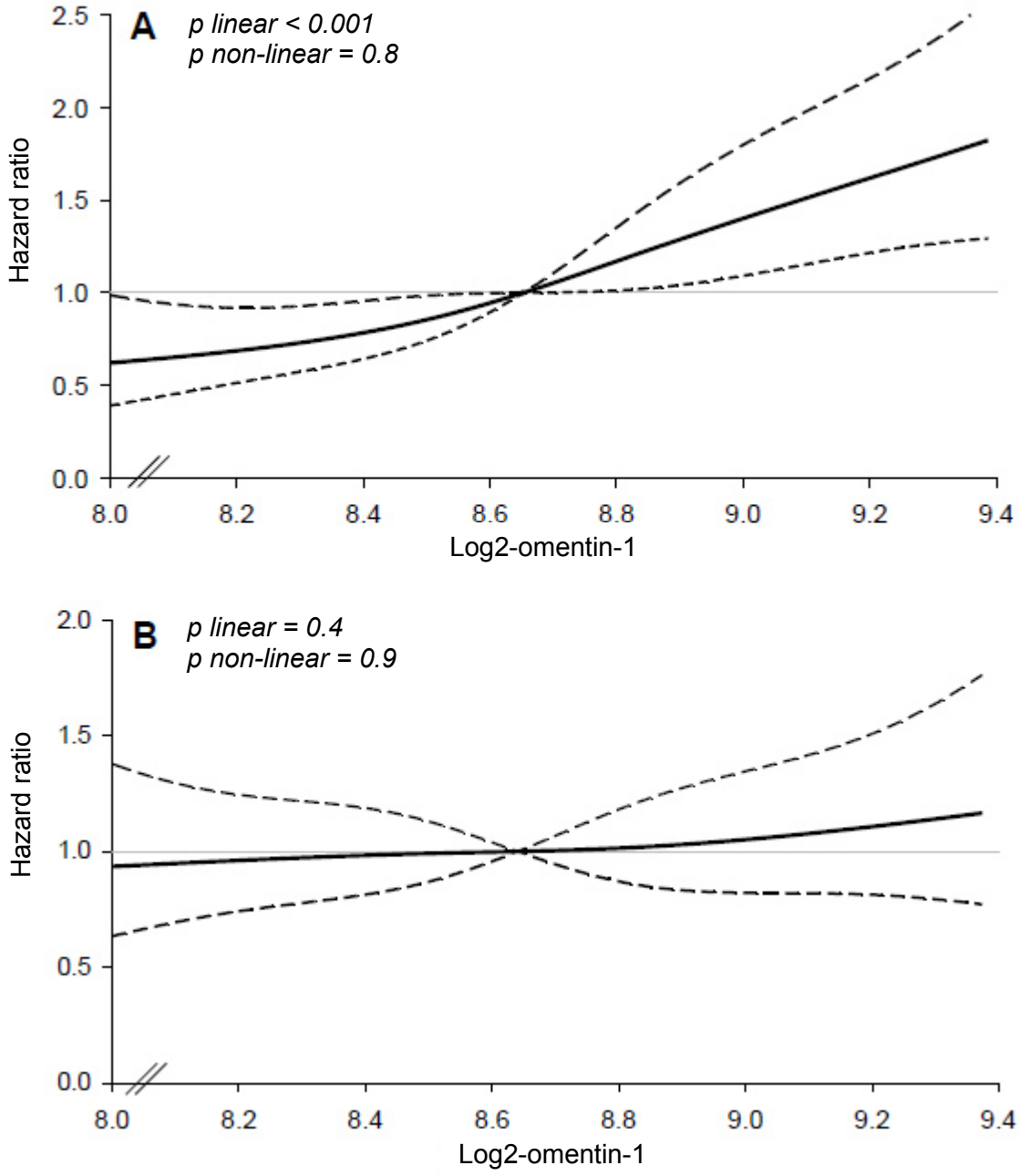

Figure 4: Hazard ratio curves for the association between omentin-1 levels and the risk stroke (A) and MI (B). The solid lines indicate hazard ratios of stroke or MI as obtained by restricted cubic spline Cox regression with knots placed at fixed values (5th, 35th, 65th and 95th percentile of the distribution of omentin-1). The reference was set at 50th percentile. Dashed lines indicate 95%-CI. 95%-CI bands are adjusted for age, sex, waist circumference, physical activity, education, smoking, alcohol consumption, prevalent hypertension and diabetes, HDL-cholesterol, total cholesterol, triglycerides, hsCRP, adiponectin. P for nonlinearity was computed by Wald chi-square test. [8]

As shown in Table 3, in subgroup analyses, associations of omentin-1 with risk of stroke were generally stronger in low versus high CVD risk groups [8]. In detail, stratified analyses according to subgroups showed increased stroke risk in individuals with high adiponectin levels (HR per doubling omentin-1: 3.52; 95%-CI 2.08-5.94; p < 0.0001) but not in those with low adiponectin levels (p for interaction = 0.02) [8]. Further, Publication 2 found increased stroke risk in individuals with low waist circumference (p for interaction = 0.03), low levels of triglyceride (p for interaction = 0.09), hsCRP (p for interaction = 0.08) and no MetS (p for interaction = 0.05), compared to those in high-risk strata [8].

Table 3: Multivariable adjusted HR for stroke risk per doubling of omentin-1 for subgroups. [8]

Group	**p for interaction** [a]	**Hazard ratio (95%-CI)** [b]	**p-value** [b]
Sex	0.68		
Men		2.65 (1.55-4.52)	0.0004
Women		1.90 (1.06-3.40)	0.03
Waist circumference [cm]	0.03		
< 102 men, < 88 women		2.59 (1.63-4.11)	<0.0001
≥ 102 men, ≥ 88 women		1.76 (0.82-3.77)	0.15
Metabolic Syndrome [c]	0.05		
No		2.58 (1.64-4.07)	<0.0001
Yes		1.21 (0.59-2.50)	0.60
HDL-cholesterol [mmol/l]	0.49		
< 1.04 men, < 1.29 women		2.76 (1.23-6.17)	0.01
≥ 1.04 men, ≥ 1.29 women		2.16 (1.38-3.38)	0.0007
Triglycerides [mmol/l]	0.09		
< 1.69		3.16 (1.90-5.25)	<0.0001
≥ 1.69		1.28 (0.73-2.26)	0.39
Adiponectin [µg/ml]	0.02		
< 5.98 men, < 9.14 women		1.14 (0.65-2.01)	0.65
≥ 5.98 men, ≥ 9.14 women		3.52 (2.08-5.94)	<0.0001
hsCRP [mg/l]	0.08		
< 1.0		2.98 (1.70-5.21)	0.0001
≥ 1.0		1.49 (0.83-2.66)	0.18

[a] p-values for interaction were calculated using dichotomous variables and log-transformed omentin-1 levels. [b] Adjusted for age, sex, waist circumference, physical activity, education, smoking, alcohol consumption, prevalent hypertension and diabetes, HDL-cholesterol, total cholesterol, triglycerides, hsCRP, adiponectin. [c] n=2249 due to missing values.

5.4. Association between omentin-1 and bone health under consideration of OPG as possible mediator

Publication 3 observed no association between omentin-1 and BUA in peri-/premenopausal women (Table 4; p for trend = 0.4) [12]. However, in postmenopausal women, omentin-1 was inversely related to BUA levels, in particular, a 10 % increase in omentin-1 levels was significantly associated with 0.44 dB/MHz lower BUA (p = 0.01) (107.0 dB/MHz (95%-CI 103.8-110.2 dB/MHz) vs. 103.0 dB/MHz (95%-CI 99.6-106.4 dB/MHz) for the highest versus the lowest quartile of omentin-1, p for trend = 0.02) (Table 4) [12].

Table 4: Quartiles of omentin-1 with adjusted BUA values according to menopausal status. [12]

Peri-/premenopausal women (n=388)				
Quartiles	n	Omentin-1 [ng/ml]	BUA [dB/MHz] [a]	p for trend
Q1	97	256.4 (230.8-285.4)	111.0 (95%-CI 108.8-113.2)	0.4
Q2	97	334.1 (321.3-350.3)	111.0 (95%-CI 108.8-113.2)	
Q3	97	395.6 (384.0-419.9)	112.9 (95%-CI 110.6-115.2)	
Q4	97	494.2 (460.5-568.4)	111.7 (95%-CI 109.4-114.1)	
Postmenopausal women (n=249)				
Quartiles	n	Omentin-1 [ng/ml]	BUA [dB/MHz] [b]	p for trend
Q1	62	322.9 (284.2-342.2)	107.0 (95%-CI 103.8-110.2)	0.02
Q2	63	417.6 (394.4-436.2)	106.9 (95%-CI 103.7-110.2)	
Q3	62	495.9 (472.1-520.8)	106.2 (95%-CI 103.2-109.2)	
Q4	62	614.2 (590.4-692.5)	103.0 (95%-CI 99.6-106.4)	

Variables are expressed as adjusted or median (IQR) or mean (95 %-CI). Adjusted for age, waist circumference, BMI, smoking status, education, physical activity, adiponectin (log transformed) oral contraceptive use [a], hormone replacement therapy [b]

Therefore, the mediating effect of OPG on the association between BUA and omentin-1 levels was tested in postmenopausal women only [12]. Even if omentin-1 was positively associated with OPG (p = 0.02) and negatively with BUA (p = 0.01), when omentin-1 and OPG were simultaneously included in the fully adjusted model, OPG was not significantly associated with BUA levels (p = 0.62) (Figure 5) [12]. Nevertheless, bootstrapping analysis noticed a statistically significant indirect effect of omentin-1 on BUA via OPG (β-coefficient mean bootstrap 0.13, 95%-CI bootstrap 0.12-0.14), but the

VAF in the mediation model was three percent, suggesting lack of mediation effect of OPG on the association between omentin-1 and BUA levels [12].

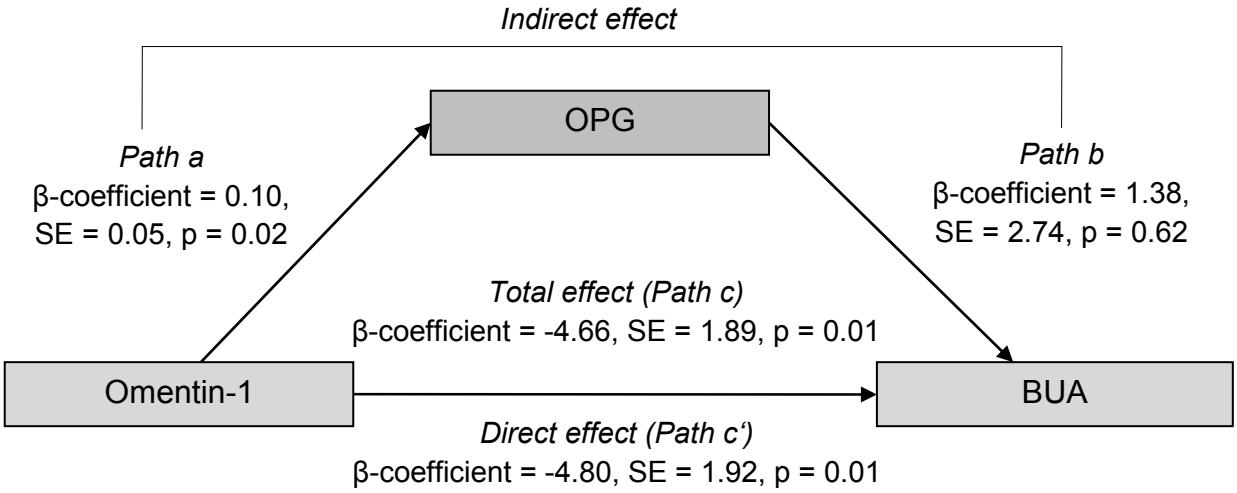

Figure 5: OPG (log transformed) mediation model of the relationship between omentin-1 (log transformed) and BUA. Mediation model decomposes the total effect of omentin-1 on BUA (path c), into indirect effect of omentin-1 on BUA via mediator OPG, quantified by the product of the β-coefficients of path a and path b, and the direct effect of omentin-1 on BUA, when the effect of the possible mediator was removed, quantified by the path c′. [12, 37] BUA: Broadband ultrasound attenuation. OPG: Osteoprotegerin. SE: Standard error.

6. Discussion

Up to date, the EPIC-Potsdam study (n=27 548) is one of the largest German cohort study with regular follow-up rounds, providing a comprehensive availability of high-quality data. The collection of blood samples in combination with extensive information from questionnaires or examinations enabled the EPIC-Potsdam study to investigate a wide range of different research questions. Therefore the three publications of the present thesis were conducted in the EPIC-Potsdam study, using different study designs. However, the present results are limited to middle-aged Caucasian participants and might be not generalized to other age or ethnic groups [8, 12].

In observational studies the investigation of biomarker, mostly relies on the assessment of biomarker concentrations of blood samples from one single time point [5]. It is well known, that the interpretability of such single measurements in terms of biological differences between participants depends on the variability of the biomarker concentrations within individuals [5]. These intraindividual variation might be influenced by environmental factors e.g. season, daytime or endogenous factors like health status, menstrual cycle, and stress level, which are mostly not considered in analyses of observational studies [5]. Therefore the present thesis first aimed to investigate the applicability of a single omentin-1 measurement as a biomarker in epidemiological studies. In line with the study of Panagiotou et al. [38], publication 1 indicated excellent reliability of a single omentin-1 measurement. Thus, it seems reasonable to rely on concentrations of omentin-1 from single baseline samples for risk estimates [5].

Based on that finding, the present thesis further aimed to investigate the novel adipokine omentin-1 in the EPIC-Potsdam study, in order to provide additional scientific evidence regarding cross-sectional associations between omentin-1 and lifestyle factors, blood lipids and other biomarkers (Publication 2). Cross-sectional analysis supports the recently reported inverse association between omentin-1 and waist circumference [3, 9, 39], as well as positive associations between omentin-1 and HDL-cholesterol [3, 9, 40-42], and adiponectin [39, 41, 43]. Based on these reported relationships, a possible protective role of omentin-1 in the pathogenesis of atherosclerosis and CVD has been hypothesized.

So far, mainly cross-sectional studies investigated the relationship between omentin-1 and cardiovascular endpoints, often performed in patients with preexisting diseases,

suggesting omentin-1 as a potential cardio-protective factor. Liu et al. found an inverse relation between omentin-1 levels and carotid artery intima-media thickness in patients with MetS [4]. Greulich et al. indicated that decreased omentin-1 levels were associated with cardiovascular dysfunction in patients with type 2 diabetes [9]. Moreover, patients with coronary artery disease had lower omentin-1 levels [40, 44-47]. Up to date, only two small prospective studies investigated the association between omentin-1 and cardiovascular endpoints in patients with heart disease, providing conflicting findings [48-50]. On the one hand, Narumi et al. conducted a study comprising 136 patients with heart failure, showing an association between lower omentin-1 levels and higher risk of cardiac death or re-hospitalization [48]. On the other hand, Saely et al. reported an association between higher plasma omentin-1 levels and higher risk of cardiovascular events in 295 patients with coronary artery disease [49, 50].

Currently, publication 2 represents the first prospective study investigating potential associations between omentin-1 and risk of stroke and MI in apparently healthy middle-aged men and women [8]. Contrary to expectations, but in line with the recently published prospective study by Saely et al. [49, 50], the present study refuted the suggested cardio-protective associations [8]. The prospective analyses demonstrated that higher levels of omentin-1 were significantly associated with a higher risk of stroke. Interestingly, subgroup analyses noticed stronger associations between omentin-1 and stroke risk in metabolically healthy individuals, i.e. with normal waist circumference, low levels of triglyceride and hsCRP, high adiponectin levels or absence of MetS [8].

Yet, the suggested cardio-protective associations were mainly based on studies comprising low number of participants with existing diseases. Therefore the present thesis may hypothesize that the role of omentin-1 in metabolic regulation probably differs between participants with preexisting metabolic disease compared to apparently healthy individuals [8]. In line with that, it might possible to speculate further an omentin-1-related stroke risk, depended on other metabolic conditions like high or low levels of adiponectin, triglycerides or hsCRP [8]. Competition for potentially shared signaling pathways with different signaling efficiencies would in principle agree with our observations, and suspect a complex molecular interplay between omentin-1 and other CVD risk factors [8].

Although experimental studies have investigated the cardiovascular protective properties of omentin-1 [51, 52], e.g. showing that omentin-1 enhances vasodilation in isolated blood vessels [53], detailed mechanistic investigation of omentin-1 with regard to the development of cardiovascular diseases are still lacking. Intense research and well-designed experiments are needed, addressing the biological processes of omentin-1 with the risk of different major cardiovascular endpoints under different metabolic conditions [8].

In general adipokines are considered as important key factors in the organ crosstalk network with a number of important systemic complex interactions in different organ systems [1]. Therefore the adipokine omentin-1 may not only be restricted to physiological processes of the cardiovascular system. In fact, scientific evidence has revealed that omentin-1 may also play an important role in the bone metabolism, including BMD [18, 19].

Interestingly, in a recently published experimental study, performed in co-culture systems of osteoblast and osteoclast precursors, omentin-1 was shown to reduce osteoclast formation via stimulation of OPG and inhibition of RANKL production in osteoblasts [22]. Furthermore, omentin-1 treatment significantly enhanced BMD in ovariectomized mice (a widely used mice model for postmenopausal women [54]) accompanied by higher serum OPG and lower RANKL levels, suggesting a bone-sparing effect of omentin-1 via OPG and RANKL [22].

Therefore, the third publication investigated for the first time, not only the association between omentin-1 and BUA, but also whether the association between omentin-1 and BUA was mediated by OPG [12] . Of note, in this publication BUA was used as a proxy of BMD measures, commonly measured with dual energy X-ray absorptiometry technique (DEXA). Nevertheless, BUA has been validated satisfactorily several times against BMD measured by DEXA [55], thus representing a non-invasive, valid, inexpensive, easy, and quick alternative measure for BMD without radiation [12].

To date, only a few epidemiological studies investigated the relationship between omentin-1 and bone health in apparently healthy humans. In line with the present study findings, Tohidi et al. also observed a significant inverse association between omentin-1 and BMD in Iranian postmenopausal women [19], whereas other studies found inverse associations, albeit not statistically significant, in both men and postmenopausal

women [20, 21]. In contrast, Wang et al. observed an inverse relationship between omentin-1 and BMD in premenopausal, but not in postmenopausal women [18].

Contrary to our hypothesis, the association between omentin-1 and BUA was not mediated by OPG levels. However, the study supports a positive association between omentin-1 and OPG in postmenopausal women, in line with the study findings of Xie et al. [22]. Nevertheless, experimental studies indicate an OPG-dependent bone remodeling mechanism, whereas human studies have provided controversial results regarding the relationship of OPG on bone remodeling marker and BMD [56-59]. The reason for this controversy might be explained by the fact that rather absolute values of OPG, the OPG / RANKL ratio most likely influences the static measure of BMD, thus maintaining an appropriate balance of bone remodeling [12, 60, 61]. Moreover, it is possible that the higher omentin-1 and lower BUA levels observed in postmenopausal women might be due to a physiological compensation and adaptation to bone loss [12]. Even if publication 3 observed an inverse association between omentin-1 and BUA levels, it cannot be ruled out that omentin-1 may attenuate the stronger bone removal in these women, as suggested by Xie et al. [12, 22]. However, the cross-sectional study design in publication 3 does not allow for causal inference, therefore it cannot clarify whether the observed omentin-1 concentrations are pathological or compensatory [12].

In conclusion, the present thesis indicates that a single measurement of omentin-1 provides highly reliable omentin-1 concentrations, suggesting that a single measurement may provide reliable risk estimates. Further, omentin-1 participates in multiple physiological processes of cardiovascular function and bone metabolism. In detail, high plasma omentin-1 concentrations were associated with a higher risk of stroke in particular in metabolically healthy individuals. Higher plasma omentin-1 levels were associated with lower BUA levels in postmenopausal women. However, there was no evidence of a mediating effect of OPG in the adipose tissue-bone pathway.

7. References

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8. Affidavit

I, Juliane Menzel, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Adipose tissue as an endocrine organ – The role of omentin-1 in cardiovascular diseases and bone health”. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations ["uniform requirements for manuscripts (URM)] indicated. The sections on methodology (statistical processing) and results (in particular images, graphics and tables) correspond to the URM and are answered by me. My contributions in the selected publications for this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author of correspond to the URM and I am solely responsible.
The importance of this affidavit and the criminal consequences of a false affidavit are known to me and I understand the rights and responsibilities stated therein.

Date	Signature

9. Declaration of publications

Parts of this dissertation have been published in the following articles.

Juliane Menzel had the following work share in the creation of the manuscripts.

Publication 1

Authors:	Wittenbecher C, di Giuseppe R, Biemann R, Menzel J, Arregui M, Hoffmann J, Aleksandrova K, Boeing H, Isermann B, Schulze MB, Weikert C
Title:	Reproducibility of retinol binding protein 4 and omentin-1 measurements over a four months period: a reliability study in a cohort of 207 apparently healthy participants
Year:	2015
Journal:	PLoS One (Impact factor 2015: 3.06)
Contribution:	10% (discussion of methods, interpretation of data, revision of the manuscript)

Publication 2

Authors:	Menzel J, di Giuseppe R, Biemann R, Wittenbecher C, Aleksandrova K, Pischon T, Fritsche A, Schulze MB, Boeing H, Isermann B, Weikert C
Title:	Omentin-1 and risk of myocardial infarction and stroke: Results from the EPIC-Potsdam cohort study
Year:	2016
Journal:	Atherosclerosis (Impact factor 2015: 3.94)
Contribution:	85% (literature review, study design, statistical analyses, interpretation of data, preparation of the manuscript, responsibility during the publication process)

Publication 3

Authors:	Menzel J, di Giuseppe R, Biemann R, Aleksandrova K, Kuxhaus O, Wittenbecher C, Fritsche A, Schulze MB, Boeing H, Weikert C
Title:	Association between omentin-1, adiponectin and bone health under consideration of osteoprotegerin as possible mediator
Year:	2016
Journal:	Journal of Endocrinological Investigation (Impact factor 2015: 1.99)
Contribution:	90% (literature review, study design, statistical analyses, interpretation of data, preparation of the manuscript, responsibility during the publication process)

_____

Signature

10. Printed copies of selected publications

10.1. Publication 1

Wittenbecher C, di Giuseppe R, Biemann R, Menzel J, Arregui M, Hoffmann J, Aleksandrova K, Boeing H, Isermann B, Schulze MB, Weikert C (2015): Reproducibility of retinol binding protein 4 and omentin-1 measurements over a four months period: a reliability study in a cohort of 207 apparently healthy participants, PLoS One, 10(9):e0138480

http://dx.doi.org/10.1371/journal.pone.0138480

Die Seiten 29-37 sind im Druckexemplar enthalten oder online erhältlich.

10.2. Publication 2

Menzel J, di Giuseppe R, Biemann R, Wittenbecher C, Aleksandrova K, Pischon T, Fritsche A, Schulze MB, Boeing H, Isermann B, Weikert C (2016): Omentin-1 and risk of myocardial infarction and stroke: Results from the EPIC-Potsdam cohort study, Atherosclerosis, 251:415-21. doi: 10.1016/j.atherosclerosis.2016.06.003. Epub 2016 Jun 2.

http://dx.doi.org/10.1016/j.atherosclerosis.2016.06.003

Die Seiten 39-45 sind im Druckexemplar enthalten oder online erhältlich.

10.3. Publication 3

Menzel J, di Giuseppe R, Biemann R, Aleksandrova K, Kuxhaus O, Wittenbecher C, Fritsche A, Schulze MB, Heiner Boeing H, Weikert C (2016): Association between omentin-1, adiponectin and bone health under consideration of osteoprotegerin as possible mediator, J Endocrinol Invest. 2016 Nov;39(11):1347-1355. Epub 2016 Sep 10.

http://dx.doi.org/10.1007/s40618-016-0544-3

Die Seiten 47-55 sind im Druckexemplar enthalten oder online erhältlich.

11. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

12. Complete list of publications

12.1. Research papers in scientific journals

Wirth J, Atzler D, di Giuseppe R, Cordts K, Menzel J, Böger RH, Boeing H, Weikert C, Schwedhelm E (2016): Asymmetric and Symmetric Dimethylarginine and the Risk of Heart Failure in the EPIC-Potsdam Study, Amino Acids, 2016 Oct 28. [Epub ahead of print]

Menzel J, di Giuseppe R, Biemann R, Aleksandrova K, Kuxhaus O, Wittenbecher C, Fritsche A, Schulze MB, Heiner Boeing H, Weikert C (2016): Association between omentin-1, adiponectin and bone health under consideration of osteoprotegerin as possible mediator, J Endocrinol Invest. 2016 Nov;39(11):1347-1355. Epub 2016 Sep 10.

di Giuseppe R, Biemann R, Wirth J, Menzel J, Isermann B, Stangl GI, Fritsche A, Boeing H, Schulze MB, Weikert C (2016): Plasma osteoprotegerin, its correlates, and risk of heart failure: a prospective cohort study. Eur J Epidemiol. 2016 Jun 15. [Epub ahead of print]

Menzel J, di Giuseppe R, Biemann R, Wittenbecher C, Aleksandrova K, Pischon T, Fritsche A, Schulze MB, Boeing H, Isermann B, Weikert C (2016): Omentin-1 and risk of myocardial infarction and stroke: Results from the EPIC-Potsdam cohort study, Atherosclerosis, 251:415-21. doi: 10.1016/j.atherosclerosis.2016.06.003. Epub 2016 Jun 2.

Aleksandrova K, di Giuseppe R, Isermann B, Biemann R, Schulze MB, Wittenbecher C, Fritsche A, Lehmann R, Menzel J, Weikert C, Pischon T, Boeing H (2016): Circulating Omentin as a Novel Biomarker for Colorectal Cancer Risk: Data from the EPIC - Potsdam Cohort Study. Cancer Res. 2016 Jul 1;76(13):3862-71. doi: 10.1158/0008-5472.CAN-15-3464. Epub 2016 May 23.

Wittenbecher C, Menzel J, Carstensen-Kirberg M, Biemann R, di Giuseppe R, Fritsche A, Isermann B, Herder C, Aleksandrova K, Boeing H, Weikert C, Schulze MB (2016): Omentin-1, Adiponectin, and the Risk of Developing Type 2 Diabetes, Diabetes Care. 2016 Jun;39(6):e79-80. doi: 10.2337/dc15-2702. Epub 2016 Apr 18.

Wittenbecher C, di Giuseppe R, Biemann R, Menzel J, Arregui M, Hoffmann J, Aleksandrova K, Boeing H, Isermann B, Schulze MB, Weikert C (2015): Reproducibility of retinol binding protein 4 and omentin-1 measurements over a four months period: a reliability study in a cohort of 207 apparently healthy participants, PLoS One. 2015 Sep 24;10(9):e0138480. doi: 10.1371/journal.pone.0138480.

Menzel J, di Giuseppe R, Wientzek A, Kroke A, Boeing H, Weikert C (2015): Physical Activity, Bone Health, and Obesity in Peri-/Pre- and Postmenopausal Women: Results from the EPIC-Potsdam, Calcif Tissue Int. 2015 Oct;97(4):376-84. doi: 10.1007/s00223-015-0027-0. Epub 2015 Jun 25.

12.2. Scientific conference presentations

Menzel J, di Giuseppe R, Biemann R, Wittenbecher C, Aleksandrova K, Pischon T, Fritsche A, Schulze MB, Boeing H, Isermann B, Weikert C: Omentin-1 and the risk of myocardial infarction and stroke: Results from the EPIC-Potsdam cohort study, Health – exploring complexity (HEC) Annual meetings of the European Epidemiological Federation of the International Epidemiological Association (IEA-EEF), of the German Society for Medical Informatics, Biometry and Epidemiology (GMDS), of the German Society for Epidemiology (DGEpi), European Federation for Medical Informatics (EFMI) and the Medical Informatics Europe (MIE2016), Munich, Germany, 28.08-02.09.2016 (oral presentation)

Wittenbecher C, Menzel J, Carstensen-Kirberg M, Biemann R, di Giuseppe R, Fritsche A, Isermann B, Herder C, Aleksandrova K, Boeing H, Weikert C, Schulze MB: Omentin-1, Adiponektin und das Risiko an Typ 2 Diabetes zu erkranken, Health – exploring complexity (HEC) Annual meetings of the European Epidemiological Federation of the International Epidemiological Association (IEA-EEF), of the German Society for Medical Informatics, Biometry and Epidemiology (GMDS), of the German Society for Epidemiology (DGEpi), European Federation for Medical Informatics (EFMI) and the Medical Informatics Europe (MIE2016), Munich, Germany, 28.08-02.09.2016 (oral presentation)

Wirth J, Atzler D, di Giuseppe R, Cordts K, Menzel J, Böger RH, Boeing H, Weikert C, Schwedhelm E: Asymmetric and Symmetric Dimethylarginine and the Risk of Heart Failure in the EPIC-Potsdam Study, Health – exploring complexity (HEC) Annual meetings of the European Epidemiological Federation of the International Epidemiological Association (IEA-EEF), of the German Society for Medical Informatics, Biometry and Epidemiology (GMDS), of the German Society for Epidemiology (DGEpi), European Federation for Medical Informatics (EFMI) and the Medical Informatics Europe (MIE2016), Munich, Germany, 28.08-02.09.2016 (oral presentation)

Aleksandrova K, di Giuseppe R, Isermann B, Biemann R, Schulze MB, Wittenbecher C, Fritsche A, Lehmann R, Menzel J, Weikert C, Pischon T, Boeing H: Circulating Omentin as a Novel Risk Marker for Colorectal Cancer: Data from the EPIC - Potsdam Cohort Study, Health – exploring complexity (HEC) Annual meetings of the European Epidemiological Federation of the International Epidemiological Association (IEA-EEF), of the German Society for Medical Informatics, Biometry and Epidemiology (GMDS), of the German Society for Epidemiology (DGEpi), European Federation for Medical Informatics (EFMI) and the Medical Informatics Europe (MIE2016), Munich, Germany, 28.08-02.09.2016 (poster presentation)

Aleksandrova K, di Giuseppe R, Isermann B, Biemann R, Schulze MB, Wittenbecher C, Fritsche A, Lehmann R, Menzel J, Weikert C, Pischon T, Boeing H: Novel Association between Omentin and Risk of Colorectal Cancer: The European

Prospective Investigation into Cancer and Nutrition (EPIC) – Potsdam, International Agency for Research on Caner (IARC) 50th Anniversary Conference, Lyon, France, 07-10.06.2016 (oral presentation)

Menzel J, di Giuseppe R, Biemann R, Wittenbecher C, Aleksandrova K, Pischon T, Fritsche A, Schulze MB, Boeing H, Isermann B, Weikert C: Omentin-1 and the risk of stroke: Results from the EPIC-Potsdam cohort study, 84th Congress of the European Atherosclerosis Society (EAS), Innsbruck, Austria, 29.05-01.06.2016 (poster presentation)

Wittenbecher C, Menzel J, Carstensen-Kirberg M, Biemann R, di Giuseppe R, Fritsche A, Isermann B, Herder C, Aleksandrova K, Boeing H, Weikert C, Schulze MB: Omentin, adiponectin, and the risk of developing type 2 diabetes, Annual Meeting of the European diabetes epidemiology group (EDEG), Dublin, Ireland, 16-19.04.2016 (oral presentation)

Menzel J, di Giuseppe R, Biemann R, Aleksandrova K, Isermann B, Boeing H, Weikert C: The relationship between omentin-1 concentration and bone health in peri-/pre- and postmenopausal women, 10th Annual Conference of the German Society for Epidemiology (DGEpi), Potsdam, Germany, 30.09-02.10.2015 (poster presentation)

Menzel J, di Giuseppe R, Wientzek A, Kroke A, Boeing H, Weikert C: Physical activity, bone health and obesity in peri-/pre- and postmenopausal women: results from the EPIC-Potsdam study, 52th Scientific congress of German Nutrition Society (DGE), Halle/Saale, Germany, 11-13.03.2015 (poster presentation)

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