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Geschlechtsspezifische Zusammenhänge zwischen Blutgerinnung, Blutdruck und Blutlipiden

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Abkürzungsverzeichnis

Abkürzung:	Bedeutung:
ACS:	Akutes Koronarsyndrom
aPTT:	Activated Partial Thromboplastin Time/Aktivierte partielle Thromboplastinzeit
PTZ:	Partielle Thromboplastinzeit
BMI:	Body Mass Index
CCS:	Chronisches Koronarsyndrom
CHD:	Coronary heart disease / Koronare Herzerkrankungen
KHK:	Koronare Herzkrankheit
HDL:	High-densitiy lipoprotein
INR:	Internationale Normalisierte Rate
IQR:	Interquartilsabstand
KORA:	Kooperative Gesundheitsforschung in der Region Augsburg
MMP:	Matrix-Metalloproteinasen
MONICA:	Monitoring trends and determinants in cardiovascular disease
PAI-1:	Plasminogenaktivator-Inhibitor 1
TIMP:	Tissue inhibitors of metalloproteinases = Metalloprotease-Inhibitoren
SD:	Standardabweichung
RCT:	Randomized Controlled Trial = Randomisierte kontrollierte Studie
CVRF:	Kardiovaskuläre Risikofaktoren
t-PA:	Gewebespezifischer Plasminogenaktivator

Publikationsliste

1. von Falckenstein J, Freuer D, Peters A, Heier M, Linseisen J, Meisinger C. Sex-specific associations between systolic, diastolic and pulse pressure and hemostatic parameters in the population-based KORA-Fit study: a cross-sectional study.

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Beitrag zu den Veröffentlichungen

Der Doktorand Johannes Vogel von Falckenstein führte alle nachfolgenden Arbeiten selbstständig aus.

1.1 Beitrag zu Publikation I

Der Doktorand entwickelte den Analyseplan, führte die statistischen Analysen durch und interpretierte deren Ergebnisse. Er erstellte die Tabellen sowie das Begleitmaterial (Supplements). Er betrieb die Literaturrecherche und verfasste daraus die Publikation im Erstentwurf. Während des Peer Review-Verfahrens bearbeitete er die Kommentare der Reviewer.

Beraten und unterstützt wurde er in jeder Phase von seiner Doktormutter Frau Prof. Dr. med. Christine Meisinger sowie Herrn Dr. Dennis Freuer als statistischer Beratung. Frau Prof. Meisinger trat als korrespondierende Autorin für den Einreichungsprozess bei der Fachzeitschrift *Thrombosis Journal* (inkl. Kommunikation mit dem Editor und den Reviewern) auf.

1.2 Beitrag zu Publikation II

Herr von Falckenstein entwickelte das Konzept, führte die statistischen Analysen durch und interpretierte deren Ergebnisse. Der Doktorand erstellte die Tabellen sowie das Begleitmaterial (Supplements). Er betrieb die Literaturrecherche und verfasste den ersten Entwurf der Publikation. Während des Peer Review-Verfahrens bearbeitete er die Kommentare der Reviewer.

Beraten und unterstützt wurde er in jeder Phase von seiner Doktormutter Frau Prof. Dr. med. Christine Meisinger sowie Herrn Dr. Dennis Freuer als statistischer Beratung. Frau Prof. Meisinger trat als korrespondierende Autorin für den Einreichungsprozess bei der Fachzeitschrift *Lipids in Health and Disease* (inkl. Kommunikation mit dem Editor und den Reviewern) auf.

2. Einleitung

2.1 Kardiovaskuläre Erkrankungen

Kardiovaskuläre Erkrankungen stellen die häufigsten Ursachen für Mortalität in reichen Ländern bzw. Industrienationen dar. Etwa 50% der Todesursachen sind auf kardiovaskuläre Ursachen zurückzuführen [1]. Meist liegt kardiovaskulären Erkrankungen eine Atherosklerose zugrunde [2]. Dabei handelt es sich um eine multifokale, schwelende, immunvermittelte inflammatorische Erkrankung mittlerer und großer Arterien, welche unter anderem durch Störungen im Lipidstoffwechsel angeheizt wird. Endothelzellen, Leukozyten, und die glatten Muskelzellen der inneren Arterienwandschicht (Tunica intima) spielen die größten Rollen bei der Entwicklung dieser Erkrankung. Als Folgen der Atherosklerose können Herzinfarkte und Schlaganfälle auftreten, welche durch eine überlagernde Thrombose verursacht werden [3].

Ausgelöst werden können solche Thromben durch Endothelläsion, d.h. Verletzungen der inneren Gewebsschicht. Eine solche Schädigung kann z.B. mechanisch erfolgen als Folge einer arteriellen Hypertonie (endotheliale Dysfunktion, Abb. 1b) [4].

Eine wichtige Rolle bei der Entstehung der Atherosklerose spielen vor allem die Monozyten, eine Unterform der Leukozyten [5] [6]. Diese sammeln sich in der inneren Gefäßwand und schädigen diese, was in der Folge zu einer chronischen Entzündung führt [5]. Sogenannte Matrix-Metalloproteinasen (MMPs) unterstützen eine Monozyten-Infiltration der Gefäßwand. Ein Anstieg in der Expression bestimmter MMPs führt zu einer Makrophagen-Ausreifung der Monozyten. Durch Aufnahme von LDL-Cholesterin werden Makrophagen zu Schaumzellen, welche sich in Endothelläsionen anlagern [7].

Ein Überfluss dieser Schaumzellen in den subendothelialen Schichten bei den glatten Muskelzellen der Intima führt zu einer fibrotischen Umwandlung mit fettigen Degenerationen (fatty streaks, Abb. 1c) und Nekrosen (lipid core, necrotic core) [7]. Durch die Ausbildung dieses Fettkerns und eine bindegewebige Reaktion kommt es zur Bildung einer Plaque (Abb. 1d). Je nach klinischem Verlauf kann diese Plaque instabil werden (Abb. 1e). Dabei spielen verschiedene Einflüsse wie Größe und Konsistenz des Plaque-Kerns, Dicke und Kollagengehalt der fibrösen Abdeckung, des Entzündungsgrads innerhalb der Plaque und nicht zuletzt hämodynamische Belastung eine Rolle [8]. Plaquerupturen führen zu einer Beschleunigung des atherosklerotischen Prozesses [9] [10]: Es kommt zur

Gerinnselbildung und bei einem Versagen der Reparaturmechanismen auch zu einer Thrombose, d.h. einem Verschluss der Gefäße mit der möglichen Folge eines myokardialen oder zerebralen ischämischen Infarkts [4].

Abbildung 1: Schema der Atheroskleroseentstehung; @iStock

Eine Atherosklerose entwickelt sich aufgrund einer Reihe von Risikofaktoren bzw. Lebensstilfaktoren, welche teilweise veränderbar sind. Dazu zählen beispielsweise eine Hyperlipidämie, ein erhöhter Body Mass Index (BMI), ein Diabetes mellitus, eine arterielle Hypertonie, Nikotinkonsum sowie Stress [4]. Zu den nicht veränderbaren Risikofaktoren zählen unter anderem das Alter und genetische Einflüsse (positive Familienanamnese) [4] [11].

2.2 Das Gerinnungssystem

2.2.1 Allgemeine Aufgaben

Das Gerinnungssystem hat zweierlei Aufgaben: Es dient sowohl dem Schutz des Organismus vor Blutungen, als auch vor einer Thromboseentstehung.

2.2.2 Koagulation – Blutstillung

Im Rahmen der Blutgerinnung (Koagulation) findet eine Kaskade von komplexen Ereignissen statt, die zu Reparaturvorgängen und schließlich zur Blutstillung (Hämostase) beitragen. Dieser komplexe Mechanismus erlaubt eine schnelle Heilung und Prävention spontaner Blutungen [12].

Die Gerinnungskaskade wird durch exogene und endogene Mechanismen aktiviert. Exogene Auslöser sind Gefäßverletzungen, die das extrinsische System aktivieren [4]. Bei endogenen Auslösern handelt es sich um

Kontaktaktivierungen, d.h. die Gerinnungskaskade wird aktiviert durch Plasma, das mit einer anderen Oberfläche als dem vaskulären Endothel in Kontakt gekommen ist.

Bei der primären Hämostase erfolgt die schnelle Blutstillung innerhalb von 1-3 Minuten durch Vasokonstriktion sowie Thrombozytenaggregation [13].

Die sekundäre Hämostase enthält die beiden Haupt-Wegstrecken, intrinsisch und extrinsisch, die mit der Aktivierung des Gerinnungsfaktors X (zu Faktor Xa) enden und sich damit in einer gemeinsamen Endstrecke, treffen. Die gemeinsame Endstrecke mündet letztendlich in der Bildung eines stabilen Thrombus (nach 6-9 Minuten) [14], indem durch enzymatische Einwirkung von Thrombin Fibrinogen in Fibrin umgewandelt wird. Diese Fibrin-Untereinheiten haben eine Affinität zueinander und kombinieren sich in Fibrinstränge, welche die Thrombozyten unter Einbettung von Erythrozyten [15] zusammenbinden und damit den Plättchenkoagel stabilisieren [12]. Dieses Geflecht löst sich durch die anschließende Fibrinspaltung wieder auf [15]. Der Mechanismus, über den die Koagulation zur Hämostase führt, ist ein komplexer kaskadenartiger Prozess mit mehreren positiven Rückkopplungsschleifen, an dem eine Serie von Gerinnungsfaktoren beteiligt ist. Die wichtigsten Faktoren der intrinsischen Aktivierung sind die Faktoren I, II, IX, X, XI und XII; am extrinsischen Weg sind die Faktoren I, II, VII und X beteiligt. Die gemeinsame Endstrecke besteht aus den Faktoren I, II, V, VIII, X.

Die Gerinnungsfaktoren zirkulieren im Blut als Zymogene, d.h. inaktive Vorstufen, und werden zu Serinproteasen aktiviert, welche letztendlich Fibrinogen aktivieren. Serinproteasen gehören zu den Endopeptidasen und haben die Eigenschaften, Proteine enzymatisch zu spalten [16]. Zu den Serinproteasen zählen die Gerinnungsfaktoren II, VII, IX, X und XII, jedoch nicht die Faktoren V, VIII, XIII [12]. Bei Faktor V handelt es sich um ein Coenzym, Faktor VIII bildet einen Komplex mit dem von-Willebrand-Faktor, und Faktor XIII hilft in seiner aktivierten Form XIIIa bei der Vernetzung von Fibrin.

Der intrinsische Weg wird durch exponiertes endotheliales Kollagen aktiviert, dagegen wird der extrinsische Weg durch Tissue Factor (Gewebefaktor, siehe Abb. 2), der durch endotheliale Zellen nach einem externen Trauma freigesetzt wird, aktiviert [12].

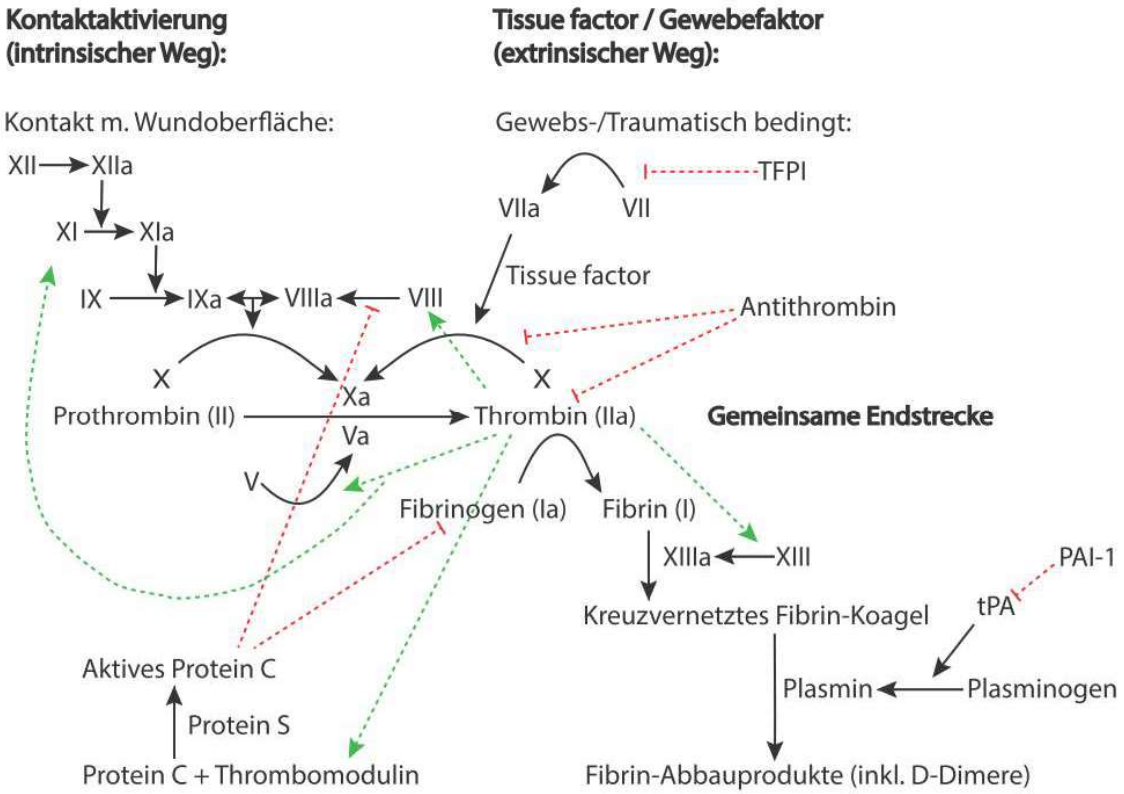

Abbildung 2: Gerinnungskaskade

2.2.3 Gerinnungsinhibition

Neben Faktoren, die eine Aktivierung der Blutgerinnung bewirken, gibt es auch Faktoren im Gerinnungssystem, die zu einer Inhibition der Gerinnung führen. Deren wichtigste Vertreter sind Antithrombin (AT), Protein C und Protein S. Diese Faktoren inaktivieren Faktor IIa (Thrombin) und Faktor Xa und sind zur Vermeidung von Thrombosen wichtig. Verringerte Konzentrationen von AT, Protein C und Protein S führen zu einer erhöhten Thromboseneigung [4] (siehe Abbildung 2).

2.2.4 Hyper- und Hypokoagulation

Wie oben beschrieben, ist eine normale Hämostase für ein funktionierendes Gerinnungssystem notwendig.

Jedoch können Koagulopathien auftreten, bei welchen eine fehlende Synthese oder Funktion eines oder mehrerer Gerinnungsfaktoren vorliegt und damit in der Folge zu einer Störung der Gerinnungskaskade führen. Diese Gerinnungsstörungen lassen sich grob unterteilen in Defektkoagulopathien (angeboren oder erworben), Immunkoagulopathien (Antikörperbildung gegen Gerinnungsfaktoren),

Verbrauchskoagulopathien (erhöhter Verbrauch von Thrombozyten und plasmatischen Gerinnungsfaktoren) oder Hyperfibrinolysen (vor allem bei Operationen an Organen mit hoher Aktivator-Konzentration) [4].

Unter Hyperkoagulabilität versteht man eine erhöhte Gerinnungsbereitschaft. Ursachen dafür können eine Verminderung des gerinnungshemmenden Potenzials wie z.B. bei Faktor V-Leiden-Mutation, Prothrombin-Gen-Mutation, erworbene oer angeborene Mängel an Protein C, Protein S oder Antithrombin sein. Dagegen kommt es zu einer Erhöhung des gerinnungsfördernden Potenzials z.B. bei erhöhten Faktor VIII-, IX- oder XI-Spiegeln, bei Dysfibrinogenämien, Polycythaemia vera, essenzieller Thrombozytämie, Morbus Waldenström, paraneoplastischer Produktion gerinnungsfördernder Proteine [4].

2.2.5 Blutgerinnung und kardiovaskuläres Risiko

Kardiovaskuläre Erkrankungen sind die Hauptursache für Tod und Gebrechlichkeit bei älteren Menschen [17]. Das Risiko für kardiovaskuläre Erkrankungen steigt durch das Vorhandensein bestimmter kardiovaskulärer Risikofaktoren (CVRF) [18].

Zu den nicht beeinflussbaren Risikofaktoren zählen das Alter, das Geschlecht, eine positive Familienanamnese und die ethnische Zugehörigkeit. Obwohl diese Faktoren einer direkten therapeutischen Intervention nicht zugänglich sind, bleiben sie wichtig für die Risikostratifizierung [19]. Zu den wichtigsten beeinflussbaren Risikofaktoren rechnet man die arterielle Hypertonie und Dyslipidämien; speziell eine Trias von hohen Triglyzerid-Werten, erhöhtem LDL-Cholesterin und niedrigem HDL-Cholesterin geht mit einem erhöhten kardiovaskulären Risiko einher, sowie auch eine Diabeteserkrankung, Nikotinabusus und Bewegungsmangel [19].

Frühere Studien haben die Rolle des Gerinnungssystems bei der Manifestation von kardiovaskulären Erkrankungen untersucht [20] [21] [22] und zeigten auf, dass die systemische Aktivierung des Gerinnungssystems zu akuten koronaren Ereignissen führen kann [23].

Der Fibrinogen-Spiegel im Plasma ist ein eindeutiger Marker für ein erhöhtes Risiko [24] [25], aber auch erhöhte Spiegel an D-Dimeren und t-PA sind verbunden mit einem erhöhten Risiko für kardiovaskuläre Ereignisse [26]. Darüber hinaus ließen sich Assoziationen zwischen Faktor VIII [26], Protein C [27] und Protein S [28] und einer koronaren Herzerkrankung (KHK) nachweisen.

2.2.6 Gerinnungsparameter in der Diagnostik

Zu den wichtigen Gerinnungsparametern in der Routinediagnostik zählen der Quick-Wert, die INR (Internationale Normalisierte Rate) sowie die PTZ (Partielle Thromboplastin-Zeit).

In der erweiterten Diagnostik spielen jedoch noch weitere Faktoren, die auf Störungen in der Hämostase hinweisen können, eine Rolle. Wichtigste Vertreter sind hier: Fibrinogen, Faktor VIII-Aktivität, Antithrombin III (AT III), Protein C-Aktivität, Protein S-Aktivität, und D-Dimere.

Fibrinogen bzw. seine proteolytisch aktivierte Form Fibrin hilft bei der Koagulation, welches mit Faktor XIIIa zur Formung eines Thrombus beiträgt [29]. Bei einem Fibrinogen-Mangel kann es zu Hämatomen der Muskulatur oder der Haut oder Blutungen in der oralen Kavität kommen. Klinisch von Relevanz ist, dass zu geringe Fibrinogen-Konzentrationen einhergehen mit einem erhöhten Blutungsrisiko z.B. bei oder nach chirurgischen Eingriffen [30] [31].

Beim Faktor VIII handelt es sich um ein Protein, das in der Gerinnung zusammen mit Faktor IX die Aktivierung des Prothrombins (Faktor X) zu Thrombin (Faktor Xa) bewirkt. Faktor VIII ist verringert bzw. fehlend bei Patienten mit klassischer Hämophilie und dem von Willebrand-Syndrom [32].

Die Proteine AT III, Protein C und Protein S wirken inhibierend auf die Koagulation. Die Bestimmung dieser Parameter ist vor allem in der Thrombosediagnostik von Bedeutung [33].

Das D-Dimer-Antigen ist ein Laborparameter zur Bestimmung der Gerinnungsaktivierung. Dieser wird in der Diagnostik zum Ausschluss von venösen Thrombosen und Lungenembolien sowie der Diagnose der disseminierten intravasalen Gerinnung eingesetzt [34].

2.3 Blutdruck, Blutdruckamplitude und Hypertonie

Druck ist in der Physik definiert als Kraft pro Fläche [35]. Druck pflanzt sich gleichmäßig in alle Richtungen und senkrecht zu den Flächen, auf die er wirkt, fort [36]. Entsprechend ist der Blutdruck als Druck (Kraft pro Fläche) des Blutes in einem Blutgefäß zu verstehen [37]. Der Blutdruck ist direkt abhängig vom Gefäßwiderstand und dem Herzzeitvolumen. Unter systolischem Blutdruck versteht man das Druckmaximum, das während der Systole erreicht wird (normaler Wert ca. 120 mmHg), das Minimum während der Diastole ist der diastolische Blutdruck (Normalwert ca. 80 mmHg) [14].

Die Blutdruckamplitude ist die Differenz zwischen systolischem und diastolischem Blutdruck und beträgt herznah ca. 40 mmHg [14]. Die Blutdruckamplitude erhöht sich in der Regel im Alter und bei Atherosklerose durch die Versteifung der Arterien [38]. Darüber hinaus kann eine hohe Blutdruckamplitude physiologisch auftreten bei körperlicher Anstrengung durch Erhöhung des systolischen Blutdrucks (z.B. 160/80 mmHg) [39] bzw. pathologisch z.B. bei Aortenklappeninsuffizienz, wo der diastolische gegenüber dem systolischen Druck absinkt (z.B. 150/50 mmHg)[40]. Eine verringerte Blutruckamplitude tritt physiologisch auf während des Stehens [41], pathologisch bei Kreislaufkollaps, Blutverlust oder Aortenstenose (z.B. 110/90 mmHg) [40].

2.3.1 Definition und Ursachen der Hypertonie

Weltweit ist die Prävalenz der arteriellen Hypertonie nach wie vor hoch und bleibt der größte Risikofaktor für Sterblichkeit mit 9,4 Millionen Sterbefällen im Jahre 2010 [42] in industrialisierten Ländern. Schätzungsweise ein Drittel der deutschen Bevölkerung zwischen 18 und 79 Jahren leidet an einer Hypertonie, und die Häufigkeit erhöht sich mit dem Alter signifikant [43].

Eine Hypertonie ist definiert als ein nach wiederholten Messungen zu verschiedenen Zeitpunkten gemessener Blutdruck über den Normwerten [11]. Die WHO definiert die arterielle Hypertonie als das Vorliegen eines systolischen Blutdrucks von mehr als 140 mmHg und/oder eines diastolischen Blutdrucks von mehr als 90 mmHg.

Gemäß WHO zählen folgende Ursachen zu den Risikofaktoren für Bluthochdruck: (höheres) Lebensalter, genetische Prädisposition, Übergewichtigkeit / Fettleibigkeit, mangelnde körperliche Aktivität, salzreiche Ernährung sowie exzessiver Alkoholkonsum [44].

Ein erhöhter Blutdruck trägt in höherem Maße zu atherosklerotischen Erkrankungen bei, wie auch zu sich daraus ergebenden Komplikationen, beispielsweise koronaren Ereignissen [45] [46]. Eine Hypertonie ist (zusammen mit Hypercholesterinämie, Diabetes mellitus und Rauchen) ein Hauptrisikofaktor für koronare Herzerkrankungen [10].

2.4 Serumlipide

Das (Gesamt-)Cholesterin ist ein ubiquitär in eukaryoten Zellen vorkommendes Molekül, das verschiedenste zelluläre Prozesse wie Membranfluidität und –durchlässigkeit sowie Gentranskription reguliert. Cholesterin dient nicht nur als

Molekül für Regulationen, sondern bildet auch die Grundstruktur aller Steroidhormone und Vitamin D-Analoga [47].

Da Menschen eine nur begrenzte Fähigkeit haben, Cholesterin zu verstoffwechseln, kommt es zu einer Erhöhung der Cholesterinwerte im Blut bei z.B. bei ungesunden Ernährungsmustern bzw. genetischer Veranlagung [47].

HDL-Cholesterin ist invers mit KHK assoziiert [48], d.h. es wird ihm traditionell eine positive Rolle bei der Arterioskleroseentstehung zugesprochen sowie ein therapeutisches Potenzial bei atherosklerotisch bedingten kardiovaskulären Erkrankungen. Es wird auch als das „gute“ Cholesterin bezeichnet. Inzwischen gibt es jedoch auch randomisierte klinische Studien (RCTs), die gezeigt haben, dass gesteigerte Konzentrationen an HDL-Cholesterin nicht zwingend zu einem gesundheitlichen Benefit führen [49].

LDL-Cholesterin bildet mit ca. 70% den größten Anteil des Cholesterins im menschlichen Körper und ist in Bezug auf das kardiovaskuläre Risiko der entscheidende Anteil am Gesamtcholesterin [4]. Bei zu hohem Serumspiegel kann es in den Blutgefäßen akkumulieren und zur Bildung von Plaques beitragen. Da eine Einengung der arteriellen Blutgefäße das KHK-Risiko erhöht, wird es auch als „schlechtes“ Cholesterin bezeichnet [50].

Non-HDL-Cholesterin, d.h. die Differenz zwischen Gesamtcholesterin und HDL-Cholesterin, bildet einen zusätzlichen kardiovaskulären Risikofaktor, der unabhängig von LDL-Cholesterin ist [51]. Non-HDL-Cholesterin hat sich in der Einschätzung möglicher zukünftiger kardiovaskulärer Ereignisse bewährt [52].

Triglyzeride oder auch Neutralfette, bestehen aus drei verschiedenen Fettsäuren, gebunden an den Alkohol Glycerin. Sie werden sowohl vom Körper selbst synthetisiert als auch mit der Nahrung aufgenommen [53] und führen zusammen mit erhöhtem Cholesterin oder Hypertonie sowie Lebensstilfaktoren wie Rauchen zu einer weiteren Zunahme des kardiovaskulären Risikos. Hypertriglyzeridämien treten sekundär als Folge von Diabetes mellitus, Alkoholabusus, Leber- und Nierenerkrankungen auf [4].

2.5 Aktueller Forschungsstand

2.5.1 Blutgerinnung und Hypertonie

Bluthochdruck wird als einer der Hauptrisikofaktoren für Arteriosklerose gesehen, weshalb Personen mit Hypertonie ein erhöhtes Risiko für die Entwicklung von

kardiovaskulären Erkrankungen, wie z.B. KHK, Herzinfarkte, Herzversagen, Nierenversagen, Schlaganfälle und arterielle Verschlusskrankheit haben [54].

Aufgrund einer Hypertonie kann es zu Schäden der inneren Schicht der Blutgefäße kommen, was zu einer erhöhten Plättchenaggregation führt [55].

Schließlich wird durch die Endothelschädigung die Gerinnungskaskade aktiviert, wodurch auch die Entwicklung von Arteriosklerose stimuliert werden kann [56].

Zu möglichen Zusammenhängen zwischen einer erhöhten Blutgerinnung und Hypertonie gibt es Studien vor allem aus den 1990er Jahren. Diese Studien führten teilweise zu widersprüchlichen Ergebnissen.

So untersuchte eine Studie von 1990 an 22 Männern die Effekte von erhöhtem Fibrinogen und Plasminogen-Aktivator-Inhibitor 1 (PAI-1) und fand eine positive Assoziation zwischen PAI-1 und Hypertonie [57].

Eine weitere Studie von 1992 schloss 54 hypertensive, anderweitig aber gesunde Patienten ein, und stellte im Vergleich zu einer klinisch gesunden Referenzgruppe statistisch signifikante Assoziationen zwischen Hypertonie und erhöhten Spiegeln an Faktor VIIIc, Fibrin-Monomeren und Faktor VII fest [58].

Eine große schottische Studie aus dem Jahr 1992 untersuchte geschlechtsspezifisch an 1264 Probanden im Alter von 25-64 Jahren den Zusammenhang zwischen Blutdruck und Hämatokrit, Blutplasma-Viskosität, Viskosität des Gesamtblutes und Plasma-Fibrinogen. Im Ergebnis zeigte Fibrinogen einen inversen Zusammenhang mit dem Blutdruck [59].

Im Rahmen der MONICA-Studie erfolgte in Nordschweden an 1558 Männern und Frauen zwischen 25 und 64 Jahren eine Untersuchung geschlechtsspezifischer möglicher Zusammenhänge, unter anderem zwischen Blutdruck und Fibrinogen sowie fibrinolytischen Variablen. Im Ergebnis zeigten sich bei Männern Assoziationen zwischen diastolischem Blutdruck, bei Frauen zwischen dem Taille-Hüft-Umfang (WHR), einem Maß für die Körperfettverteilung und jeweils einer geringeren Fibrinolyse-Aktivität [60].

Epidemiologische Daten aus großen, populationsbasierten Studien mit Männern und Frauen mit und ohne Bluthochdruck und einer Reihe hämatologischer Parameter sind jedoch rar [57-60].

2.5.2 Blutgerinnung und Serumlipide

Fettstoffwechselstörungen sind einer der Hauptrisikofaktoren für kardiovaskuläre Erkrankungen [61] und die Entstehung einer Atherosklerose [62] wird vor allem mit erhöhten LDL-Cholesterin-Spiegeln sowie mit erniedrigten HDL-Cholesterin-Spiegeln [63] [64] in Verbindung gebracht.

LDL-Cholesterin wird hier als wichtigster Risikofaktor angesehen, wobei jüngere Studien die Rolle des non-HDL-Cholesterins herausarbeiteten und dieses als Risikofaktor bei der Entstehung kardiovaskulärer Erkrankungen als dem LDL-Cholesterin möglicherweise überlegen einstuften [65] [66].

Nach wie vor gibt es nur wenige Studien, die geschlechtsspezifische Assoziationen zwischen Männern und Frauen aus der Allgemeinbevölkerung in Bezug auf Blutlipide und eine Reihe von Koagulationsfaktoren untersuchten. Frühere Studien evaluierten Komponenten des Gerinnungssystems bei Studienteilnehmern mit familiärer kombinierter Hyperlipidämie, die ein substantiell erhöhtes Risiko für koronare Herzerkrankungen haben, und berichteten über eine erhöhte Koagulationsaktivität bei diesen Personen [67]. Andere epidemiologische Studien haben eine Verbindung zwischen verschiedenen Koagulationsfaktoren und Lipidparametern aufgezeigt. So fand eine MONICA-Studie aus Glasgow, Großbritannien, bei zufällig ausgewählten Männern und Frauen zwischen 25-74 Jahren aus der Gesamtbevölkerung, dass das Serum-Cholesterin und Triglyzeride mit erhöhten Spiegeln von Faktor VII und IX, wie auch Antithrombin, Protein C und Protein S, und bei Frauen mit erhöhtem Fibrinogen und Faktor VIII assoziiert waren [68].

2.6 Fragestellung und Ziele der Arbeit

Bluthochdruck und Fettstoffwechselstörungen gelten als Risikofaktoren für die Entwicklung von Atherosklerose, insbesondere durch eine Schädigung der Intima der Blutgefäße, was zu einer erhöhten Thrombozytenaggregation führt. Darüber hinaus wird das Gerinnungssystem aktiviert, wodurch ebenfalls die Entwicklung von Atherosklerose und damit von kardiovaskulären Erkrankungen wie koronare Herzkrankheit, Herzinfarkt, Herzversagen, Nierenversagen, Schlaganfall und arterielle Verschlusskrankheit begünstigt wird.

Diese Studie soll der Frage nachgehen, inwieweit Parameter der Blutgerinnung mit dem systolischen, diastolischen Blutdruck, der Blutdruckamplitude bzw. einer Hypertonie assoziiert sind. Darüber hinaus wird untersucht, ob Gerinnungsfaktoren wie Antithrombin III, Fibrinogen, D-Dimere, Protein C, Protein S und Faktor VIII, Quick Wert, INR und aPTT mit Gesamtcholesterin, HDL-Cholesterin, LDL-

Cholesterin, non HDL-Cholesterin sowie Triglyzeriden im Serum einen Zusammenhang zeigen. Dabei sollte insbesondere auch der Frage nachgegangen werden, ob sich geschlechtsspezifische Unterschiede zeigen.

2.7 Spezifizierung und Inhalt der Arbeit

Diese Dissertationsarbeit besteht aus zwei Publikationen, die der Doktorand als Erstautor verfasst hat und die in peer-reviewed Fachzeitschriften veröffentlicht wurden.

2.7.1 Erste Publikation

In der ersten Analyse wurde der Frage nachgegangen, inwieweit der systolische und diastolische Blutdruck bzw. die Blutdruckamplitude mit den Hämostasefaktoren Antithrombin III-Aktivität, Fibrinogen, D-Dimere, Protein C-Aktivität, Protein S-Aktivität, Faktor VIII-Aktivität, Quick-Wert, INR und aPTT assoziiert sind. Die Analysen wurden jeweils getrennt für Frauen und für Männer durchgeführt. Die Auswertungen basierten auf Daten der KORA-Fit Studie, die 54-73-jährige Personen (Durchschnittsalter 63,1 Jahre) aus der Allgemeinbevölkerung einschloss und zwischen dem 22.01.2018 und dem 29.06.2019 durchgeführt worden war.

2.7.2 Zweite Publikation

In einer zweiten Publikation wurde untersucht, ob Assoziationen bestehen zwischen den Blutgerinnungsparametern Antithrombin III, Fibrinogen, D-Dimere, Protein C-Aktivität, Protein S-Aktivität, Faktor VIII-Aktivität, aPTT und den Serumlipiden (Gesamt-)Cholesterin, HDL-Cholesterin, LDL-Cholesterin (nach Friedewald), non-HDL-Cholesterin, und Triglyzeriden. Auch dazu wurden die Daten aus der bevölkerungsbasierten KORA-Fit Studie herangezogen und geschlechtsspezifisch ausgewertet.

3. Zusammenfassung

Kardiovaskuläre Erkrankungen, stellen weltweit und vor allem in industrialisierten Ländern die Hauptursachen für Morbidität und Mortalität dar und gehören damit zu den global bedeutendsten Erkrankungen.

Das kardiovaskuläre Risiko bezeichnet die Wahrscheinlichkeit, an kardiovaskulären Erkrankungen wie z.B. Herzinfarkt, Schlaganfall oder pAVK zu erkranken. Als Hauptrisikofaktoren für kardiovaskuläre Erkrankungen gelten unter anderem Bluthochdruck und Fettstoffwechselstörungen. Diese erhöhen das Risiko für eine Atherosklerose, wodurch das Risiko u.a. für eine koronare Herzerkrankung steigt.

Arteriosklerotische Wandveränderungen und damit verbundene thrombotische Auflagerungen begünstigen eine systemisch als auch lokal bestehende Aktivierung von Hämostasesystemen und eine Störung der Fibrinolyse. Die vorliegende Arbeit, bestehend aus zwei Publikationen, ging deshalb der Frage nach, ob die kardiovaskulären Risikofaktoren Bluthochdruck und Fettstoffwechselstörungen einen Zusammenhang mit Blutgerinnungsparametern zeigen.

Die Arbeit stützte sich auf einen Datensatz, der im Rahmen der KORA Fit-Studie erhoben wurde. KORA bedeutet Kooperative Gesundheitsforschung in der Region Augsburg. Dabei wurden zwischen 2017 und 2019 Daten bei gut 800 Studienteilnehmern, die zwischen 1945 und 1964 geboren waren, Befragungen durchgeführt sowie Untersuchungen und Labordaten erhoben.

In beiden Publikationen wurden neben deskriptiven Analysen die Zusammenhänge zwischen den Blutdruckexpositionen (systolischer, diastolischer und Pulsdruck) bzw. den Lipidparametern (Gesamtcholesterin, HDL-Cholesterin, LDL-Cholesterin, Non HDL-Cholesterin, Triglyzeride) und den Gerinnungsparametern INR, aPTT, Antithrombin III, Fibrinogen, D-Dimer, Protein C, Protein S und Faktor VIII als Outcomes mittels multivariabler linearer Regressionsmodelle untersucht. Die Modelle wurden für eine Reihe von Confoundern, wie z.B. Alter, Taillenumfang, körperliche Aktivität in der Freizeit, Alkoholkonsum, sozioökonomischen Status, BMI, Diabetes, Raucherstatus etc. adjustiert. Personen, die mit gerinnungshemmenden Medikamenten behandelt wurden, wurden von den Analysen ausgeschlossen. Ein Hauptfokus der Arbeit lag auf geschlechtsspezifischen Auswertungen.

Im Rahmen der ersten Arbeit ergaben sich Unterschiede bei Männern mit bzw. ohne Hypertonie in Bezug auf die Gerinnungsparameter Fibrinogen und Faktor VIII-Aktivität. Bei den Frauen zeigten sich entsprechend statistisch signifikante Unterschiede bei den Parametern Fibrinogen, D-Dimere, Protein S-Aktivität und

Faktor VIII-Aktivität. Die Analyse mittels linearer Regression zeigte bei den Männern keine signifikanten Assoziationen zwischen Blutdruck- und Blutgerinnungsparametern. Bei Frauen zeigte sich eine signifikant positive Assoziation zwischen systolischem Blutdruck und D-Dimer-Leveln.

In der zweiten Arbeit konnten ebenfalls signifikante Unterschiede zwischen Männern und Frauen festgestellt werden: Bei Männern war Gesamt-Cholesterin invers mit aPTT, aber positiv mit der Protein C-Aktivität assoziiert. HDL-Cholesterin war bezogen auf aPTT und Fibrinogen invers assoziiert. LDL-Cholesterin, Non HDL-Cholesterin und Triglyzeride zeigten eine positive Assoziation mit Protein C- und Protein S-Aktivitäten. Bei Frauen zeigten LDL-Cholesterin, Gesamtcholesterin und Non HDL-Cholesterin einen positiven Zusammenhang mit AT III-Konzentrationen und Protein C- und S-Aktivitäten. Zusätzlich war Non-HDL-Cholesterin positiv assoziiert mit der Faktor VIII-Aktivität, HDL-Cholesterin und invers mit Fibrinogen. Triglyzeride zeigten einen positiven Zusammenhang mit der Protein C-Aktivität.

Zusammenfassend lässt sich sagen, dass sich in beiden Arbeiten deutliche geschlechtsspezifische Assoziationen zeigten. Die weitere Erforschung und Ausarbeitung dieser Unterschiede muss eine wichtige Rolle bei zukünftigen Studien spielen, um sowohl kardiovaskuläre Risiken als auch die Einflüsse von Serumlipiden in Bezug auf die Blutgerinnung bei Männern und Frauen aus der Allgemeinbevölkerung besser verstehen zu können.

4. Summary

Cardiovascular diseases are the main causes of morbidity and mortality worldwide, especially in industrialized countries, and are therefore among the most important diseases worldwide.

Cardiovascular risk refers to the probability of developing cardiovascular diseases such as myocardial infarction, stroke, or peripheral arterial disease. The main risk factors for cardiovascular disease include high blood pressure and dyslipidemia. These increase the risk of atherosclerosis, which increases the risk of coronary heart disease, among other things.

Arteriosclerotic wall changes and associated thrombotic deposits favor a systemic as well as local activation of hemostasis systems and a disturbance of fibrinolysis. The present study, consisting of two publications, therefore investigated whether the cardiovascular risk factors hypertension and dyslipidemia are related to blood coagulation parameters.

The work was based on data collected as part of the KORA Fit study. KORA stands for Cooperative Health Research in the Augsburg Region. Between 2017 and 2019, data were collected from about 800 study participants born between 1945 and 1964, surveys were conducted, and examinations and laboratory data were collected.

In both publications, in addition to descriptive analyses, the associations between blood pressure exposures (systolic, diastolic and pulse pressure) as well as lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides) and the coagulation parameters INR, aPTT, antithrombin III, fibrinogen, D-dimer, protein C, protein S and factor VIII as outcomes were investigated using multivariable linear regression models. The models were adjusted for a number of confounders, such as age, waist circumference, leisure-time physical activity, alcohol consumption, socioeconomic status, BMI, diabetes, smoking status, etc. Individuals treated with anticoagulant medications were excluded from the analyses. A main focus of the work was on gender-specific evaluations.

In the first study, differences were found in men with and without hypertension with regard to the coagulation parameters fibrinogen and factor VIII activity. In women, statistically significant differences were found for the parameters fibrinogen, D-dimer, protein S activity, and factor VIII activity. Linear regression analysis showed no significant associations between blood pressure and coagulation

parameters in men. In women, there was a significant positive association between systolic blood pressure and D-dimer levels.

In the second work, significant differences were also found between men and women: In men, total cholesterol was inversely associated with aPTT but positively associated with protein C activity. HDL cholesterol was inversely associated related to aPTT and fibrinogen. LDL cholesterol, non HDL-cholesterol, and triglycerides showed a positive association with protein C and protein S activities. In women, LDL cholesterol, total cholesterol, and non HDL-cholesterol showed a positive association with AT III concentrations and protein C and S activities. In addition, non HDL cholesterol was positively associated with factor VIII activity, HDL cholesterol and inversely with fibrinogen. Triglycerides showed a positive association with protein C activity.

In conclusion, significant gender differences were evident in both investigations. Further exploration and elaboration of these differences must play an important role in future studies to better understand both cardiovascular risks and the influences of serum lipids in relation to blood coagulation in men and women from the general population.

5. Publikation I

- Siehe die folgenden 8 Seiten -

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RESEARCH

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Sex-specific associations between systolic, diastolic and pulse pressure and hemostatic parameters in the population-based KORA-Fit study: a cross-sectional study

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Abstract

Background Several prior studies postulated an effect of hypertension on coagulation factors. However, population-based studies investigating the sex-specific associations between hypertension and hemostatic parameters are scarce. Therefore, we investigated the relationship between blood pressure and parameters of coagulation, namely activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, factor VIII, antithrombin III, protein C, protein S, and D-dimer in men and women from the general population.

Methods Based on 803 participants (376 men, 427 women) from the KORA-Fit Study the sex-specific relationship between systolic, diastolic, and pulse pressure and commonly measured coagulation factors were investigated using multivariable-adjusted linear regression models.

Results Hypertensive males had significantly higher median fibrinogen levels and factor VIII activity in comparison to normotensive males. There was a statistically significant difference between females with and without hypertension regarding the parameter fibrinogen, D-dimers, Protein S activity, and factor VIII activity. In multivariable linear regression analyses no significant association between systolic blood pressure, diastolic blood pressure, as well as pulse pressure and the investigated hemostatic parameters was found in men. In women, a significant positive association could be observed between systolic blood pressure and D-dimer level [β-estimate per mmHg increase 3.37 (95% CI 0.935–5.804; $p = 0.007$)] and between pulse pressure and D-dimer level [β-estimate per mmHg increase 5.351 (95% CI 1.772–8.930; $p = 0.003$)].

Conclusions It appears that sex differences exist in the association between blood pressure parameters and commonly measured coagulation markers in the general population. Further studies are needed to identify the underlying causes.

Keywords Blood pressure, Hypertension, Coagulation, General population, KORA study

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Background

Worldwide, the prevalence of arterial hypertension is still high and it remains the greatest risk factor for mortality with 9.4 million deaths in 2010 [1] in industrialized countries. It is estimated that about one third of the 18 to 79 years old German population suffers from hypertension, and the frequency increases significantly with age [2]. Hypertension is recognized as a risk factor for the development of atherosclerosis via damage of the intima of blood vessels which leads to increased platelet aggregation [3]. Eventually, the coagulation system is activated, which may also stimulate the development of atherosclerosis. Thus, persons with hypertension are at increased risk of cardiovascular diseases, such as coronary heart disease (CHD), heart attack, heart failure, kidney failure, stroke and arterial occlusive disease [4, 5].

Previous studies, mostly from the 90 s, addressed the question whether hypertension confers a hypercoagulable state [6]. However, these investigations in subjects with and without hypertension led to conflicting results [7–10]. So far, epidemiological data from large population-based studies including men and women with and without hypertension and with the standardized measurement of blood pressure and a number of hematologic parameters are still scarce. Thus, the present study examines whether there are sex-specific associations between systolic and diastolic blood pressure and the parameters international normalized ratio (INR), activated partial thromboplastin time (aPTT), antithrombin III, fibrinogen, D-dimer, protein C, protein S, and factor VIII in a sample of the general adult population. Furthermore, in this context we also examined the role of pulse pressure, which is also a predictor of cardiovascular and mortality risk [11].

Materials and methods

Study sample

KORA (Cooperative Health Research in the Region of Augsburg, Germany) is a regional research platform for population-based studies. It consists of 4 cross-sectional baseline surveys (S1 1984/85, S2 1989/90, S3 1994/95 and S4 1999/2001) [12].

The KORA-Fit follow-up study was conducted from 22.01.2018 to 29.06.2019; all KORA participants born between 1945 and 1964 who agreed to be re-contacted were invited to the KORA study centre ($n=3059$ or 64.4% of all appropriate participants).

In the present analysis, all S4 participants in KORA-Fit were considered ($n=1394$ eligible persons). Of those, 856 participants took part in the KORA-Fit examination (61.4% of all eligible S4 persons), and citrate plasma samples were collected. For the present analysis, 803 participants (376 men, 427 women) with available data on hemostatic parameters were included.

The study methods were approved by the Ethics Committees of the Bavarian Chamber of Physicians (KORA-Fit EC No 17040). The study was performed in accordance with the Declaration of Helsinki. All study participants gave written informed consent.

Data collection

During a face-to-face interview information on smoking habits, physical activity level, alcohol consumption, medication use, and socioeconomic status was gathered by trained and certified study nurses. Furthermore, the study participants underwent a standardized medical examination including collection of a fasting blood sample. All study participants should take their morning medications as usual prior to the study. Height and weight measurements were performed with the subjects in light clothing and without shoes; body mass index (BMI) was calculated as weight in kilograms divided by the height in m^2. Education years were categorized into low (<10 years of schooling) and high (≥ 10 years of schooling). Alcohol intake was classified into low risk (men ≤ 24 g/d, women ≤ 12 g/d) and risky consumption (men >24 g/d, women >12 g/d). The physical activity level was estimated by means of two separate four-category interview questions asking about the time per week spent on sports activities during leisure time in summer and winter. The winter and summer responses were combined to create one variable of leisure time physical activity [13]. A participant was defined as physically active during leisure time if he/she participated in sports in summer and winter and for more than one hour per week in at least one season [14]. In participants with or without hypertension, blood pressure was measured after a rest of at least 5 min at the right arm in the morning at the examination center. Three measurements were taken with 3 min intervals between the measurements and the results of the second and third measurements were averaged. Subjects who were aware of having hypertension, who were therefore taking antihypertensive medication and/or had blood pressure measurements of 140/90 mmHg or higher at the examination were defined as having actual hypertension. However, participants without known hypertension with normal blood pressure readings on examination but taking medications that affect blood pressure were not considered hypertensive.

Pulse pressure was calculated by building the difference between systolic and diastolic blood pressure. Anticoagulation therapy was defined as yes, if a participant was treated either with a novel oral anticoagulant (e.g.

apixaban, rivaroxaban) or with phenprocoumon. Further information on the data collection procedures and examinations in the KORA studies have been described in detail elsewhere [15].

Laboratory measurements

All hemostatic factors were measured in citrat plasma samples, which were collected in an overnight fasting state, and processed, aliquoted, and stored at -80° C until analysis. INR (reference value: 0.9–1.15) was calculated from the prothrombin ratio (Thromborel S, Siemens Healthcare). aPTT (reference value: 26–36 s) was measured photometrically (Pathromtin SL, Siemens Healthcare); antithrombin III activity (reference value: 78–113%) was determined by a chromogenic activity assay (Innovance Antithrombin-Assay, Siemens Healthcare). Fibrinogen (reference value: 210–400 mg/dl) was measured photometrically and turbidimetrically (Multifibren U, Siemens Healthcare). D-dimers (reference value: < 500 µg/L) were measured by a particle-enhanced immunoturbidimetric assay (Innovance D-dimer Kit, Siemens Healthcare). Protein-C and protein-S activities (reference values prot C: 70–140%, prot S men: 73–130%, women: 52–126%) were measured photometrically (Berichrom Protein C, Siemens Healthcare; Hemoclot Protein S). Factor VIII activity (reference value: 70–150%) was measured photometrically (Coagulation factor VIII Deficient Plasma reagents used with Pathromtin SL reagents, Siemens Healthcare). All measurements were performed on a Siemens BCS-XP analyzer (Siemens, Eschborn, Germany) except the measurement of protein S activity, which was measured on a CaoChrom analyzer (Wien, Austria).

Total cholesterol (reference value: ≤ 200 mg/dl) and HDL cholesterol (reference value: > 45 mg/dl) were measured enzymatically (Hoffmann-La Roche AG, Basel/Switzerland) on a Cobas 8000 c702 Roche chemistry analyzer. Non-HDL cholesterol (reference value: ≤ 130 mg/dl) was calculated by subtracting HDL cholesterol from total cholesterol.

Statistical analysis

Continuous variables were checked for normal distribution by the Shapiro–Wilk test and were described by mean ± standard deviation (SD) in case of normal distribution; non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were given as absolute frequencies and percentages. Medians of continuous variables were compared by the Mann–Whitney-U-Test, arithmetic means by the t-test, and the categorical variables by the Fisher's exact test. The associations between the blood pressure exposures (systolic, diastolic, and pulse pressure) and the outcomes INR, aPTT, antithrombin III, fibrinogen, D-dimer, protein C, protein S, and factor VIII were investigated using multivariable linear regression models. The models were adjusted for age, waist circumference, leisure time physical activity, alcohol consumption, socioeconomic status, BMI, diabetes, smoking status, non-HDL cholesterol, and use of medications acting on blood pressure. Persons treated with anticoagulation drugs were excluded from the analyses with INR as outcome. We investigated whether the exposure-outcome associations were modified by sex or age by conducting formal tests for interaction (significance level 5%). Because there was a significant interaction with sex, separate analyses for men and women were carried out. All required model assumptions were ensured. Multicollinearity and autocorrelation were assessed by the variance inflation factor and Durbin-Watson statistics, respectively. The linearity assumption between continuous covariables and the respective outcome were tested using restricted cubic splines. The Breusch-Pagan test was applied to test for heteroscedasticity, and if present, robust standard errors were calculated. Influential observations were identified calculating Cook's distances (D_i) and removed when $D_i > 1$. P-values < 0.05 were considered as statistically significant. The statistical softwares IBM SPSS 26 and R (version 4.0.1) were used for data analysis.

Results

Table 1 shows the sex-specific characteristics for participants with and without hypertension. Men and women with hypertension were significantly older than subjects without hypertension (mean age in men 64.1 vs 61.8 years; in women: 65.1 vs. 61.8 years; $p < 0.0001$ in both sexes). Mean systolic, diastolic, and pulse pressure values in men with hypertension were significantly higher than in normotensive men (systolic blood pressure: 136.0 vs. 122.8 mmHg; diastolic blood pressure: 78.9 vs. 74.0 mmHg; pulse pressure: 57.1 vs. 48.8 mmHg; $p < 0.0001$ for all comparisons). This was also the case in women (systolic blood pressure: 128.0 vs. 115.1 mmHg; diastolic blood pressure: 75.1 vs. 70.1 mmHg; pulse pressure: 52.9 vs. 45.1 mmHg; $p < 0.0001$ for all comparisons).

Also, mean BMI was significantly higher in male and female participants with hypertension in comparison to normotensive subjects (men: 29.94 vs. 27.22; women: 29.59 vs. 26.12 mmHg; $p < 0.0001$ in both sexes). In both sexes, participants with hypertension suffered significantly more often from diabetes than subjects without hypertension. Females with hypertension more often were treated with anticoagulation drugs, and had higher

Table 1 Sex-specific characteristics given as means ± SD or n (%) for participants with and without hypertension

		MEN			WOMEN		
		HTN yes, $n=211$	HTN no, $n=165$	*p*-value	HTN yes, $n=170$	HTN no, $n=257$	*p*-value
Blood pressure systolic	mmHg	136.0 (16.4)	122.8 (9.7)	**< 0.0001**	128.0 (19.8)	115.1 (11.4)	**< 0.0001**
Blood pressure diastolic	mmHg	78.9 (10.3)	74.0 (7.3)	**< 0.0001**	75.1 (10.2)	70.1 (8.1)	**< 0.0001**
Pulse pressure	mmHg	57.1 (12.7)	48.8 (7.6)	**< 0.0001**	52.9 (13.6)	45.1 (7.9)	**< 0.0001**
Age	years	64.1 (5.6)	61.8 (5.8)	**< 0.0001**	65.1 (5.1)	61.8 (5.4)	**< 0.0001**
BMI	kg/m^2	29.9 (5.6)	27.2 (3.5)	**< 0.0001**	29.6 (5.7)	26.1 (4.6)	**< 0.0001**
Education	education ≤ 10 yrs	70 (33.2)	47 (28.5)	0.370	89 (52.4)	82 (31.9)	**< 0.0001**
	education > 10 yrs	141 (66.8)	118 (71.5)		81 (47.6)	175 (68.1)	
Diabetes	yes	27 (12.8)	8 (4.8)	**0.011**	25 (14.8)	8 (3.1)	**< 0.0001**
	no	184 (87.2)	157 (95.2)		144 (85.2)	248 (96.9)	
Leisure time physical activity	yes	150 (71.1)	111 (67.3)	0.432	114 (67.1)	190 (73.9)	0.128
	no	61 (28.9)	54 (32.7)		56 (32.9)	67 (26.1)	
Smoking	Smoker	30 (14.2)	26 (15.8)	0.437	22 (12.9)	32 (12.5)	0.878
	Ex smoker	114 (54.0)	78 (47.3)		67 (39.4)	96 (37.4)	
	Never smoker	67 (31.8)	61 (37.0)		81 (47.6)	129 (50.2)	
Alcohol consumption	low risk	161 (76.3)	134 (81.7)	0.253	99 (58.2)	147 (57.2)	0.842
	risky	50 (23.7)	30 (18.3)		71 (41.8)	110 (42.8)	
Drugs acting on blood pressure	yes	160 (75.8)	8 (4.8)	**< 0.0001**	153 (90.0)	11 (4.3)	**< 0.0001**
	no	51 (24.2)	157 (95.2)		17 (10.0)	245 (95.3)	
Anticoagulative medication	yes	15 (7.1)	6 (3.6)	0.177	5 (2.9)	1 (0.4)	**0.039**
	no	196 (92.9)	159 (96.4)		165 (97.1)	255 (99.2)	
Total cholesterol	normal ≤ 200 mg/dl	113 (53.8)	77 (46.7)	0.212	67 (39.4)	65 (25.3)	**0.003**
	high > 200 mg/dl	98 (46.4)	88 (53.5)		103 (60.6)	192 (74.7)	
HDL cholesterol	low ≤ 45 mg/dl	69 (32.7)	41 (24.8)	0.110	19 (11.2)	7 (2.7)	**0.001**
	normal > 45 mg/dl	142 (67.3)	124 (75.2)		151 (88.8)	250 (97.3)	
non-HDL cholesterol	normal ≤ 130 mg/dl	89 (42.2)	56 (33.9)	0.110	55 (32.4)	82 (31.9)	1.000
	high > 130 mg/dl	122 (57.8)	109 (66.1)		115 (67.6)	175 (68.1)	

HTN Hypertension

total cholesterol as well as lower HDL cholesterol values in comparison to normotensive women. Other parameters did not differ significantly for men and women with and without hypertension (see Table 1).

The hemostatic parameters of men and women with and without hypertension are given in Table 2. In men, median fibrinogen levels and factor VIII activity were significantly higher in the hypertensive group than in normotensive participants (fibrinogen: 300.3 vs. 281.7 mg/dl, $p=0.006$; factor VIII: 123.5 vs. 113.6%, $p=0.043$). The other investigated hemostatic parameters did not significantly differ between hypertensive and non-hypertensive men (see Table 2).

In women, there was a statistically significant difference between participants with and without hypertension regarding the parameters fibrinogen, D-dimers, protein S activity and factor VIII activity; females with hypertension showed higher levels of these parameters (fibrinogen: 317.1 vs. 292.4 mg/dl, $p=0.001$; D-dimers: 459.5 vs. 370.0 µg/l, $p=<0.001$; protein S: 124.8 vs. 117.9%, $p=0.008$; factor VIII: 125.7 vs. 118.7%, $p=0.031$). Other hemostatic parameters did not differ significantly in women (see Table 2).

Linear regression analyses

In multivariable-adjusted linear regression analyses (see Table 3) a significant positive association could be observed between systolic blood pressure and D-dimer level [β-estimate per mmHg increase 3.37 (95% CI 0.935–5.804; $p=0.007$)] and between pulse pressure and D-dimer level [β-estimate per mmHg increase 5.351 (95% CI 1.772–8.930; $p=0.003$)] in women. No further significant associations were observed in women. Furthermore, no notable associations between the three exposures and the investigated coagulation factors were found in men.

Table 2 Coagulation factors of the subjects investigated (sex-specific values, that is median and IQR, for the total sample and stratified by hypertension yes/no)

(a) men							
Coagulation factor	**Overall (*n* = 378)**		**Hypertensive men**				***p*-Value**
			Yes		**No**		
Quick % (excl. Anticoag)	Median (IQR)	106.7 (100.1; 112.6)	Median (IQR)	106.8 (100.8; 113.5)	Median (IQR)	106.4 (99.4: 111.7)	0.284
INR in sec. (excl. Anticoag)	Median (IQR)	0.97 (0.93; 1.01)	Median (IQR)	0.97 (0.93; 1.00)	Median (IQR)	0.97 (0.94; 1.01)	0.307
aPTT (excl. Anticoag)	Median (IQR)	31.15 (29.3; 33.5)	Median (IQR)	31.0 (29.3; 33.2)	Median (IQR)	31.3 (29.3; 33.7)	0.586
Antithrombin III in mg/dl	Median (IQR)	99.2 (93.3; 106.2)	Median (IQR)	99.1 (92.5; 106.1)	Median (IQR)	99.2 (93.8; 106.3)	0.944
Fibrinogen in mg/dl	Median (IQR)	290.4 (258.3; 330.4)	Median (IQR)	300.3 (267.2; 342.6)	Median (IQR)	281.7 (252.9; 319.6)	**0.006**
D-dimers in µg/l	Median (IQR)	404.0 (303.8; 563.0)	Median (IQR)	420.0 (326.0; 576.0)	Median (IQR)	390.0 (288.5; 544.0)	0.162
Protein C in %	Median (IQR)	116.7 (107.3; 131.´3)	Median (IQR)	116.5 (107.1; 130.8)	Median (IQR)	116.8 (107.2; 131.8)	0.776
Protein S in %	Median (IQR)	131.9 (109.3; 157.2)	Median (IQR)	134.4 (113.3; 160.8)	Median (IQR)	129.1 (104.9; 153.5)	0.058
Factor VIII in %	Median (IQR)	119.1 (95.4; 141.7)	Median (IQR)	123.5 (97.0; 144.1)	Median (IQR)	113.6 (93.7; 138.6)	**0.043**
(b) women							
Coagulation factor	**Overall (*n* = 427)**		**Hypertensive women**				***p*-Value**
			Yes		**No**		
Quick % (excl. Anticoag)	Median (IQR)	110.4 (104.5; 115.8)	Median (IQR)	111.0 (104.4; 116.7)	Median (IQR)	110.3 (104.5; 115.1)	0.480
INR in sec. (excl. Anticoag)	Median (IQR)	0.94 (0.91; 0.98)	Median (IQR)	0.94 (0.91; 0.98)	Median (IQR)	0.95 (0.92; 0.98)	0.558
aPTT (excl. Anticoag)	Median (IQR)	30.2 (28.4; 32.6)	Median (IQR)	30.1 (28.3; 32.7)	Median (IQR)	30.3 (28.5; 32.4)	0.998
Antithrombin III in mg/dl	Median (IQR)	104.7 (98.3; 110.8)	Median (IQR)	103.8 (97.1; 109.6)	Median (IQR)	105.6 (99.2; 112.8)	0.062
Fibrinogen in mg/dl	Median (IQR)	300.3 (263.5; 341.0)	Median (IQR)	317.1 (266.8; 356.7)	Median (IQR)	292.4 (259.8; 325.5)	**0.001**
D-dimers in µg/l	Median (IQR)	406.0 (306.0; 554.0)	Median (IQR)	459.5 (353.0; 684.8)	Median (IQR)	370.0 (282.0; 505.0)	**< 0.0001**
Protein C in %	Median (IQR)	129.0 (116.2; 142.1)	Median (IQR)	128.7 (116.6; 147.1)	Median (IQR)	129.4 (115.2; 140.2)	0.405
Protein S in %	Median (IQR)	120.1 (101.3; 138.9)	Median (IQR)	124.8 (106.5; 145.1)	Median (IQR)	117.9 (99.4; 133.2)	**0.008**
Factor VIII in %	Median (IQR)	123.2 (101.1; 143.4)	Median (IQR)	125.7 (105.4; 152.1)	Median (IQR)	118.7 (97.8; 140.8)	**0.031**

Discussion

The present observational study explored the sex-specific association between hypertension and a number of commonly measured coagulation factors. It was found that fibrinogen levels and factor VIII activity differed significantly between normotensive and hypertensive men. Hypertensive women had statistically significantly higher levels of fibrinogen, D-dimers, protein S activity and factor VIII activity in comparison to normotensive women. In multivariable linear regression analysis only the associations between systolic blood pressure and pulse pressure and D-dimer in women remained statistically significant, while no other significant results were found in both sexes.

Available literature reported that hypertension is associated with a hypercoagulable state [6], which may contribute to the pathogenesis of atherothrombotic diseases [16]. Decades ago, Letcher et al. found that in haematocrit-matched hypertensives, the levels of fibrinogen are increased, a change that might partly be responsible for a higher blood viscosity [17]. However, a number of early epidemiological studies showed only weak associations [10, 18, 19]. Most prior studies could show that individuals with hypertension had higher fibrinogen levels than normotensive persons [7, 20], and that women have higher fibrinogen levels than men [7, 21, 22], a finding which could be confirmed by our study. Some former investigations reported no independent association between blood pressure and fibrinogen levels after multivariable adjustment for other cardiovascular risk factors [10, 23, 24]. Other studies [9, 18] showed a weak but independent association in women only. For example, the association between fibrinogen levels and blood pressure was investigated in the population-based Northern Sweden MONICA study including 1558 men and women aged 25 to 64 years [9]. However, it remained unclear whether there are sex differences in relationships between blood pressure and fibrinogen

Table 3 Association between blood pressure measurements and coagulation factors. Results of the multivariable linear regressions in men and women

MEN	**Systolic BP**		**Diastolic BP**		**Pulse pressure**	
	ß-estimate (95% CI)	*P*-value	ß-estimate (95% CI)	*P*-value	ß-estimate (95% CI)	*P*-value
INR	0 (-0.001, 0)	0.497	0 (-0.001, 0.001)	0.942	0 (-0.001, 0)	0.394
aPTT (sec)	0.012 (-0.01, 0.034)	0.289	0 (-0.037, 0.038)	0.987	0.021 (-0.009, 0.051)	0.161
Protein C activity (%)	0.043 (-0.077, 0.163)	0.483	-0.041 (-0.243, 0.161)	0.69	0.108 (-0.054, 0.271)	0.192
Protein S activity (%)	-0.02 (-0.254, 0.214)	0.868	-0.047 (-0.438, 0.343)	0.812	-0.004 (-0.321, 0.313)	0.980
Antithrombin III (mg/dl)	0.012 (-0.058, 0.081)	0.739	0.01 (-0.107, 0.126)	0.868	0.014 (-0.08, 0.108)	0.768
Fibrinogen (mg/dl)	-0.185 (-0.592, 0.223)	0.374	-0.145 (-0.837, 0.548)	0.682	-0.255 (-0.805, 0.294)	0.362
D-dimers µg/l	-1.941 (-4.674, 0.793)	0.164	-0.501 (-5.108, 4.107)	0.831	-3.030 (-6.713, 0.653)	0.107
Factor VIII activity (%)	0.045 (-0.186, 0.277)	0.702	0.182 (-0.206, 0.569)	0.358	-0.038 (-0.349, 0.275)	0.816
WOMEN	**Systolic BP**		**Diastolic BP**		**Pulse pressure**	
	ß-estimate (95% CI)	*P*-value	ß-estimate (95% CI)	*P*-value	ß-estimate (95% CI)	*P*-value
INR	0.000 (0.000, 0.000)	0.896	0.000 (0.000, 0.001)	0.461	0.000 (-0.001, 0.000)	0.651
aPTT (sec)	-0.003 (-0.022, 0.016)	0.759	0.02 (-0.014, 0.054)	0.253	-0.02 (-0.049, 0.008)	0.164
Protein C activity (%)	0.065 (-0.042, 0.173)	0.233	0.127 (-0.063, 0.317)	0.19	0.055 (-0.103, 0.213)	0.492
Protein S activity (%)	0.024 (-0.154, 0.202)	0.795	-0.033 (-0.332, 0.267)	0.831	0.072 (-0.180, 0.324)	0.576
Antithrombin III (mg/dl)	-0.02 (-0.077, 0.038)	0.506	-0.044 (-0.143, 0.055)	0.385	-0.012 (-0.098, 0.075)	0.793
Fibrinogen (mg/dl)	-0.24 (-0.612, 0.132)	0.206	-0.341 (-1.004, 0.322)	0.313	-0.291 (-0.836, 0.255)	0.296
D-dimers (µg/l)	**3.37 (0.935, 5.804)**	**0.007**	2.718 (-1.614, 7.051)	0.218	**5.351 (1.772, 8.930)**	**0.003**
Factor VIII activity (%)	-0.029 (-0.235, 0.177)	0.785	-0.081 (-0.446, 0.283)	0.662	-0.004 (-0.307, 0.299)	0.978

Exposures: systolic, diastolic, and pulse pressure; Outcomes: INR, aPTT, protein C, protein S, antithrombin III, fibrinogen, D-dimers, Factor VIII. Level of significance at $P < 0.05$. *ß* regression coefficient, *CI* Confidence interval, *BP* Blood pressure

Adjusted for age, BMI, diabetes, smoking status, non HDL-Cholesterol, and medications acting on blood pressure. Participants with anticoagulative medication were excluded from the linear regression models

levels [9, 10, 18, 23]. In the present population-based study no independent association between blood pressure and fibrinogen levels in multivariable-adjusted regression analysis was observed, neither in men nor in women.

Factor VIII is mainly synthesized in hepatocytes, but also endothelial cells, kidneys, and lymphatic tissue [25]. In the blood-stream it is present in a non-covalent complex in association with the von Willebrand factor [26, 27]. We found significantly higher factor VIII levels in men and women with hypertension in comparison to normotensive individuals. In the population-based third MONICA Glasgow survey, factor VIII was correlated with diastolic blood pressure in men but not women in age-adjusted Spearman rank correlation analysis [28]. However, in our study in both sexes the results of the multivariable linear regression models do not support an independent association between systolic and diastolic blood pressure as well as pulse pressure and factor VIII levels. To the best of our knowledge, no population-based studies have investigated the association between blood pressure and factor VIII in detail. There are only a few studies on the association between von Willebrand factor and blood pressure, and they found no independent relationship [29]. Unfortunately, no von Willebrand factor measurements were available in our study. Further investigations on the association between blood pressure and factor VIII in the general population are necessary.

Protein S and protein C are vitamin K dependent inhibitors of blood coagulation [30]. Contrary to protein C, which is synthesized in the liver only, protein S is synthesized in a number of cells including endothelial cells. In this study, significantly higher protein S levels were found in women with than without hypertension. Prior studies investigating the relationship between protein S and blood pressure are scarce. In the third Glasgow MONICA survey an age-adjusted Spearman rank correlation between protein S levels and blood pressure was found in both, men and women [28]. However, in regression analysis, in both sexes there was no significant association [28]. In another study blood protein S levels were higher in relatives of hypertensive men than in men without a family history of hypertension [31].

Plasma D-dimer is a degradation product of cross-linked fibrin and a marker of hypercoagulability and thrombosis [32]. Higher fibrin D-dimer concentrations may reflect an increased turnover of fibrin [18]. Moderately high levels of D-dimer have been associated with an increased risk of subsequent thrombotic events, particularly in patients with prior vascular

disease [32]. Serum D-dimer levels correlate with the extent of the total thrombolytic activity [32]. In our study, the D-dimer levels were significantly higher in hypertensive women compared to non-hypertensive ones, but this difference was not seen in men. Higher D-dimer levels in women compared to men were also reported from an Italian study [33]. Linear regression models attempting to assess the independent association between the systolic, diastolic and pulse pressure showed a significant relationship between systolic blood pressure and pulse pressure and D-dimer levels in women only. Our finding is in accordance with results from the Edinburgh Artery Study [34], in which systolic blood pressure in women was independently associated with D-dimer levels. Higher fibrin D-dimer levels in hypertensive than normotensive patients have been shown in further studies [33, 35].

The strengths of the present study are primarily the population-based design, and the availability of laboratory data, information on medication intake, and standardized assessed cardiovascular risk factors, including standardized blood pressure measurement. The sample size allowed for a sufficiently powered sex-specific analysis. This study also has limitations. Because the analyses were based on a follow-up examination of the population-based KORA study, it could be argued that the responders are not representative of the initial population-based sample. Thus, selection bias that may have affected the present results cannot be excluded. Furthermore, residual confounding by unmeasured variables cannot be entirely ruled out. The cross-sectional design of the study, the evaluation of leisure physical activity by self-report only, and the missing information on other types of physical activity represent further shortcomings [36]. Finally, because this study included German subjects born between 1945 and 1964, the results are not transferable to other age-groups and persons of other ethnicity.

In conclusion, while in both sexes there were significant differences in fibrinogen and factor VIII levels between hypertensive versus non-hypertensive subjects, the blood levels of protein S and D-dimers in hypertensives versus non-hypertensives differed only in women. There was no significant association between systolic, diastolic, and pulse pressure and any of the coagulation factors in both sexes, except for an independent association between systolic and pulse pressure and D-dimers in women. Thus, it seems that sex differences exist in the association between blood pressure parameters and commonly measured coagulation markers in the general population. Further studies are needed to identify the underlying causes.

Abbreviations

aPTT	Activated partial thromboplastin time
BMI	Body mass index
CHD	Coronary heart disease
HDL	High-densitiy lipoprotein
INR	International normalized ratio
IQR	Interquartile range
KORA	Cooperative Health Research in the Region of Augsburg, Germany
SD	Standard deviation

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Authors' contributions
JVvF analysed and interpreted the data and wrote the manuscript. DF and CM supervised the analysis and interpreted the data. JL and CM were responsible for the design of the study. AP and MH were responsible for the implementation and conduct of the KORA-Fit Study. All authors critically reviewed the manuscript and finally approved the version to be published.

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Availability of data and materials
The data that support the findings of this study are available from Helmholtz Zentrum München but restrictions apply to the availability of these data, which are not publicly available. Data are however available from the authors upon reasonable request and with permission of Helmholtz Zentrum München.

Declarations

Ethics approval and consent to participate
The study protocol was approved by by the Ethics Committees of the Bavarian Chamber of Physicians (KORA-Fit EC No 17040). The study was performed in accordance with the Declaration of Helsinki. All study participants gave written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Lipids in Health and Disease

RESEARCH Open Access

Sex-specific associations between serum lipids and hemostatic factors: the cross-sectional population-based KORA-fit study

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Abstract

Background: Studies on the associations between lipid parameters and different hemostatic factors in men and women from the general population are scarce. It was therefore examined whether there are possible relationships between routinely measured serum lipids (total cholesterol, HDL-cholesterol, non-HDL-cholesterol, LDL-cholesterol, and triglycerides) and different hemostatic factors (activated partial thromboplastin time (aPTT), fibrinogen, factor VIII, antithrombin III (AT III), protein C, protein S, and D-dimer).

Methods: The analysis was based on data from the Cooperative Health Research in the Region of Augsburg (KORA)-Fit study, which included 805 participants (378 men, 427 women) with a mean age of 63.1 years. Sex-specific associations between serum lipids and coagulation factors were investigated using multivariable linear regression models.

Results: In men, total cholesterol was inversely related to aPTT but positively associated with protein C activity. HDL cholesterol was inversely related to aPTT and fibrinogen. LDL cholesterol, non-HDL cholesterol, and triglycerides showed a positive association with protein C and protein S activity.

In women, LDL-cholesterol, total cholesterol, and non-HDL-cholesterol were positively related to AT III concentrations and protein C and S activity. Additionally, non-HDL-cholesterol was positively associated with factor VIII activity. HDL cholesterol was inversely related to fibrinogen. Triglycerides showed a positive relationship with protein C activity.

Conclusions: There seem to be sex differences regarding various associations between blood lipid levels and hemostatic factors. Further studies are needed to address the possible impact of these associations on cardiovascular risk and the underlying mechanisms.

Keywords: Serum lipids, Blood coagulation, KORA study, General population, Sex differences

Background

Dyslipidemia is a major risk factor for cardiovascular disease (CVD) [1]. Among others, elevated low-density lipoprotein cholesterol (LDL-c), decreased high-density lipoprotein cholesterol (HDL-c), and increased triglyceride (TG) levels in the blood are associated with an increased risk of coronary atherosclerosis [2, 3]. While LDL-c is considered the most important lipoprotein-based risk factor, recent epidemiological studies suggest that non-HDL-c may be superior to LDL-c in determining coronary heart disease (CHD) risk [4, 5].

A number of previous studies have examined the role of the hemostatic system in the manifestation of CVD [6–8] and have shown that systemic coagulation activity contributes to acute coronary events [9]. For example,

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associations between fibrinogen [10], Faktor VIII [11], and protein C and protein S [12] and incident CHD were found. Certain studies evaluated components of the blood coagulation system in subjects with familial combined hyperlipidemia, who have a substantially increased risk of CVD, and reported increased coagulation activity in these individuals [13]. Finally, other epidemiological studies have demonstrated a link between various coagulation factors and lipid parameters [8, 14].

Previous studies postulated that a hypercoagulable state was present in individuals with hypercholesterolemia [15]. It has been shown that blood lipids are associated with prothrombotic and endothelial-damaging properties [16]. Circulating lipids affect the vascular endothelium, platelets, and coagulation factors. They are associated with an alteration in the expression and/or function of thrombotic, fibrinolytic and rheological factors [16].

Data from large studies including men and women from the general population examining possible associations between different blood lipid parameters and a variety of coagulation factors are still scarce. Therefore, in the present study, sex-specific associations between LDL-c, HDL-c, non-HDL c, total cholesterol, and TG levels and the parameters activated partial thromboplastin time (aPTT), fibrinogen, D-dimers, antithrombin III (AT III), protein C, protein S, and factor VIII in the adult general population were investigated.

Methods

Study sample

The KORA (Cooperative Health Research in the Region of Augsburg, Germany) platform was established in 1996 and succeeded and advanced the MONICA study (Monitoring of trends and determinants in cardiovascular disease). The KORA cohort study consists of four cross-sectional baseline surveys (S1 1984/85, S2 1989/90, S3 1994/95 and S4 1999/2001, S1-S3 under the MONICA label [17]); since then, all study participants have been followed-up. In early 2018, a follow-up study called "KORA-Fit" started and was conducted in mid-2019. All living attendees of the KORA cohort born between 1945 and 1964 who agreed to be recontacted were invited for a new examination ($n = 3059$ or 64.4% of all appropriate participants).

In the present analysis, a subgroup of all KORA-Fit study participants was considered, meaning participants who took part in the S4 baseline survey ($n = 1394$ eligible persons). Of those, 856 S4 participants (61.4%) also took part in the KORA-Fit examination. Overall, 805 participants (378 men, 427 women) with available data on hemostatic parameters could be included in the analysis.

The Ethics Committee of the Bavarian Chamber of Physicians gave its approval for the study (KORA-Fit EC No 17040). All study participants gave written informed consent, and the study was performed in accordance with the Declaration of Helsinki.

Data collection

The study participants were interviewed by certified and trained study nurses on education/socioeconomic status, lifestyle factors, and medication use. In addition, a standardized medical examination was undertaken that included fasting blood sampling. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in m^2. Blood pressure was measured with an automated oscillometric device (HEM-705CP, Omron Corporation, Tokyo, Japan) after a five-minute rest while sitting. Education years up to 10 years were categorized as "low", over 10 years of schooling/studying as "high "education levels. A history of diabetes was categorized as yes or no. A participant was defined as physically active if he/she participated in sports in summer and winter and for more than 1 h per week in at least one season [18, 19]. Alcohol intake was calculated in grams per day [18]. Smoking status was classified into smoker, ex smoker and never smoker [18, 20]. Detailed information on the data collection, examination processes, and variable definitions in the KORA studies is described in detail elsewhere [18].

Laboratory measurements

All hemostatic factors were measured in citrate plasma. During blood sampling, the patients were in an overnight fasting state. The samples were then processed and stored at −80 °C until analysis. The parameter aPTT (reference value 26–36 sec) was determined photometrically (Pathromtin SL, Siemens Healthcare). AT III activity (ref. value 78–113%) was measured via a chromogenic activity assay (Innovance Antithrombin-Assay, Siemens Healthcare). Fibrinogen (ref. value 210–400 mg/dl) was quantified photometrically and turbidimetrically (Multifibren U, Siemens Healthcare). D-dimers (ref. value < 500 µg/L) were analyzed using a particle-enhanced immunoturbidimetric assay (Innovance D-Dimer Kit, Siemens Healthcare).

Protein C and S activity (ref. value for protein C 70–140%; ref. value for protein S 73–130% for men, 52–126% for women) were determined by photometry (Berichrom Protein C, Siemens Healthcare; Hemoclot Protein S). Factor VIII activity (ref. value 70–150%) was measured by photometry (coagulation factor VIII deficient plasma reagents used with Pathromtin SL reagents, Siemens Healthcare). All measurements, except for the protein S activity (CaoChrom analyzer (Wien, Austria)),

were performed on a Siemens BCS-XP analyzer (Siemens, Eschborn, Germany).

After overnight fasting, serum blood samples were collected and kept at room temperature until centrifugation. Serum was separated after 30 minutes. Samples were assayed immediately at the laboratory of the University Hospital Großhadern (Ludwig-Maximilians Universität, München). Serum total cholesterol and HDL-c were measured enzymatically on a Cobas 8000 c702 Roche chemistry analyzer (Hoffmann-La Roche AG, Basel/Switzerland). The Friedewald formula was used for calculating LDL-c [21]. Non-HDL-c was calculated via subtraction of HDL-c from total cholesterol. Serum triglycerides were determined by an enzymatic color test (according to Trinder) (Hoffmann-La Roche AG Basel/Switzerland) on a Cobas 8000 c702 (Hoffmann-La Roche AG Basel/Switzerland).

Statistical analysis

Continuous variables were described by means ± standard deviations (SD) in the case of normal distribution. Nonnormally distributed variables were given as median and interquartile range (IQR). The Shapiro–Wilk test was used to check if the data were normally distributed. Means of normally distributed variables were compared by the two-sided t test. Median values (not normally distributed variables) were compared by the Mann–Whitney U test. Categorial variables were compared via Fisher's exact test.

Multivariable linear regression models were used to investigate possible associations between the different serum lipid parameters (continuous variables) and aPTT, AT III, fibrinogen, D-dimer, protein C, protein S, and factor VIII. Participants taking anticoagulative medication were excluded from the analyses. The models were adjusted for the following confounders: BMI, age, sex (only in the total sample), education years, alcohol consumption, systolic blood pressure, smoking status, history of diabetes, and intake of lipid-lowering drugs. We performed additional analyses to account for clinical perspective and interpretation, using the lipid parameters in a binary way (abnormal vs. normal).

It was investigated whether the exposure-outcome associations (that is, lipid-coagulation factor associations) were modified by sex or age using formal tests for interaction (significance level 5%). The linearity assumption was tested by adding additional second-degree polynomial transformations of continuous covariates. Multicollinearity and heteroscedasticity were assessed by calculating the variance inflation factor and performing the Breusch–Pagan test, respectively. Finally, the assumption of normally distributed residuals was ensured by visual assessment of the respective Q-Q plots. P values < 0.05 were considered statistically significant. The statistical software IBM SPSS, version 28, was used for data analysis.

Results

Table 1 shows the sex-specific characteristics of the study sample. The mean age was the same for men and women (63.1 years). On average, men had a higher BMI (28.4 vs. 27.4) and were more often highly educated (68% vs. 60%) than women. Smoking status also differed between the sexes. While 65.6% of all men were smokers or ex-smokers, this was the case for only 50.8% of all women.

The aPTT values in men were higher than those in women (31.5 sec vs. 30.6 sec). Furthermore, protein C activity was higher in women (119.9% vs. 127.9%), while protein S activity was higher in men (137.1% vs. 120.9%). All other coagulation parameters showed no notable differences between males and females.

Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were different between the two sexes: total cholesterol levels in men were significantly lower than in women, as well as HDL-c and LDL-c. TGs were higher in men than in women.

In the whole population, LDL-c, total cholesterol, and non-HDL-c were positively associated with AT III, protein C and protein S activity. HDL-c was inversely related to aPTT and fibrinogen. Furthermore, there was a positive association between triglycerides and protein C and protein S activity (see Table 2).

Due to significant interactions with sex indicating different effect sizes for men and women in the multivariable linear regression models, the analyses were stratified by sex. In men, total cholesterol was inversely associated with aPTT and positively associated with protein C activity. HDL-c was inversely related to both aPTT and fibrinogen. LDL-c, non-HDL-c and TG values showed positive associations with protein C and protein S activity (see Table 3).

In women, total, LDL and non-HDL cholesterol were positively related to AT III concentrations as well as protein C and protein S activity. In addition, non-HDL-c was positively associated with factor VIII activity. For men, HDL-c was inversely related to fibrinogen. TG concentrations showed a positive association with protein C activity (see Table 4).

All findings were supported by regression models using the lipid parameters in a binary way (abnormal versus normal) (see Additional file 1, Tables 1, 2 and 3).

Table 1 Sex-specific characteristics, serum lipids, and hemostatic factors (means ± SDs or median and IQR): the population-based KORA-Fit Study

	Participants ($n=805$)	Units	Ref. values	MEN ($n=378$)	WOMEN ($n=427$)	*p* value
Age	805 (0 missings)	years		63.1 (5.8)	63.1 (5.5)	0.942
BMI	805 (0 missings)	kg/m^2		28.4 (4.2)	27.4 (5.2)	0.003
Systolic blood pressure	803 (2 missings)	mmHg		130.2 (15.3)	120.2 (16.5)	< 0.001
Education	805 (0 missings)	education ≤10 yrs		118 (31.2)	171 (40.0)	0.010
		education > 10 yrs		260 (68.8)	256 (60.0)	
Diabetes	803 (2 missings)	yes		36 (9.5)	33 (7.7)	0.381
		no		342 (90.5)	392 (91.8)	
Physical activity	805 (0 missings)	yes		261 (69.0)	304 (71.2)	0.537
		no		117 (31.0)	123 (28.8)	
Smoking status	805 (0 missings)	Smoker		56 (14.8)	54 (12.6)	< 0.001
		Ex smoker		192 (50.8)	163 (38.2)	
		Never smoker		130 (34.4)	210 (49.2)	
Alcohol intake	804 (1 missing)	g/day		5.7 (0.0; 21.5)	6.6 (0.0; 22.9)	0.147
aPTT	803 (2 missings)	sec	26–36	31.5 (3.4)	0.6 (3.2)	< 0.001
Antithrombin III activity	804 (1 missing)	%	83–118	99.4 (10.3)	104.9 (10.4)	< 0.001
Fibrinogen	758 (47 missings)	mg/dl	210–400	298.9 (62.8)	305.2 (60.2)	0.163
D-dimers	805 (0 missing)	ng/ml	≤500	408.0 (314.8; 563.0)	405.5 (306.0; 554.0)	0.642
Protein C activity	805 (0 missing)	%	70–140	119.9 (17.4)	127.9 (17.5)	< 0.001
Protein S activity	789 (16 missings)	%	m 73–130, w 52–126	137.1 (38.5)	120.9 (27.6)	< 0.001
Factor VIII activity	804 (1 missing)	%	70–150	122.6 (36.9)	124.9 (34.4)	0.371
Total cholesterol	805 (0 missing)	mg/dl	normal 0–200	190 (50.3)	132 (30.9)	< 0.001
			high > 200	188 (49.7)	295 (69.1)	
HDL cholesterol	805 (0 missing)	mg/dl	low ≤45	111 (29.4)	26 (6.1)	< 0.001
			normal > 45	267 (70.6)	401 (93.9)	
LDL cholesterol (Friedewald)	760 (45 missings)	mg/dl	normal ≤160	319 (86.7)	354 (84.1)	0.315
			high > 160	49 (13.3)	67 (15.9)	
Non-HDL cholesterol	805 (0 missing)	mg/dl	normal ≤130	145 (38.4)	137 (32.1)	0.065
			high > 130	233 (61.6)	290 (67.9)	
Triglycerides	805 (0 missing)	mg/dl	normal 0–200	325 (86.0)	394 (92.3)	0.004
			high > 200	53 (14.0)	33 (7.7)	

Discussion

The present study showed that commonly measured hemostatic factors were associated with several blood lipid markers in individuals from the general population. There were significant sex-specific differences; in particular, more notable associations, especially with non-HDL-c, could be observed in women. However, commonalities between the sexes could be found in the inverse relationship of HDL-c and fibrinogen and positive relationships of LDL-c as well as non-HDL-c with protein C.

Protein C and its cofactor protein S are vitamin K-dependent coagulation inhibitors and play an important role in fibrinolytic processes [22]. In both sexes, these two coagulation factors showed similar associations with total cholesterol, LDL-c, and non-HDL-c; TGs were associated with both coagulation inhibitors in men, but in women, they were only related to protein C. A positive correlation of protein C with LDL-c was also found in the ARIC Study [23], and in a Polish study, protein C activity was associated with hypercholesterolemia [24]. Women had higher protein C activity than men, and protein S activity was significantly higher in men. Protein C activity is known to change in women taking oral contraceptives or who are pregnant [25]. Since this was not the case in the present study, because the mean age of the women was 63.1 years, it could be assumed that in postmenopausal women, protein C activity might be higher compared to men. Similar to protein C and protein S, AT III also has antithrombotic properties and inhibits serine protease factors II, IX, X, XI, and XII [26]. In the present study,

Table 2 Results of the linear regression (ß value, 95% CI, *p* value) on the associations between serum lipids and coagulation parameters in both sexes (KORA-Fit)

	Total cholesterol mg/dl	HDL cholesterol mg/dl	LDL cholesterol (Fried) mg/dl	non-HDL cholesterol mg/dl	Triglycerides mg/dl
aPTT	−0.002 (−0.009, 0.004)	−0.022 (−0.037, −0.006)	0.001 (−0.006, 0.008)	0.002 (−0.005, 0.008)	0.001 (−0.003, 0.005)
	0.523	0.005	0.822	0.584	0.571
AT III	0.039 (0.019, 0.059)	0.023 (−0.024, 0.070)	0.037 (0.015, 0.059)	0.034 (0.014, 0.053)	0.002 (−0.008, 0.011)
	< 0.001	0.334	< 0.001	< 0.001	0.753
Fibrinogen	−0.015 (−0.137, 0.106)	−0.505 (−0.785, −0.225)	0.084 (−0.051, 0.219)	0.076 (−0.044, 0.196)	0.001 (−0.068, 0.071)
	0.804	< 0.001	0.220	0.212	0.975
D-dimers	0.515 (−0.299, 1.329)	−1.083 (−2.979, 0.813)	0.625 (−0.242, 1.491)	0.698 (−0.107, 1.501)	0.151 (−0.244, 0.546)
	0.215	0.263	0.157	0.089	0.453
Protein C	0.156 (0.124, 0.189)	0.064 (−0.016, 0.144)	0.139 (0.102, 0.175)	0.141 (0.108, 0.173)	0.033 (0.016, 0.049)
	< 0.001	0.118	< 0.001	< 0.001	< 0.001
Protein S	0.150 (0.084, 0.215)	0.012 (−0.141, 0.165)	0.125 (0.053, 0.196)	0.143 (0.078, 0.208)	0.061 (0.029, 0.092)
	< 0.001	0.876	< 0.001	< 0.001	< 0.001
Factor VIII	0.069 (0.001, 0.137)	0.068 (−0.091, 0.227)	0.055 (−0.020, 0.131)	0.055 (−0.012, 0.123)	0.019 (−0.014, 0.052)
	0.046	0.400	0.150	0.106	0.260

Participants with anticoagulative medication were excluded from the linear regression analyses

Independent variables: lipid parameters (continuously). Adjusted for age, sex, BMI, education (≤/> 10 years), diabetes, smoking (yes/no/never), systolic blood pressure, and intake of antihypertensive medication

aPTT activated partial prothrombin time

Table 3 Results of the linear regression (ß value, 95% CI, *p* value) on the associations between serum lipids and coagulation parameters in men (KORA-Fit)

	Total cholesterol mg/dl	HDL cholesterol mg/dl	LDL cholesterol mg/dl	Non-HDL cholesterol mg/dl	Triglycerides mg/dl
aPTT	−0.011 (−0.022, −0.001)	−0.039 (−0.065, −0.013	−0.008 (−0.020, 0.003)	−0.005 (−0.016, 0.005)	0.000 (−0.004, 0.005)
	0.030	0.004	0.164	0.304	0.963
AT III	0.005 (−0.025, 0.035)	−0.030 (−0.107, 0.047)	0.012 (−0.020, 0.045)	0.009 (−0.020, 0.038)	−0.002 (−0.013, 0.010)
	0.748	0.446	0.450	0.547	0.769
Fibrinogen	−0.127 (−0.318, 0.063)	−0.696 (−1.194, −0.198)	−0.037 (−0.248, 0.173)	−0.026 (−0.213, 0.161)	0.012 (−0.081, 0.105)
	0.189	0.006	0.728	0.784	0.799
D-dimers	0.621 (−0.785, 2.027)	−2.894 (−6.491, 0.702)	0.507 (−0.940, 1.955)	1.008 (−0.360, 2.376)	0.286 (−0.241, 0.813)
	0.386	0.114	0.491	0.148	0.286
Protein C	0.125 (0.074, 0.176)	0.015 (−0.121, 0.150)	0.112 (0.056, 0.169)	0.116 (0.066, 0.166)	0.023 (0.004, 0.043)
	< 0.001	0.828	< 0.001	< 0.001	0.020
Protein S	0.238 (0.121, 0.355)	0.059 (−0.241, 0.360)	0.173 (0.046, 0.300)	0.216 (0.102, 0.330)	0.060 (0.017, 0.103)
	0.121	0.698	0.008	< 0.001	0.006
Factor VIII	0.043 (−0.065, 0.152)	0.248 (−0.030, 0.526)	0.001 (−0.119, 0.121)	0.005 (−0.101, 0.112)	0.011 (−0.030, 0.052)
	0.434	0.081	0.984	0.920	0.593

Participants with anticoagulative medication were excluded from the linear regression analyses

Independent variables: lipid parameters (continuously). Adjusted for age, BMI, education (≤/> 10 years), diabetes, smoking (yes/no/never), systolic blood pressure, and intake of antihypertensive medication

aPTT activated partial prothrombin time

the AT III activity in women was significantly higher than that in men. Furthermore, in females, a significant association between total cholesterol, LDL-c and non-HDL-c and AT III was observed, but none of the lipid parameters were associated with AT III in men. This result is in accordance with findings from the ARIC study [27], which observed higher AT III concentrations in women than in men. Furthermore, in a study from Japan including hyperlipidemic and normolipidemic elderly individuals, in both groups, serum total

Table 4 Results of the linear regression (ß value, 95% CI, *p* value) on the associations between serum lipids and coagulation parameters in women (KORA-Fit)

	Total cholesterol mg/dl	HDL cholesterol mg/dl	LDL cholesterol mg/dl	Non-HDL cholesterol mg/dl	Triglycerides mg/dl
aPTT	0.004 (−0.004, 0.013)	−0.013 (−0.032, 0.005)	0.007 (−0.002, 0.017)	0.007 (−0.001, 0.016)	0.003 (−0.003, 0.009)
	0.313	0.155	0.129	0.094	0.294
AT III	0.065 (0.038, 0.092)	0.053 (−0.007, 0.113)	0.056 (0.026, 0.087)	0.054 (0.026, 0.081)	0.009 (−0.010, 0.028)
	< 0.001	0.081	< 0.001	< 0.001	0.360
Fibrinogen	0.050 (−0.110, 0.211)	−0.401 (−0.739, −0.063)	0.164 (−0.016, 0.345)	0.141 (−0.020, 0.301)	−0.027 (−0.136, 0.083)
	0.538	0.020	0.074	0.086	0.631
D-dimers	0.474 (−0.482, 1.430)	0.214 (−1.845, 2.272)	0.621 (−0.446, 1.687)	0.428 (−0.528, 1.385)	−0.164 (−0.830, 0.502)
	0.330	0.838	0.253	0.379	0.629
Protein C	0.180 (0.137, 0.223)	0.093 (−0.007, 0.193)	0.160 (0.110, 0.209)	0.160 (0.116, 0.204)	0.059 (0.027, 0.091
	< 0.001	0.069	< 0.001	< 0.001	< 0.001
Protein S	0.083 (0.009, 0.157)	0.009 (−0.149, 0.167)	0.092 (0.011, 0.173)	0.081 (0.008, 0.155)	0.041 (−0.010, 0.092)
	0.027	0.912	0.026	0.031	0.111
Factor VIII	0.088 (−0.001, 0.178)	−0.032 (−0.225, 0.162)	0.095 (−0.005, 0.196)	0.095 (0.006, 0.185)	0.042 (−0.021, 0.104)
	0.053	0.749	0.061	0.037	0.192

Participants with anticoagulative medication were excluded from the linear regression analyses

Independent variables: lipid parameters (continuously). Adjusted for age, BMI, education (≤/> 10 years), diabetes, smoking (yes/no/never), systolic blood pressure, and intake of antihypertensive medication

aPTT activated partial prothrombin time

cholesterol correlated positively with AT III activity [28]. In contrast, there was no notable association between LDL-c and AT III in the ARIC study [27]. A Polish study including a random sample of community-dwelling older individuals also did not find an association between AT III activity and total cholesterol and LDL-c [29]. In addition, total cholesterol was not associated with AT III in a study on 130 healthy adults aged 20–60 years from Poland [24].

Contrary to prior studies [27, 30, 31], fibrinogen values did not differ between men and women in the present investigation. A number of previous studies [30–33], but not all [34, 35], reported a positive association between fibrinogen and LDL-c. In the present study, no independent association between fibrinogen and LDL-c was observed, but an inverse relationship between fibrinogen and HDL-c in both sexes was found. This result agrees with findings from ARIC [8, 14] but could not be confirmed by other investigations [31, 32, 36]. D-dimer levels did not differ between males and females and showed no significant association with any of the different lipid parameters. In contrast, in the Dallas Heart Study, in linear regression analyses, D-dimer, a marker of fibrin formation and lysis, was significantly higher in females than in males even after multivariable adjustment for a number of covariables, including body composition [37].

In the present study, a significant relationship between factor VIII activity and non-HDL-c was observed in women. No other lipid parameters showed a relationship with factor VIII. Furthermore, no notable differences in factor VIII concentrations were found between the two sexes. This is in contrast to the ARIC study, where the mean levels of Factor VIII were higher in men than in women [23]. In addition, in ARIC in univariable analysis, factor VIII was negatively associated with HDL-c and positively associated with LDL-c [23]. In the third Glasgow MONICA Survey II [14], factor VIII correlated with cholesterol in women but not men. There are no prior studies on the association between non-HDL-c and hemostatic factors. Thus, the findings of the present study have to be confirmed by further investigations.

An inverse association between HDL-c and aPTT, a summary index for intrinsic and common pathways, was found in men but not in women in the present study. Furthermore, in males but not females, total cholesterol was inversely related to aPTT, which is a widely used routine screening test of the coagulation system. It could be shown that patients with hypercholesterolemia had shorter aPTT values than patients with lower cholesterol levels [38]. The results of the present study in men are consistent with this finding, but it is unclear why women do not show this relationship. Furthermore, contrary to this finding, no correlation between HDL-c and aPTT was observed in a prior study [39]. In contrast to the study of Chan et al. [40], where TGs were also related to

aPTT, in the present study, such an association could not be observed.

As an underlying mechanism for the association between blood lipid levels and hemostasis factors, a previous study suggested that hypercholesterolemia may affect the regulation of blood coagulation via tissue factor pathway inhibitor (TFPI) [41]. TFPI, formerly also called lipoprotein-associated coagulation inhibitor [42] or extrinsic pathway inhibitor [43], is a protease inhibitor of the first steps of the extrinsic blood coagulation pathway. Increased TFPI activity was found in patients with hyperlipidemia [44], and there are positive correlations between plasma TFPI activity and total cholesterol [45] as well as LDL cholesterol levels [44]. In addition, studies have shown that hyperlipidemia may be associated with decreased activation of protein C, which in its activated form can inhibit several steps in the blood coagulation pathways.

Comparisons with other studies and what does the current work add to the existing knowledge

Prior studies observed possible effects of dyslipidemia on the coagulation system [23, 24, 27, 28, 30–35]. The present study found that sex is a moderator responsible for different effects in men and women regarding the relationships between lipid concentrations and coagulation factors.

Study strengths and limitations

The strengths of this study are the sample size, the availability of standardized measured laboratory data, information on medication intake, and standardized assessed cardiovascular risk factors. There are also certain limitations. The analysis was based on a follow-up study of a population-based study. Thus, it could be assumed that the participants are not representative of the initial population-based sample. Selection bias that may have affected the present results cannot be entirely excluded. This study included German subjects born between 1945 and 1964, so the results do not apply to other age groups and individuals of other ethnic origins.

Conclusions

There appear to be sex-specific differences regarding various associations between blood lipid levels and hemostatic factors in individuals from the general population. Therefore, in clinical practice, the role of lipid concentrations in the pathogenesis of venous thromboembolism (VTE) should not be neglected. Patients at high risk for developing venous thromboembolism could benefit from a reduction in lipid concentrations, e.g., by treatment with lipid-lowering drugs.

Abbreviations

aPTT: Activated partial thromboplastin time; AT III: Antithrombin III; BMI: Body mass index; CHD: Coronary heart disease; CVD: Cardiovascular disease; HDL-c: High-density lipoprotein cholesterol; IQR: Interquartile range; KORA: Cooperative Health Research in the Region of Augsburg, Germany; LDL-c: Low-density lipoprotein cholesterol; Non-HDL-c: Non-HDL cholesterol; SD: Standard deviation; TG: Triglycerides; VTE: Venous thromboembolism.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-022-01757-0.

Additional file 1: Table 1. Results of the linear regression (ß value, 95% CI, *p* value) on the associations between categorized serum lipids (abnormal vs. normal) and coagulation parameters in both sexes (KORA-Fit). **Table 2.** Results of the linear regression (ß value, 95% CI, p value) on the associations between categorized serum lipids (abnormal vs. normal) and coagulation parameters in men (KORA-Fit). **Table 3.** Results of the linear regression (ß value, 95% CI, p value) on the associations between categorized serum lipids (abnormal vs. normal) and coagulation parameters in women (KORA-Fit).

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Authors' contributions

JVvF analyzed and interpreted the data and wrote the manuscript. DF and CM supervised the analysis and interpreted the data. JL and CM were responsible for the design of the study. AP and MH were responsible for the implementation and conduct of the KORA-Fit Study. DT was responsible for the measurement of the lipid parameters. All authors critically reviewed the manuscript and approved the final version to be published.

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Availability of data and materials

The data that support the findings of this study are available from Helmholtz Zentrum München, but restrictions apply to the availability of these data, which are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Helmholtz Zentrum München.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committees of the Bavarian Chamber of Physicians (KORA-Fit EC No 17040). The study was performed in accordance with the Declaration of Helsinki. All study participants gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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