Pädiatrische Referenzintervalle und Zusammenhänge soziodemographischer Kenngrößen zu Serumkonzentrationen von Lipoproteinen

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eingereicht von: Anne Dathan-Stumpf, geb. Dathan

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Direktor: Prof. Dr. med. Wieland Kiess

Betreuer: Prof. Dr. med. Wieland Kiess
Mandy Vogel

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I ABKÜRZUNGSVERZEICHNIS

Wortabkürzungen

Abk.	Erläuterung
AI	Atherogener Index
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
BIP	Bruttoinlandsprodukt
BMI	Body-Mass-Index
CEPT	Cholesterylester-Transferprotein
CIMT	carotid intima media thickness
CLSI	Clinical & Laboratory Standards Institute
gamlss	Generalized Additive Model for Location, Scale and Shape (GAMLSS)
HDL	High Density Lipoprotein Cholesterol
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland
LDL	Low Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein a
OECD	Organisation für wirtschaftliche Zusammenarbeit und Entwicklung
TC	Gesamtcholesterol
TG	Triglyceride
VLDL	Very Low Density Lipoprotein Cholesterol
WHO	World Health Organization

1 BIBLIOGRAPHISCHE BESCHREIBUNG

Anne Dathan-Stumpf:

Pädiatrische Referenzintervalle und Zusammenhänge soziodemographischer Kenngrößen zu Serumkonzentrationen von Lipoproteinen

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Die hier vorliegende Arbeit basiert auf Untersuchungen und Ergebnissen der LIFE-Child Studie und schließt Kinder und Jugendliche im Alter von 0 bis 18 Jahren ein. LIFE-Child, welches Teil des Leipziger Forschungszentrums für Zivilisationserkrankungen ist, untersucht das Wachstum und die Entwicklung von Neugeborenen, Kindern und Jugendlichen sowie den Einfluss von Umweltfaktoren auf diese. Schwerpunkt der ersten Publikation ist die Erhebung alters- und geschlechtsabhängiger Referenzwerte für Gesamtcholesterin, LDL- und HDL-Cholesterol, Triglyceride sowie für die Apolipoproteine A1 und B mittels aktueller und moderner laboranalytischer und statistischer Methoden. Mit Hilfe der LMS- Methode nach Cole, welche Teil des „gamlss"- Paket der Statistiksoftware R ist, erfolgte die Ermittlung der Perzentilenkurven und Referenzintervalle kontinuierlich über das Alter. Durch die Anwendung dieses statistischen Ansatzes fanden sowohl das longitudinale Design der Studie als auch die Rekrutierung von Familien Berücksichtigung. Zudem wurde anhand von Kontingenztafeln die Prävalenz gemischter Dyslipidämien bestimmt. Soziodemographische Faktoren wie Bildung, Einkommen oder Lebensform beeinflussen in vielerlei Hinsicht den Werdegang und damit das Leben von Kindern und Jugendlichen. Da die bisher in der Literatur beschriebenen Studien zu unterschiedlichen Ergebnissen kommen, wurde in einer zweiten Publikation die Abhängigkeit der oben genannten Serumlipide und Apolipoproteine von den soziodemographischen Kenngrößen des Winkler Index und der Family Affluence Scale, mittels uni- und multivariater Regressionsanalysen, untersucht.

Die in dieser Arbeit erhobenen Daten liefern neue Erkenntnisse zu gesundheitsrelevanten Einflussgrößen, wie beispielsweise die soziale Schichtzugehörigkeit und der familiäre Wohlstand. Anhand der altersabhängigen Referenzintervalle ist eine Orientierung zum kardiovaskulären Risiko der Kinder und Jugendlichen gegeben.

2 EINLEITUNG

2.1 Hintergrund

Kardiovaskuläre Erkrankungen stellen ein zentrales Problem unseres Gesundheitswesens dar und sind in Deutschland mit 39% die häufigste Todesursache überhaupt [1]. Allein im Jahre 2014 beliefen sich die Gesamtkosten (direkte und indirekte Kosten) für kardiovaskuläre Erkrankungen auf 37,4 Milliarden Euro (entspricht 1,4% des Bruttoinlandsprodukt (BIP)) in unserem Land, wobei diese Ausgaben schätzungsweise um weitere 4 Milliarden Euro bis zum Jahre 2020 steigen werden [2]. Herz- und Kreislauf-Erkrankungen manifestieren sich in der Regel erst nach dem vierten Lebensjahrzehnt, während die Ausbildung einer Atherosklerose bereits in jungen Jahren beginnt [3]. Für diesen Prozess werden die Serumlipide als entscheidende Risikofaktoren gesehen [4]. Daher ist es das Anliegen dieser Arbeit neue Referenzintervalle für Serumlipide und Apolipoproteine zu eruieren sowie relevante Einflussgrößen auf diese zu detektieren, um künftig bereits im Kindesalter kardiovaskuläre Erkrankungen präventiv vorzubeugen.

2.2 Serumlipide, Apolipoproteine und Dyslipidämien

Es gibt eine Vielzahl von Studien die belegen, dass Übergewicht, Adipositas sowie verschiedene Laborparameter, wie beispielsweise Leptin oder eine Hyperinsulinämie [5], mit einem erhöhten Risiko für die Ausprägung einer kardiovaskulären und/oder metabolischen Erkrankung korrelieren [6-10]. Die Serumlipide, denen eine zentrale Rolle in der Ausbildung der Atherosklerose beigemessen wird [4], sind ein häufig untersuchtes Forschungsobjekt. Umso verwunderlicher ist es, dass Erkenntnisse bezüglich dieser Problematik bei Kindern und Jugendlichen, wie beispielsweise der Manifestationszeitpunkt der Atherosklerose im Kindesalter [3], erst in jüngster Vergangenheit gewonnen wurden.
Serumlipide unterliegen einer Vielzahl an Einflussfaktoren und Abhängigkeiten. Sowohl Bewegung, Nahrungsaufnahme, Zusammensetzung und das soziale Umfeld, der Lebensstil als auch die familiäre Vorbelastung spielen eine entscheidende Rolle [11]. Im Folgenden soll ein kleiner Einblick in die Vielfältigkeit der Störgrößen auf die Konzentrationen der Serumlipide und Apolipoproteine gegeben werden:

Es ist belegt, dass übergewichtige Kinder im Vergleich zu Normalgewichtigen deutlich erhöhte Triglycerid- (TG), Gesamtcholesterol- (TC), Low Density Lipoprotein Cholesterol- (LDL), Very Low Density Lipoprotein Cholesterol- (VLDL), Apolipoprotein B- (ApoB) und verminderte High Density Lipoprotein Cholesterol- (HDL) Werte aufweisen [12]. Weiterhin scheinen Transferproteine wie das Cholesterylester Transferprotein (CEPT), welchem im Lipidstoffwechsel eine zentrale Rolle zukommt und das tendenziell pro-atherogen wirkt, mit der kindlichen Adipositas positiv zu korrelieren [12]. Andere Untersuchungen zeigen deutliche Differenzen der Ionenmobilität der Lipide und der Apolipoprotein-Subfraktionen zwischen schlanken und adipösen Kindern. Bei präpubertären Heranwachsenden konnte mit fortschreitender Gewichtszunahme und zunehmendem Entwicklungsstadium eine sinkende Konzentration des HDL-Cholesterols beobachtet werden [13]. Auch untereinander beeinflussen sich die Blutfette. Beispielsweise zeigt sich ein positiver Zusammenhang zwischen der Partikelgröße der LDL und den Serumkonzentrationen der Triglyceride, des HDL-Cholesterols sowie dem Atherogenem Index[1] (AI) [14].

In Bezug auf familienanamnestische kardiovaskuläre Vorerkrankungen oder eine Hypercholesterinämie erwies sich der Parameter Lp(a) als besonders sensitiv. Dieses Lipoprotein ist bei Patienten mit einer positiven Familienanamnese signifikant erhöht [15]. Ursächlich für die Hypercholesterinämie kann dabei einerseits eine Mutation im LDL-Rezeptor oder im PCSK9-Gen sein [16]. Der Lp(a)-Wert der Kinder korreliert dabei nicht nur mit dem der Eltern, sondern auch mit dem der Großeltern [17]. Die familiäre Hypercholesterinämie ist assoziiert mit einem erhöhten Risiko für die Ausbildung einer frühzeitigen Atherosklerose. Die Kinder weisen eine verstärkte oxidierte LDL-Subfraktion auf, welche die Expression spezifischer Tumor-Nekrose-Faktor-Subfamilien begünstigt und somit ausschlaggebend für die durch Entzündungsprozesse entstehende Atherosklerose sind [18]. Dieser Entstehungsprozess unterliegt noch anderen Einflussgrößen: Es hat sich gezeigt, dass die bei Kindern gemessenen Apolipoprotein-Konzentrationen sensitive Prädiktoren für die Entwicklung einer subklinischen Atherosklerose im Erwachsenenalter darstellen. Die dafür gemessene ApoB-Fraktion und die ApoB/ApoA1- Ratio korrelieren positiv mit der Karotis-Intima-Media-Dicke (CIMT), während Apolipoprotein A1 (ApoA1) invers assoziiert ist [19]. Auch eine erhöhte arteriellen Steifigkeit, gemessen an der Pulswellengeschwindigkeit, welche bei Patienten mit metabolischem Syndrom zu beobachten

[1] AI = Gesamtcholesterol/ HDL-Cholesterol

ist, wird mit der erhöhten ApoB/ApoA1- Ratio in Zusammenhang gebracht [20]. Es gibt daher Empfehlungen, wonach künftig neben den klinischen Laborbestimmungen der klassischen Serumlipide auch die Erhebung der Apolipoproteine erfolgen sollte, da diese zusätzliche Informationen zu Dyslipidämien liefern. So ist eine erhöhte Konzentration von ApoB, trotz normaler Gesamtcholesterin- und LDL-Werte, mit Adipositas, einem metabolischen Syndrom oder Typ-2-Diabetes assoziiert [21].

Problematische gestaltet sich vor allem der protektive Ansatz zur Vorbeugung von kardiovaskulären und metabolischen Erkrankungen, der neben körperlicher Fitness/ Bewegung und Ernährungsgewohnheiten auch das sozioökonomische Umfeld einschließt. Regelmäßiges Training senkt signifikant die TC-, TG-, VLDL- und LDL- Spiegel und korreliert mit einem Anstieg der HDL [22]. Ebenso kann die Konzentration der Lp(a) durch die sportliche Betätigung reduziert werden [23]. Die Ernährungswissenschaft hat gezeigt, dass öl-und fetthaltige Lebensmittel nicht nur nachhaltig die Wachstumshomöostase beeinflussen [24], sondern auch mit einer gesteigerten Inzidenz für Dyslipidämien einhergehen [25]. Doch selbst hier muss differenziert werden. So kann in der *Österreichischen Ärztezeitung* nachgelesen werden, dass Maiskeimöle vor allem die Konzentration des LDL-Cholesterols nachhaltig senken, während dies bei Oliven- und Sonnenblumenöl nicht der Fall ist. Zudem können Omega-3-Fettsäuren aus Meeresfischen die Triglyceridkonzentrationen um bis zu 25% senken [26]. Des Weiteren kann ein langfristiger und regelmäßiger Konsum von 40g Magermilch/d nachhaltig den Gesamtcholesterin-Spiegel senken und führt zu einem signifikanten Anstieg des HDL-Cholesterols sowie der ApoA1-Werte[2] [27].

Neben all diesen bisher auszugsartig gelisteten Wechselwirkungen werden die Serumlipide und Apolipoproteine auch durch sozioökonomische Faktoren beeinflusst. So hat sich gezeigt, dass Rauchen zu den Verhaltensindikatoren für die Ausprägung einer Dyslipidämie gehört und damit letztlich ein Risikofaktor für die Entstehung kardiovaskulärer Erkrankungen darstellt [28]. Ein niedriger Bildungsstand korreliert zudem invers mit den Serumkonzentrationen für Gesamtcholesterin [29]. Interessanter Weise können bei Vorschulkindern, deren Mütter ein niedriges Bildungsniveau haben, niedrigere LDL-Level beobachtet werden [30]. Letztlich spielt auch die Ethnie eine Rolle. Während Schwarze eher höhere HDL-Cholesterol- und niedrigere Triglycerid-Level aufweisen, finden sich bei

[2] Effekt nachgewiesen bei postmenopausalen Frauen

Menschen hispanischer Abstammung höhere TG- und LDL-Konzentrationen als bei Weißen [31].

Zudem können auch anthropometrische Größen mit den Serumlipiden in Assoziation gebracht werden. So zeigen sich beispielsweise positive Korrelationen zwischen dem Hüftumfang und den TC-, TG-, LDL-Werten sowie ein inverser Zusammenhang zum HDL-Cholesterol [32]. Außerdem konnten den Serumlipiden eine Verbindung zum Taillenumfang, dem Gewicht, dem Body-Mass-Index (BMI) und vor allem der Hautfaltendicke nachgewiesen werden [33]. Des Weiteren sind Dyslipidämien und Hypertension assoziiert [34].

Die hier dargestellte Ausführung stellt keinen Anspruch auf Vollständigkeit. Vielmehr soll ein Überblick der Sensibilität und Vielfältigkeit der Wechselwirkungen bzw. Einflüsse auf und zwischen den Serumlipiden und Apolipoproteinen gezeigt werden.

2.3 Referenzintervalle

Eine offizielle Definition für *Referenzwerte* zu finden erweist sich als sehr schwierig. Salopp gesagt können sie als „Wertebereich einer Messgröße, auf den der aktuelle Messwert bezogen wird“ charakterisiert werden [35]. In der modernen Medizin kommen Referenzintervallen und deren klinischen Interpretationen eine zentrale Bedeutung zu. Besonders in der Pädiatrie bilden alters- und geschlechtsbezogene Referenzen die Basis für wichtige klinische Entscheidungen. Sie fungieren als eine Orientierungshilfe, ob ein Parameter als primär pathologisch anzusehen ist oder nicht. Die „Normalbereiche“ werden klassischerweise an einem großen Kollektiv gesunder Probanden erhoben. Dabei „[…] gibt man die Ober- und Untergrenzen des Bereichs an, in dem sich 95 % aller Messwerte befinden.“ [36]. Dies entspricht in einer Normalverteilung dem arithmetischem Mittel plus/minus zwei Standardabweichungen und wird bei komplexer Verteilung häufig in Form der 2,5. bis 97,5. Perzentile angegeben [37-39]. In vielen Studien, so auch in der hier vorliegenden Arbeit, wird jedoch eine Rundung der Grenzwerte auf die 3. bzw. 97. Perzentile vorgenommen. Trotzdem ist ein Wert außerhalb der Ober- und Untergrenze nicht zwangsläufig als krank zu interpretieren, da jeder 20. Wert „[…] definitionsgemäß bei Gesunden außerhalb der angegebenen Grenzen“ liegt [36].

Im April 2006 veröffentlichte die World Health Organization (WHO) neue Normwerte für anthropometrische Größen [40, 41]. Diese zeigen das normale menschliche Wachstum unter

optimalen Umgebungsbedingungen, unabhängig von der ethnischen Zugehörigkeit, dem sozioökonomischen Status und Art der Ernährung/ Fütterung [42]. Die Kurven für Gewicht, Körpergröße und Kopfumfang gehören längst zum Standard der gelben U-Hefte. In den letzten Jahren hat man jedoch die enorme Relevanz derartiger Perzentilenkurven für laboranalytische Messwerte erkannt, sodass es zunehmend zu nationalen [43] und internationalen [44-51] Bemühungen kam, aktuelle Referenzwerte für Serumlipide zu erstellen. Leider blieben hierbei die Apolipoproteine A1 und B meist außen vor.

Vergleicht man erhobene Referenzwerte zweier Studien, so lassen sich immer (kleine) Differenzen beobachten. Diese sind letztlich auf die Studienpopulation sowie auf die Art der laboranalytischen und statistischen Methode zurückzuführen. Sowohl die *International Federation of Clinical Chemistry and Laboratory Medicine* (IFCC) als auch das *Clinical & Laboratory Standards Institute* (CLSI) haben genauste Empfehlungen darüber abgegeben, wie mit der statistischen Analyse von Referenzintervallen zu verfahren ist. Allerdings beziehen sich diese eher auf festgelegte Altersgruppen. Konnten für eine Subgruppe mehr als 120 gesunde Probanden rekrutiert werden, so sollte eine nicht-parametrische Analyse erfolgen, da diese keine Kenntnisse über die Art der Datenverteilung voraussetzt [52-53, 38]. Bei weniger als 120, aber wenigstens 40 gesunden Individuen, können parametrische Verfahren angewandt werden, vorausgesetzt es liegt eine Gauß‘sche Normalverteilung vor. Bei weniger als 40 Messpunkten werden robuste Methoden nach Horn und Pesce zur Schätzung der Referenzintervalle empfohlen [54]. Die in dieser Arbeit angewandte LMS-Methode nach Cole [55, 56], die eine kontinuierlich Betrachtung über das korrekte Alter, also ohne Erstellung von Altersgruppen, ermöglicht, ist ein bisher in der laboranalytischen Medizin eher selten angewandtes Verfahren. Dabei weiß man bereits seit den späten 80er Jahren vom Nutzen dieser Methode bei der Erstellung der Wachstumsstandards [57]. Die LMS-Methode nach Cole fand Anwendung bei der Erstellung von Referenzintervallen für HDL- und LDL-Cholesterol sowie für Gesamtcholesterin in der großangelegten Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS) [43], auf die im ersten Paper immer wieder Bezug genommen wird.

2.4 Soziodemographische Faktoren

Die WHO definiert Gesundheit als "[…] state of complete physical, mental and social well-being and not merely the absence of disease or infirmity[3]." [58]. Für diesen Zustand des inneren Gleichgewichts sind neben genetischen Veranlagungen, äußerer Exposition, etc. noch andere Faktoren von zentraler Bedeutung. Soziodemographische Faktoren, wie Bildung, Einkommen oder Lebensform beeinflussen in vielerlei Hinsicht den Werdegang und damit das Leben von Kindern und Jugendlichen. In diesem Kontext ist beispielsweise Armut „gleichbedeutend mit einem Mangel an Verwirklichungschancen und damit dem Ausschluss von einer gleichberechtigten gesellschaftlichen Teilhabe" [59]. Es gibt eine Vielzahl von Untersuchungen die zeigen, dass Kinder aus sozial schwachen Familien neben schlechteren Startchancen im Bildungsweg und schlechterem Gesundheitszustand, auch häufiger ungünstige Verhaltensmuster aufweisen [60, 67]. Dieses Risikoverhalten äußert sich beispielsweise durch überdurchschnittlichen Medienkonsum, unregelmäßige Mahlzeiteneinnahme und frühzeitigen Kontakt zu Suchtmitteln wie Alkohol und Zigaretten [61]. Zudem kommt es bei Kinder aus ressourcenarmen Familien häufiger zu sozialer Ausgrenzung, emotionaler Instabilität [62] und verminderten schulischen Leistungen, welche auf strukturelle Entwicklungsunterschiede in verschiedenen Bereichen des Gehirns zurück zu führen sind [63].

Insgesamt bewerten Kinder und Jugendliche aus sozial benachteiligten Verhältnissen ihre Gesundheit seltener als gut. Sie geben häufiger Unfallverletzungen sowie zahnmedizinische Probleme an [64]. Zudem ist ein niedrigerer sozialer Status bedeutsam für das gehäufte Auftreten psychischer Auffälligkeiten wie Ängste, Störungen im Sozialverhalten, Depressionen [65] sowie ADHS [66]. Wesentliche Einflussfaktoren auf gesundheitsprotektives Verhalten scheinen dabei die Unterstützung und Förderung durch das soziale Umfeld darzustellen [67]. Generell ist die Inanspruchnahme von Präventionsangeboten in höheren sozialen Schichten deutlich stärker ausgeprägt. Gemessen an den U-Untersuchungen (U1-U8) weisen 64% der Kinder aus der niederen sozialen Schicht, verglichen mit 84% der oberen sozialen Schicht, einen vollständigen Untersuchungsstatus auf [67].

[3] „[…] Zustand des vollständigen körperlichen, geistigen und sozialen Wohlergehens und nicht nur das Fehlen von Krankheit oder Gebrechen."

In einer Veröffentlichung der *Organisation für wirtschaftliche Zusammenarbeit und Entwicklung* (OECD) heißt es: „Seit dem Jahr 2000 haben in Deutschland Einkommensungleichheit und Armut stärker zugenommen als in jedem anderen OECD-Land.“ [68]. Unter dieser Ungleichheit und Ungerechtigkeit leiden vor allem Kinder und Jugendliche. Einkommen stellt nicht nur die Möglichkeit der Befriedigung von individuellen Grundbedürfnissen dar, sondern gibt auch die Voraussetzungen zur sozialen Absicherung. Unter anderem prägt das Einkommen einer Familie deren Lebensstandard, Wohnumfeld und Zugang zu gesundheitsfördernden Ressourcen. So leben weniger gut situierte Familien eher in Gegenden mit „stärkerem Verkehrsaufkommen, höherer Lärm- und Luftbelastung sowie in geringerem Umfang vorhandenen Grünflächen und Spielmöglichkeiten“ [67].

Es scheint einen Zusammenhang zwischen soziodemographischen Faktoren und der Adipositas zu geben. Jedoch wird dieser in der Literatur sehr kontrovers diskutiert. So heißt es in einer deutschen Studie von 2008, dass ein geringes Familieneinkommen und ein hoher Grad an Bewegungsmangel positiv mit Übergewicht korreliert sind [69], während andere proklamieren, dass Übergewichtigkeit, Stoffwechselstörungen und damit das Risiko für Typ-2-Diabetes nicht häufiger bei ärmeren Kindern zu finden seien, sondern vielmehr ein Problem aller sozialer Schichten darstellt [70]. Andere Arbeiten unterstützen die Aussage des vernachlässigbaren Einflusses des sozioökonomischen Status auf Risikofaktoren wie Adipositas, Blutdruck, Cholesterin, Triglyceride, LDL-Cholesterol [71] und das daraus resultierende KHK-Risiko [72]. Dennoch gibt es eine Vielzahl von Studien, die sich für diese Beeinflussung aussprechen [73-76]. Auch in der großangelegten deutschen KiGGS-Studie wurde ein wesentlich größerer Anteil adipöser Kinder und Jugendlicher in der sozial niedrigeren Schicht beobachtet [67]. Fakt ist: Übergewichtigkeit, Adipositas und mangelnde Bewegung korrelieren mit einem erhöhten Risiko für die Ausprägung einer kardiovaskulären und/oder metabolischen Erkrankung [77-80].

Durch die hier angebrachten Beispiele wird deutlich, dass ein enger Zusammenhang zwischen sozialer und gesundheitlicher Lage besteht. Soziodemographische Faktoren haben somit nicht nur eine zentrale Bedeutung für das einzelne Individuum, sondern für die gesamte Gesellschaft und stellen ein gesundheitspolitisches Problem dar. Aus diesem Grund zielt die hier vorliegende Arbeit darauf ab, neue Erkenntnisse zum Zusammenhang soziodemographischer Kenngrößen und den Serumkonzentrationen der Lipoproteine bei Kindern und Jugendlichen zu detektieren.

Als soziodemographische Basisgrößen für den sozialen Status wird hierfür der Winkler Index zugrundegelegt. Dieser Index beinhaltet Items zur Schulbildung, beruflichen Qualifikation, beruflichen Stellung und dem Netto-Haushaltseinkommen der Eltern und kann die Werte von 3-21 Punkten annehmen. Anhand des sich ergebenden Indexwertes wird die Schichtzugehörigkeit kategorisiert [81-83]. Als Maß für den familiären Wohlstand wird die Family Affluence Scale verwendet, die Items zum familiären Besitz in Form eines eigenen Autos und einem eigenen Zimmer des Kindes, der Anzahl der Urlaubsreisen in den letzten 12 Monaten und der Anzahl von Computer im Haushalt enthält [84, 85]. Beide soziodemographischen Kenngrößen wurden in der LIFE-Child Studie mittels standardisierter Fragebögen erhoben. Als ein Aspekt der Gesundheit werden im Folgenden die Serumlipide und Apolipoproteine untersucht.

2.5 Die LIFE-Child Studie

Die hier vorgestellten Daten und Ergebnisse stammen aus Untersuchungen von Teilnehmern der LIFE-Child Studie, welche Teil des „Leipziger Forschungszentrums für Zivilisationserkrankungen“ (LIFE) der Universität Leipzig ist und Probanden im Alter von 0 bis 18 Jahren einschließt. Ziel dieses großangelegten, seit 2011 laufenden, Projektes ist die Untersuchung von Wachstums- und Entwicklungsprozessen bei Neugeborenen, Kindern und Jugendlichen sowie die Evaluation des Einflusses von Umweltfaktoren auf oben Genannte [86]. Hierfür werden die anthropometrischen, labordiagnostischen und soziodemographischen Merkmale von Freiwilligen aus dem Leipziger Raum erfasst. Die Rekrutierung dieser erfolgt über niedergelassene Kinderärzte, Flyer in sonstigen Arztpraxen, das Gesundheitsamt, Öffentlichkeitsarbeit und über die Ambulanz des Kinderklinikums der Universität Leipzig. Zudem werden Einladungen an Schulklassen verschickt. Neben den Daten von Kindern und Jugendlichen werden auch ganze Familien rekrutiert. Das hier im konkreten Fall untersuchte Studienkollektiv setzt sich aus Probanden der LIFE-Child Health und der LIFE-Child Obesity Kohorte zusammen.

Für diese Arbeit wurden ausschließlich gesunde Probanden berücksichtigt. Aufgrund ihres longitudinalen Studiendesigns gehen mehrere Messzeitpunkte der einzelnen Studienteilnehmer bzw. der Familien in die Analysen ein.

Die LIFE-Child Studie ist von der Ethikkommission der Universität Leipzig zugelassen (Aktenzeichen: Reg. Nr. 264-10-19042010). Für die Untersuchungen werden die schriftlichen Einverständniserklärungen der Eltern und ab einem Alter von 12 Jahren, zusätzlich von den Kindern selbst, abverlangt.

2.6 Hypothesen, Frage- und Zielstellungen

Durch den oben aufgezeigten Einstieg in die Problematik wird deutlich, dass aktuellen Referenzintervallen der Serumlipide und Apolipoproteinen durchaus eine wichtige Bedeutung in Hinblick auf die Beurteilung des kardiovaskulären Risikoprofils bei Kindern und Jugendliche zukommt. Die Verteilung der Laborparameter wird dabei erheblich von soziodemographischen Einflüssen geprägt. Bisherige Veröffentlichungen zu diesen Schwerpunkten sind entweder mangelhaft oder beruhen auf veralteten diagnostischen und/ oder statistischen Erhebungsmethoden. Daher wurden folgende Fragestellungen und Ziele formuliert:

1. Ermittlung von aktuellen geschlechtsspezifischen Referenzintervallen für Gesamtcholesterin, LDL- und HDL-Cholesterol, Triglyceride sowie Apolipoproteinen A1 und B kontinuierlich über das Alter an einer gesunden bevölkerungsbezogene Kohorte.
2. Graphische Darstellung dieser geschlechtsspezifischen, physiologischen Verläufe der oben genannten Laborparameter anhand von Perzentilenkurven.
3. Ermittlung der Prävalenz von Dyslipidämien und Vergleich mit internationalen Referenzen.
4. Besteht ein statistisch signifikanter Zusammenhang zwischen den Serumlipiden bzw. Apolipoproteinen und dem sozialen Status, gemessen am Winkler Index, bei Kindern und Jugendlichen?
5. Besteht ein statistisch signifikanter Zusammenhang zwischen den Serumlipiden bzw. Apolipoproteinen und dem familiären Wohlstand, gemessen an der Family Affluence Scale, bei Kindern und Jugendlichen?
6. Sind diese statistisch signifikanten Zusammenhänge geschlechts- oder altersabhängig?

3 PUBLIKATIONEN

Pediatric reference data of serum lipids and prevalence of dyslipidemia: results from a population-based cohort in Germany

Anne Dathan-Stumpf, Mandy Vogel, Andreas Hiemisch, Joachim Thiery, Ralph Burkhardt, Jürgen Kratzsch, Wieland Kiess

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Serum lipid levels were related to socio-demographic characteristics in a German population-based child cohort. Serum lipid levels and social class

Anne Dathan-Stumpf, Mandy Vogel, Kristin Rieger, Joachim Thiery, Andreas Hiemisch, Wieland Kiess

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Pediatric reference data of serum lipids and prevalence of dyslipidemia: Results from a population-based cohort in Germany

Anne Dathan-Stumpf [a,b,c], Mandy Vogel [a,c], Andreas Hiemisch [a,b,c], Joachim Thiery [a,d], Ralph Burkhardt [a,d], Jürgen Kratzsch [a,d], Wieland Kiess [a,b,c,*]

[a] Leipzig University, LIFE-Child-Leipzig Research Center for Civilization Diseases, 04103 Leipzig, Germany
[b] Hospital for Children and Adolescents, University of Leipzig, 04103 Leipzig, Germany
[c] Centre of Paediatric Research (CPL), Leipzig University, 04103 Leipzig, Germany
[d] Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Leipzig University, 04103 Leipzig, Germany

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ABSTRACT

Background: Serum lipid concentrations are thought to be risk factors for the development of cardiovascular disease. The present study aims to investigate the prevalence of dyslipidemia and provide sex- and age-related reference values for triglycerides, total cholesterol, LDL and HDL cholesterol as well as apolipoproteins A1 and B by using modern analytical approaches.

Materials and methods: Venous blood and anthropometric data were collected from 2571 subjects of the LIFE Child study, aged between 0.5 and 16 years. Age- and gender-related reference intervals (3rd and 97th percentiles) were established by using Cole's LMS method.

Results: Serum concentrations of TC, LDL-C, TG and ApoB were higher in girls than in boys. In girls TC reached peak levels two years earlier than in boys. Triglyceride levels initially declined until the school age. Until early adolescence there was a steady increase. The LDL-C concentrations in girls and boys followed similar patterns to that of TC. Up to the age of 8 years, a continuous increase in HDL levels for both sexes was found. Due to the strong correlation between HDL-C and ApoA1 ($r = 0.87$) or rather between LDL-C and ApoB ($r = 0.93$), the respective percentiles showed very similar patterns. Dyslipidemia prevalence were as follows: increased TC 7.8%, increased LDL 6.1%, increased TG 0–9 years 22.1%, increased TG 10–16 years 11.7%, and decreased HDL 8.0%.

Conclusion: Age- and sex-related trends for all parameters are similar to those of the German KIGGS study. With the exception of HDL cholesterol, the prevalence of dyslipidemias in the German LIFE Child cohort are similar to the US-American prevalence.

1. Introduction

There are a lot of studies showing that overweight and obesity correlate with an increased risk for the occurrence of cardiovascular and/or metabolic disease [1]. Unfortunately, some of these mechanisms in children have not been fully understood until now. Heart and circulatory diseases are manifested after the fourth decade of life, whereas the formation of atherosclerosis starts at a distinctly earlier age [2]. The serum lipids are seen as crucial risk factors for the formation of the atherosclerotic disease in later life [3]. Obese children exhibit significantly increased values for TG, TC, LDL, VLDL, and ApoB compared to patients with normal weight [4]. In addition, a significant correlation between the cholesteryl ester transfer protein (CETP) and pediatric obesity could be established [4]. Normal weight children have in general higher HDL cholesterol levels than obese ones. The concentration of HDL decreases in prepubertal children with progressive weight gain and developmental stage [5]. Moreover, there is a positive relationship between the particle size of LDL and triglycerides. TG are negatively associated with the particle size of HDL [6]. Children with hypercholesterolemia have increased oxidized LDL subfractions and higher concentrations in several inflammatory factors such as tumor necrosis factor related molecules like TNF α. Inflammatory processes are thought to play a role in the development of atherosclerosis [7]. In addition to the clinical laboratory assays of classical serum lipids, there are recommendations to measure apolipoproteins (APO's) [8]. Concentrations of proteins provide additional information about a potential dyslipidemia. Thus, an increased concentration of ApoB, despite normal values of total cholesterol and LDL, is associated with obesity, metabolic syndrome or diabetes, type 2 [8]. The ApoB/ApoA1 ratio is correlated with an increased arterial stiffness in patients with metabolic syndrome, measured by pulse wave

* Corresponding author at: Hospital for Children and Adolescents, University of Leipzig, Liebigstraße 20a, 04103 Leipzig, Germany.
E-mail addresses: anne_dathan@web.de (A. Dathan-Stumpf), mandy.vogel@life.uni-leipzig.de (M. Vogel), andreas.hiemisch@medizin.uni-leipzig.de (A. Hiemisch), mb-sek-ilm@medizin.uni-leipzig.de (J. Thiery), ralph.burkhardt@medizin.uni-leipzig.de (R. Burkhardt), juergen.kratzsch@medizin.uni-leipzig.de (J. Kratzsch), wieland.kiess@medizin.uni-leipzig.de (W. Kiess).

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velocity [9]. The discussion illustrates the central importance of reference values in general and of their clinical interpretation. Age- and gender-related references represent the basis for clinically diagnostic and therapeutic decisions particularly in pediatrics. In recent years, there have been national [10] and international [11] efforts to create expedient reference values for serum lipids. Unfortunately, the apolipoproteins A1 and B were largely excluded. The present study aims to update reference ranges for TG, TC, LDL and HDL cholesterol using modern and current laboratory methods and to determine reference intervals for apolipoproteins A1 and B.

2. Study population and design

The LIFE-Child cohort is a longitudinal study, initiated in July 2011, of the Leipzig Medical Faculty, Department for Child and Adolescent Medicine. The aim of this project is to collect data on growth and development of subjects during the time between birth and adolescence as well as on environmental health determinants [12]. The population, recruited for this study consisted of 2571 children and adolescents of the LIFE-Child Health cohort and the LIFE-Child Obesity cohort aged between 0 and 16 years, in the time between 2011 and August, 2015. A representative cohort for the population of the city of Leipzig and Caucasian/German population was created by the inclusion of the Obesity cohort. There were 1345 boys and 1226 girls included in this analysis. Probands who were treated with lipid-lowering medication were intended to be excluded. However, none of the subjects fulfilled this criterion. Only healthy subject were included: children with diseases such as diabetes mellitus, inherited metabolic diseases, chromosomal aberrations and chronic kidney and liver disease as well as children with acute illnesses such as bronchitis or otitis media were excluded.

In order to avoid a violation of the independence criteria in the statistical analysis, 75% of families were selected and from these in turn a measured value was used. A weighting procedure was carried out depending on the family size and the number of measured values. So every measurement was drawn with equal probability. For the sample thus obtained reference values were determined. This procedure was repeated 1000 times to determine the average estimated values and their confidence limits. This procedure allows the inclusion of all existing measurement data [13]. Fig. 1 shows the composition of the reference population. Fig. 2 illustrates the age and sex composition of the reference population, with the example of ApoB. To underline the relevance of the newly created reference values for clinical practice, the prevalence of dyslipidemia in the LIFE-Child cohort, as a representative example of Germany, was determined. Therefore, the cut-off values of the S2k guideline [30], which are consistent with the American cut-off values [31], have been taken as a basis.

The study was approved by the Ethical Committee of the University of Leipzig (reference number: Reg. No. 264-10-19042010). LIFE-Child is registered by the trial number: NCT02550236. Participants aged 12 years or older actively consent to every examination, while parents always have to give their written consent in advance.

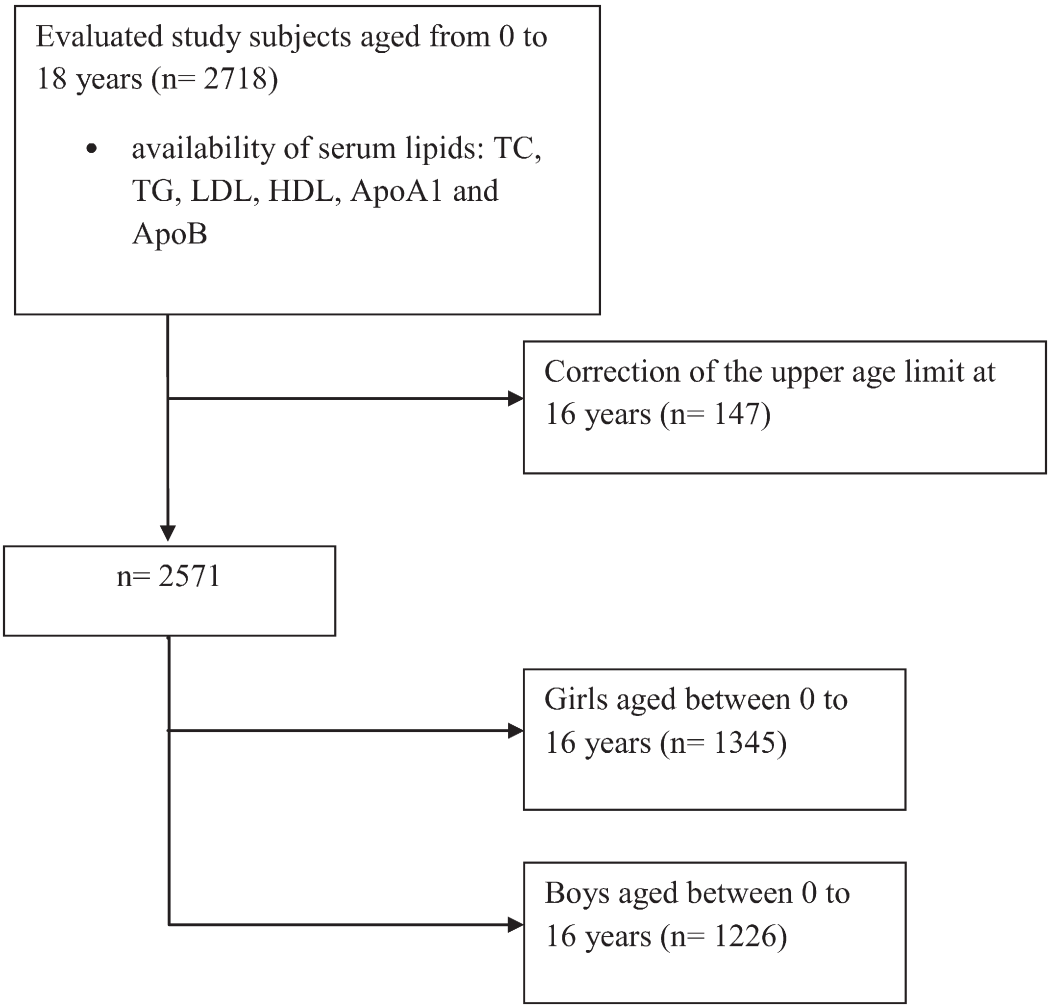

Fig. 1. Composition of the reference population from the LIFE-Child cohort. The flowchart contains information about excluded subjects.

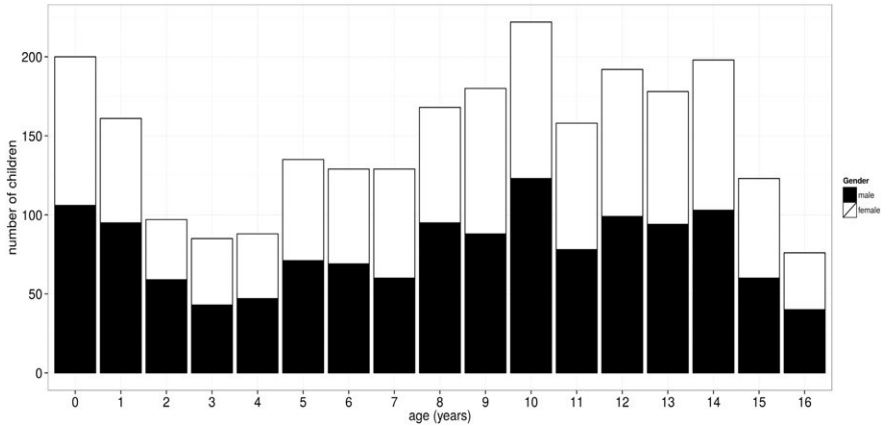

Fig. 2. Histogram for age and sex distribution of the reference population from the LIFE-Child cohort (total: n = 2571, males: n = 1345, females: n = 1226).

3. Lipid measurements

Venous blood was taken from the fasting subjects of the LIFE study. It was documented if adequate fasting times were not observed. The measurement of laboratory parameters was carried out at the Institute for Laboratory Medicine of the University Hospital. The measurement of serum lipids was performed on a 'Cobas 8000 Clinical Chemistry Analyzer' with test kits of the company Roche Diagnostics GmbH. The determination of the total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides was performed using a validated specific homozygous enzymatic color test. ApoA1 and ApoB were determined by an immunological turbidity testing. A conversion of the KiGGS values [mg/dl] to mmol/l was performed by factor 0.026 in TC, LDL and HDL cholesterol for the comparative charts (Figs. 4–6).

4. Questionnaires

Standardized questionnaires for fasting state as well as for sociodemographic factors in families were used as previously described [12].

5. Statistical analysis

The distributions of all laboratory parameters were modeled continuously dependent on age and stratified by gender. Data wrangling and analyses were carried out using R [14]. No outliers were eliminated. Plausibility for all values was tested and ascertained. Age-dependent distributions and resulting reference intervals were estimated using an LMS-type method [15], using the respective methods provided by the gamlss package [16,17]. To avoid violations against the independence assumption a resampling method on the entire sample was applied and the parameters were reestimated 1000 times and results in final estimates and respective confidence intervals [13]. The 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles were demonstrated (Figs. 3–8). The corresponding tables for reference values of all serum lipids (Tables 1–6) and the tables for lambda, mu and sigma (Tables 7–12) are shown in the Supplements section. The model quality was checked using Wormplots [18] by the wp function of the "gamlss" package. The 95%-confidence intervals were calculated as pointwise envelopes simply by calculating the quantiles of the replicates at each point (Tables 1–6). To determine the correlation of two laboratory parameters, a linear regression analysis was performed. To identify the prevalence of mixed dyslipidemia Flat Contingency Tables were created.

6. Results

Tables 1–6 summarize the reference intervals for the serum lipids dependent on gender and age. In addition, the smoothened percentiles (Fig. 3–8) were presented for girls and boys. All in all, 2571 measured values per parameter were evaluated. Due to relatively low numbers of subjects in each of the age groups the upper age limit was reduced from 18 to 16 years.

Initially, the measured values of total cholesterol showed a similar course for both sexes. First, the values increased continuously to finally reach a plateau, only the values of the 90th and 97th percentiles of the girls were an exception. Until entering school age they showed a steady decrease. Based on the median, the girls reached this plateau aged about 8 years, the boys two years later. Compared to the boys, girls reported significantly higher cholesterol values already in early childhood ($p < 0.01$). With progressing age the levels of the males approach those of the females. After reaching the plateau, a gender specific course was observed. While the values of the boys fell continuously, the serum concentrations of the girls were only subject to minor fluctuations. From the 50th percentile onward there was a rise in the curves of the 14-year-old girls, so the values of the 90th and 97th percentiles recorded the maximum at 16 years. Table 1 summarizes the gender references. Fig. 3a and b illustrate the corresponding percentiles.

The course of the low density lipoproteins (LDL) of the boys was very similar to that of the total cholesterol. Based on the median, serum concentrations remained constant from age 7 for almost 5 years and fell slightly afterwards. In the range of the 3rd and 10th percentiles this trend was less pronounced. Apart from the period between 10 and 15 years, girls had significantly higher serum concentrations than boys ($p < 0.01$). This difference was mainly observed in babyhood to infancy. In the upper percentiles the values fell up to the age of 13 years in girls. Initially the concentrations of the 3rd and 10th percentiles recorded slight increases. After age 9 downward trends were documented. Subsequently, the other curves showed only small fluctuations in the serum concentrations. Table 2 as well as Fig. 4a and b abstract this behavior.

The data of high density lipoproteins (HDL) showed higher concentrations in boys than in girls at the age of 2 to 12.5 years ($p < 0.01$). Up to the age of 8 years continuous increases in HDL levels could be determined for both sexes with the particularity of the fall of values in the 90th and 97th percentiles up to the age of 1.5 years in girls. At the age of 9 a stronger gender distribution was shown. While the values of boys, especially in the upper percentiles, reached a plateau and fell continuously afterwards, the curves of the females ran wavy with increasing upward trends from the age of about 14 years. The generated reference values for age and sex are shown in Table 3. Fig. 5a and b illustrate the progression of the percentiles.

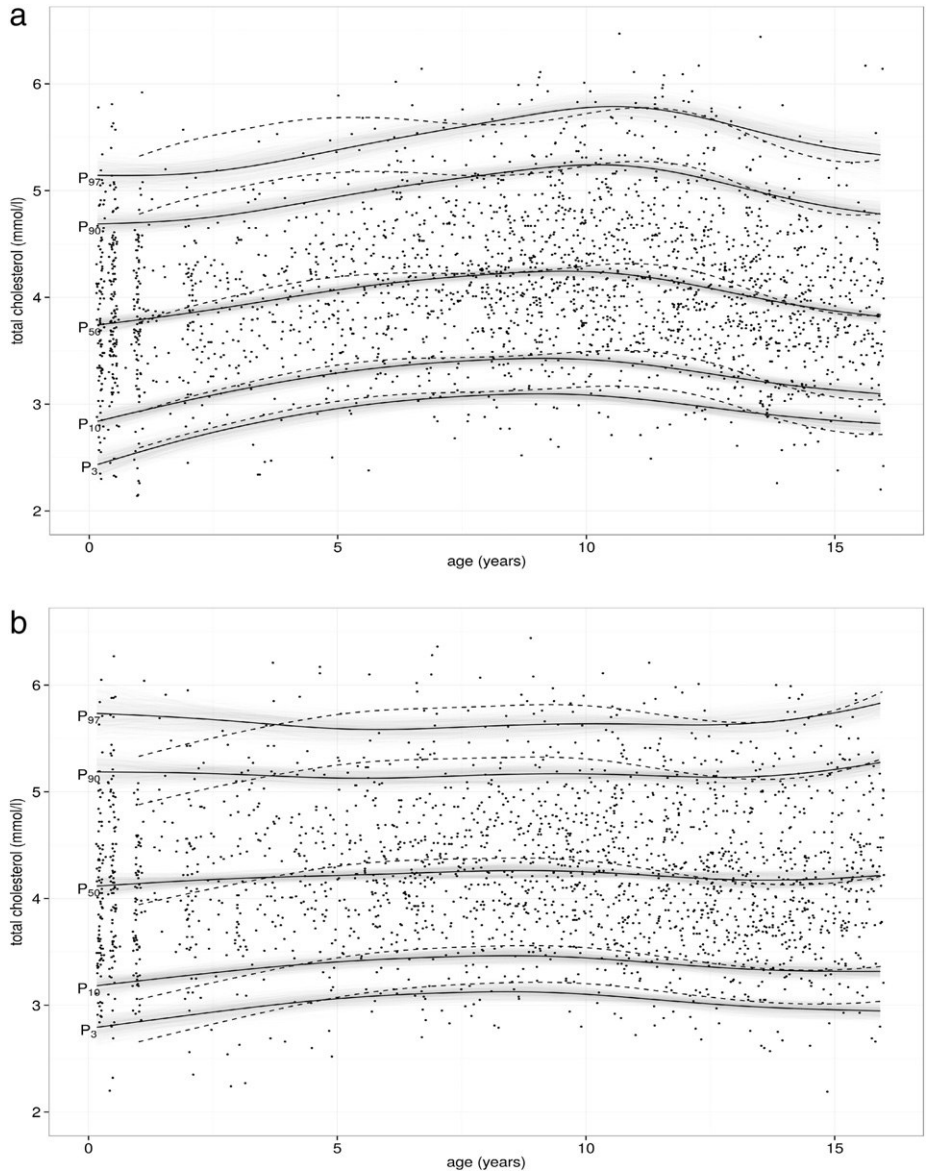

Fig. 3. Smoothed percentile curves for total cholesterol (mmol/l) in a) males/b) females over the age (0 to 16 years) based on the reference population of the LIFE-Child Cohort (total: n = 2504, males: $n_{pers} = 1311$, $n_{meas} = 2478$; females: $n_{pers} = 1193$, $n_{meas} = 2251$). Shown are the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles. The dashed lines show the comparative values of the KiGGS study.

The profiles of the triglycerides developed equally for both sexes, only the serum concentrations in girls were significantly higher ($p < 0.05$). First, a sharp drop of the values could be observed up to the age of 6 and 6.5 years. This reduction was much less pronounced in the lower percentiles (P3, P10). Following, these curves showed a constant course with a minimal upward trend with increasing age. After the sharp drop in the values, a steady increase was recorded for both sexes, and the maximum was observed at 12.5 years. Afterwards the triglyceride levels fell slightly. The examined reference values of the TG are summarized in Table 4. Fig. 6a and b illustrate the corresponding percentiles.

From the 50th percentile the serum concentrations of ApoA1 in 6 to 12-year-old boys were significantly higher compared to those of the female subjects ($p < 0.05$). In both sexes the concentrations fell down until the age of 2 years. Thereafter, the values increased concurrently until the age of 10. While the serum concentrations of the boys remained constant from the age of 13, the values of the girls rose again. Table 5 and Fig. 7a and b sum up this behavior.

With increasing age a slightly decreasing trend in the concentrations for apolipoprotein B was observed, which was most clearly seen in the first 5 years of life. Negligible increases in the 3rd and 10th percentiles were detected for both sexes up to the age of 3 years. Above the 50th percentile, changes were hardly visible in girls from the age of about 14 years. Serum concentrations of apolipoprotein B were higher in girls than in boys ($p_{0-10\ years} < 0.01$), except for the lower limits from 12.5 years. The corresponding percentiles are shown in Fig. 8a and b. Table 6 exhibits their schedular summary. Similarly to adulthood, a strong correlation between LDL cholesterol and apolipoprotein B ($r = 0.93$) as well as HDL cholesterol and ApoA1 ($r = 0.87$) was shown.

In addition, the prevalence of dyslipidemia in the LIFE-Child cohort in Leipzig was regarded as a representative example of Germany and was compared with the US-American prevalence (Table 13). As evidence of the existence of familial hypercholesterolemia, LDL cholesterol >4.9 mmol/l was used [32]. Six children had such high LDL concentrations. With 22.1% the presence of a pure hypertriglyceridemia

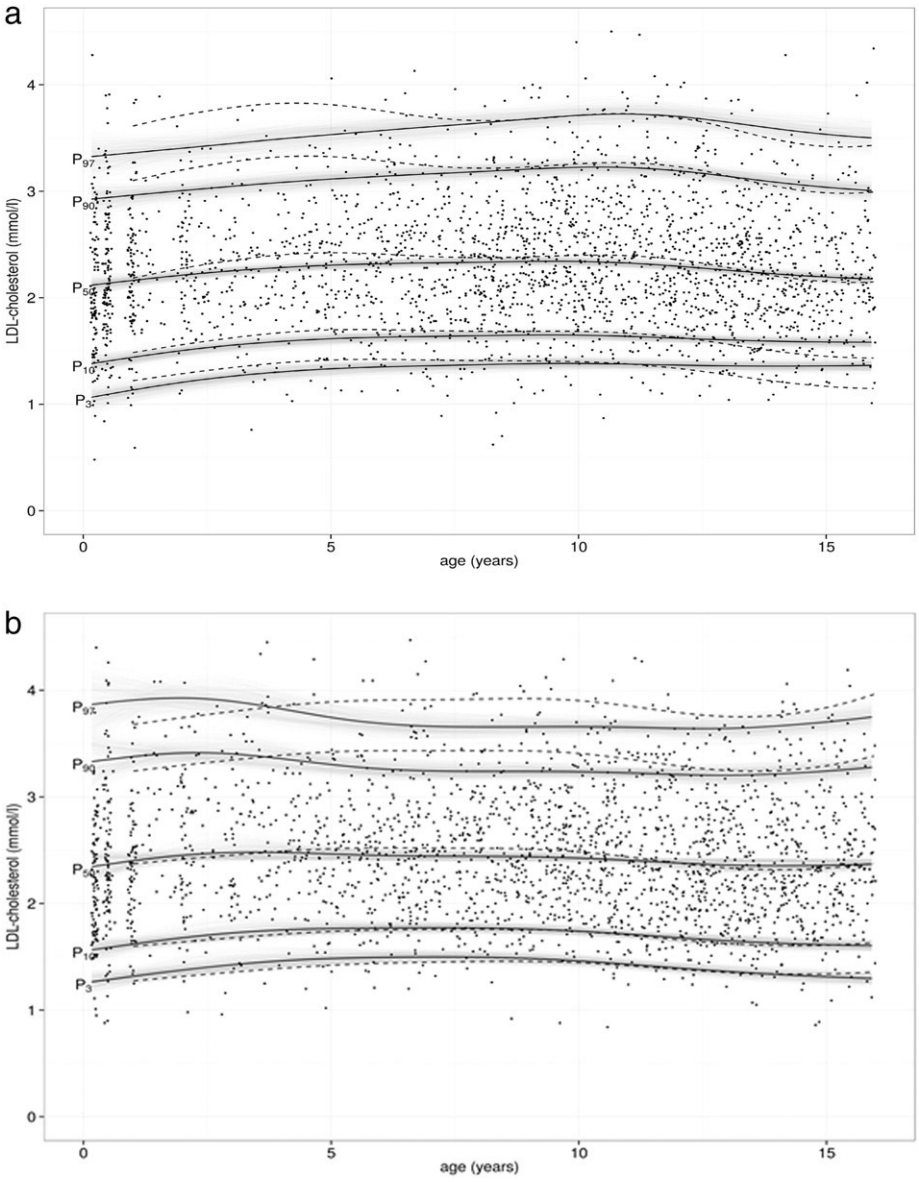

Fig. 4. Smoothed percentile curves for LDL cholesterol (mmol/l) in a) males/b) females over the age (0 to 16 years) based on the reference population of the LIFE-Child Cohort (total: n = 2503, n_{pers} = 1311, n_{meas} = 2478; females: n_{pers} = 1192, n_{meas} = 2249). Shown are the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles. The dashed lines show the comparative values of the KiGGS study.

(TG > 1.1 mmol/l) in children between 0 and 9 years was recorded most frequently.

7. Discussion

It was documented by the investigators if adequate fasting times were not observed, but it must be added that in children younger than seven years sobriety cannot be assumed. Values presented for this age group do not lose their validity, because also in clinical practice sobriety cannot be guaranteed in very young children. However, for children from the age of 5 to 6 years families have stated that the recommendation of fasting was adhered to. Nevertheless, this fact is only important for triglycerides. A relevant influence on the other serum lipids is not assumed. In the present study LDL cholesterol was directly determined and not calculated using the Friedewald formula, which allowed to avoid the influence of fasting periods and thus of falsely high calculated LDL levels.

Obese children and adolescents have an increased risk for the occurrence of cardiovascular disease [1]. De Koning et al. show that anthropometric parameters such as waist circumference or BMI are associated with an adverse lipid profile in the pediatric population [36]. In our study overweight and obesity are classified using the 90th and 97th body mass index (BMI) percentile cut-offs of Kromeyer–Hauschild [12]. By the purposeful inclusion of the OBESITY cohort in this investigation, a population representative of the city of Leipzig was created. The prevalence of obesity in the LIFE-Child cohort is equal to the prevalence of obesity in the German population (KiGGS) and the city of Leipzig [37].

When interpreting serum lipids and apolipoproteins in childhood and adolescence, important aspects, such as gender-based courses and greater concentration fluctuations, compared to adulthood, are taken into account. Generally, in healthy children up to 18 years increased concentrations of lipids can be expected, particularly during the first 3 years of life and at the end of puberty [29]. Based on these test results the age and gender distributions of serum lipids show similar tendencies to those described in previous studies. Possible variations of values are due to differences in the composition and size of the reference population, the laboratory analytical methods or the statistical approaches to determine the reference values. The method used in this study for

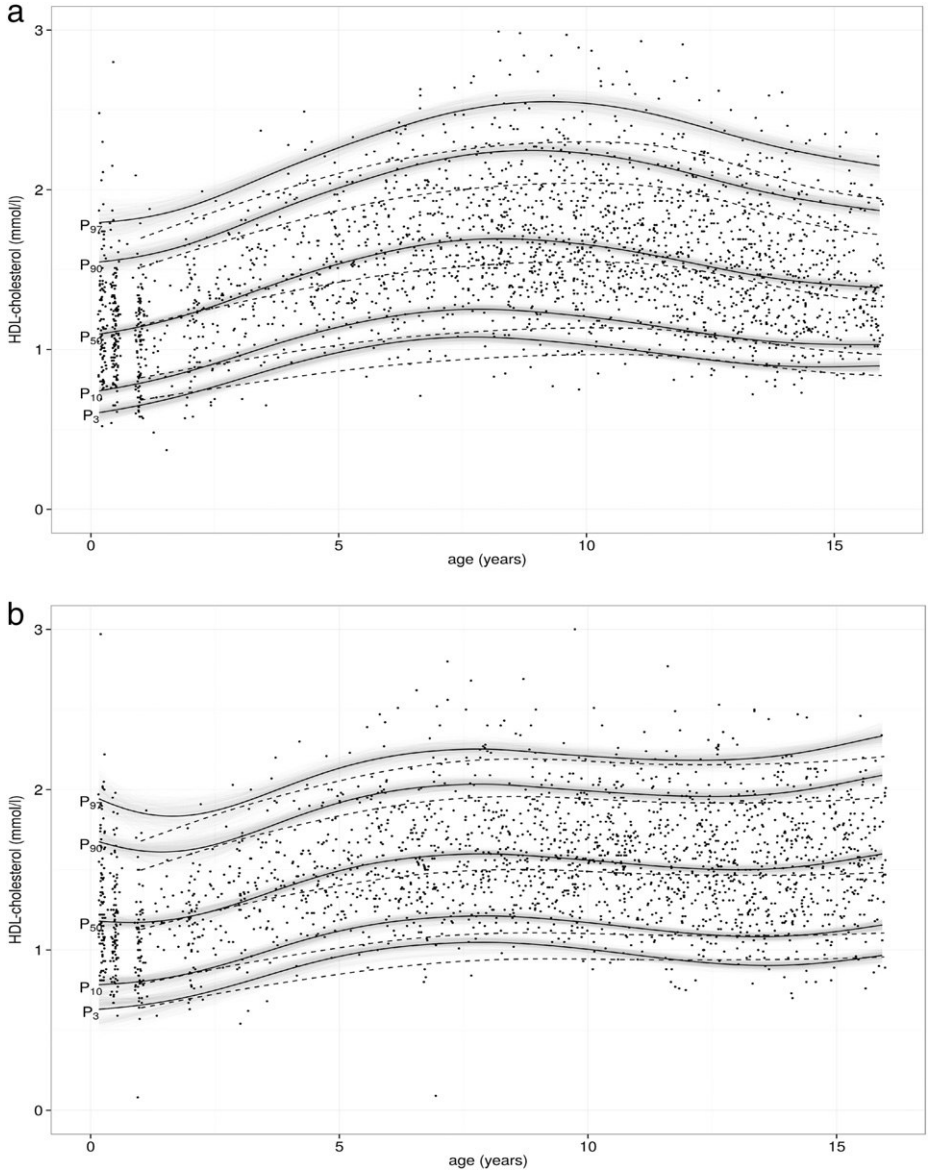

Fig. 5. Smoothed percentile curves for HDL cholesterol (mmol/l) in a) males/b) females over the age (0 to 16 years) based on the reference population of the LIFE-Child Cohort (total: n = 2504, n_{pers} = 1311, n_{meas} = 2478; females: n_{pers} = 1193, n_{meas} = 2251). Shown are the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles. The dashed lines show the comparative values of the KiGGS study.

collecting the reference values continuously – rather than for artificially created age groups – was only practiced in records of the KiGGS study [10]. According to a recommendation of the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) and NCCLS the minimum of a reference population should include 120 subjects in each age group, providing that analyzed values are distributed symmetrically [19]. These required sizes could not be realized in different age groups. The guideline EP28-A3 of the CLSI (Clinical and Laboratory Standards Institute) noted that quite lower numbers can be tolerated in special subject collectives, like here in pediatrics [20,21]. In this study, the statistical approach does not necessarily require the minimum of 120 subjects for any age group: since the complete data set was smoothed by statistical progressive fitting of the percentiles. Therefore, for preparation of the reference values of serum lipids, age groups were not necessary. Rather, a distribution over the corrected age was created.

The measured reference values in total cholesterol are well in agreement with results of other studies [22–24]. In relation to KiGGS, which provides a good equivalent regarding location, time frame and use of statistical method of calculation by Cole, good matches of reference intervals are largely shown in age and gender [10]. With the exception of the values in the 97th percentile in girls up to the age of 3.5 years, the serum concentrations collected in the LIFE-Child study are lower. We determined peak deviation of 0.3 mmol/l at the age of 1.5 years. In the 90th and 97th percentiles in boys we observed a maximum deviation of 0.4 mmol/l up to the age of approximately 8 years.

At a glance, the percentile curves for LDL cholesterol in KiGGS already show greater fluctuations in developing of values [10]. In KiGGS the curves of boys describe an additional peak at about 4 years. Overall, the collected values of the Robert Koch Institute were slightly higher up to the age of 13.5 years. In the 97th percentile, smaller values of 0.3 mmol/l were recorded in LIFE in the range of the first peak. In infancy, the curves of LDL levels in girls exceed those of KiGGS. From the 50th percentile differences of up to 0.3 mmol/l can be detected in this age. In the range of the lower percentiles, the measurement results conform to KiGGS values. Compared to a study published in Washington in 2003, the values of LIFE-Child are considerably higher for both sexes. This difference is pronounced much more among girls [25]. However, the French LDL-reference data are still higher than ours [26].

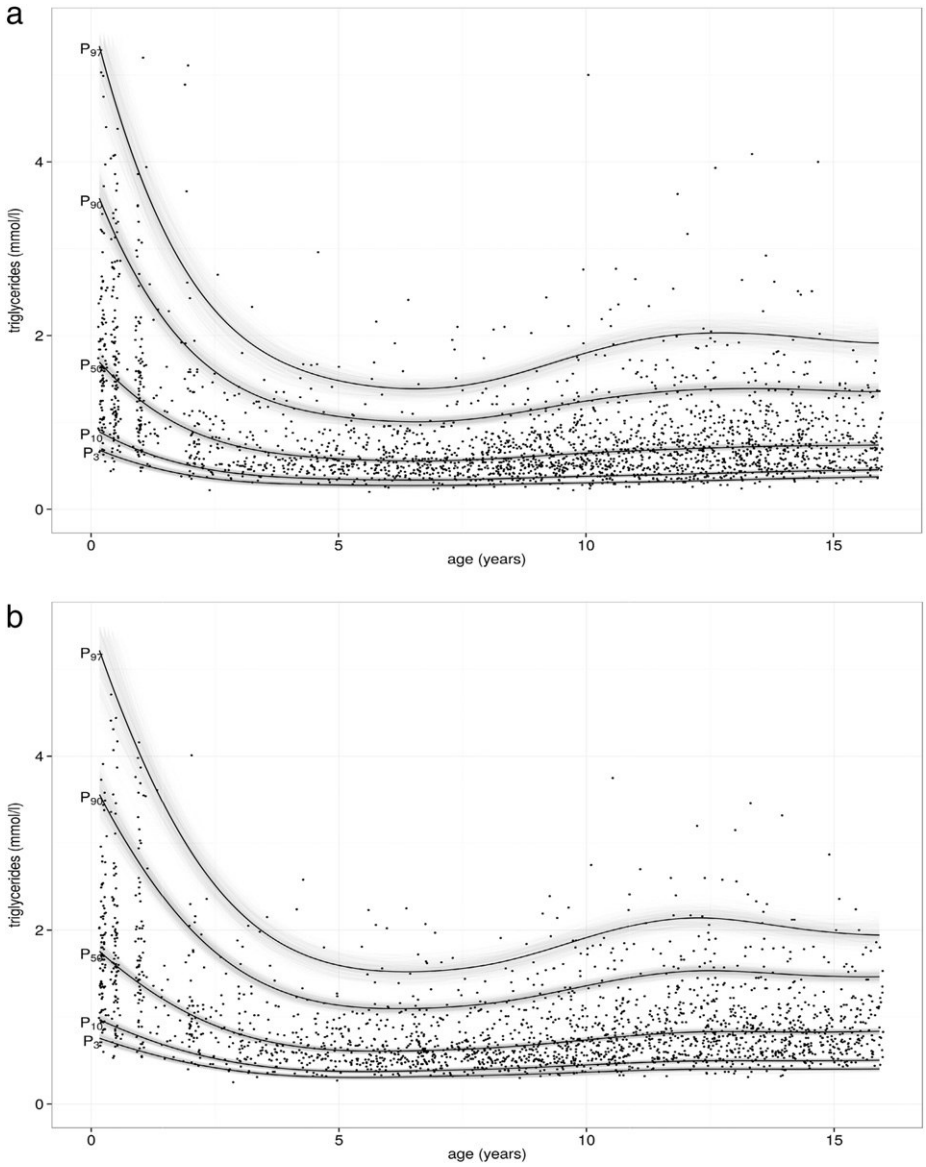

Fig. 6. Smoothed percentile curves for triglycerides (mmol/l) in a) males/b) females over the age (0 to 16 years) based on the reference population of the LIFE-Child Cohort (total: n = 2504, n_{pers} = 1311, n_{meas} = 2478; females: n_{pers} = 1193, n_{meas} = 2251). Shown are the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles.

Comparing the trends of the HDL levels of the two German studies, no large deviations can be observed [10]. Only our readings were higher in both sexes. Especially in the 90th and 97th percentiles of boys maximum deviations of 0.3 mmol/l are detected. In addition, the high points of the percentiles in LIFE will be achieved earlier. Compared to international results, the HDL levels in our project measured higher to some 0.4 mmol/l [23]. These differences are particularly clear in the range of the upper reference intervals [24]. To illustrate the described comparisons between KiGGS and the LIFE-Child study visually, graphics (Figs. 4–6) have been created, and they show the respective 3rd, 10th, 50th, 90th and 97th percentiles of both sexes. The values of the KiGGS study are shown in dashed lines.

Subsequently, we refer to international references because the following serum lipids are not discussed in KiGGS. In juxtaposition to a study from Saudi Arabia, which included only children from 6 years, boys in LIFE aged 9–13 years exhibit higher serum concentrations of triglycerides (TG). In 8- to 9-year-old girls the values are below those of the Arab comparative study. In early adolescence differences to 0.3 mmol/l are indicated for both sexes [23]. Compared to the French population higher TG values can be noticed from the 90th percentile in boys and girls [26]. The database of the Canadian Laboratory Initiative on Pediatric Reference Interval (CALIPER) is a major project that is repeatedly referred to in literature [27]. Therein, the published reference intervals for TG are not listed by gender, but the intervals are much more generous in scope than in LIFE-Child. In a pilot study of CALIPER, which also carried out the laboratory analyses using a Roche Cobas system the reference data are 0.7 mmol/l higher in children >1 year than those in our project [28].

In recent years, the apolipoproteins have become increasingly important [8,9]. In the pubescence the established values for ApoA1 in Leipzig confirm the results of CALIPER [27]. For boys and girls in the younger age the Canadian reference intervals are defined less up to 0.2 g/l. This perception is consistent with other studies [24,28]. The collected reference intervals for ApoB are similar to values of the Canadian Laboratory Initiative [27]. Comparatively, in other studies smaller serum concentrations were measured [24,28].

In order to make a diagnosis of familial hypercholesterolemia, the following criteria must be fulfilled: positive family history of hypercholesterolemia and premature coronary artery disease or proof of xanthomas [31]. Due to lack of anamnestic data, pathologically elevated LDL values >4.9 mmol/l in these 6 children are only seen as an indication of the presence of familial hypercholesterolemia. In literature, the

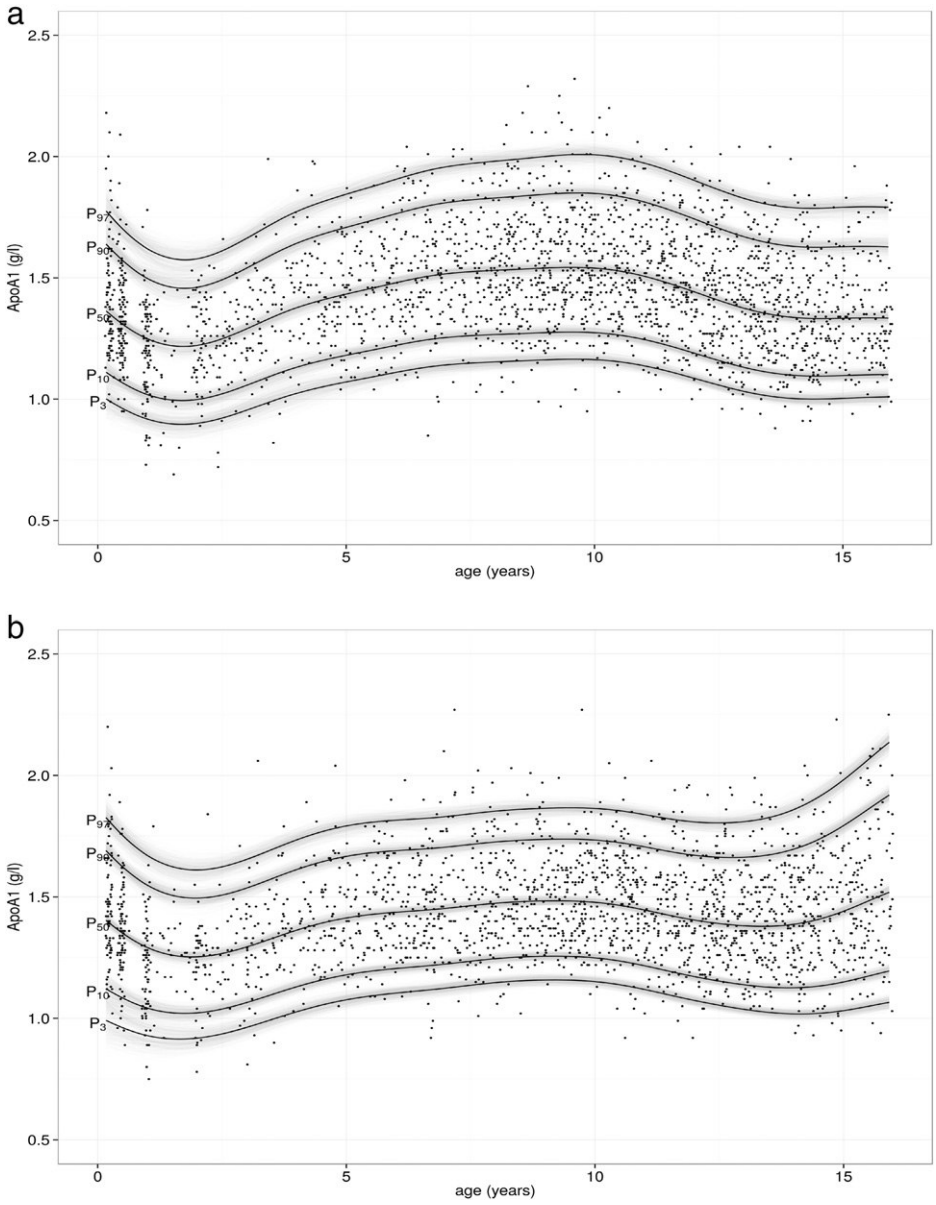

Fig. 7. Smoothed percentile curves for ApoA1 (g/l) in a) males/b) females over the age (0 to 16 years) based on the reference population of the LIFE-Child Cohort (total: n = 2569, n_{pers} = 1345, n_{meas} = 2546; females: n_{pers} = 1224, n_{meas} = 2327). Shown are the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles.

prevalence of familial hypercholesterolemia is reported at least 1:500 (=0.2%) [31]. This information coincides with our result.

In other sources higher prevalence of up to 1:137 are referred [32, 33]. Comparing the prevalence of dyslipidemias between Leipzig and the United States, according to data from the NHANES [30], similar percentage frequencies were found (Table 13). The prevalence at LIFE-Child were lower by less than 1% than the American comparative values. Only the frequency of HDL cholesterol <1 mmol/l was found 5–7% lower than that in the US. In comparison to China the prevalence in Leipzig was continuously higher by 2–3% for each dyslipidemia [34]. The most frequently represented pure hypertriglyceridemia (TG > 1.1 mmol/l) in children between 0 and 9 years should be evaluated critically, because most of the children in the age range of 0–6 years were often not sober due to lack of practicality. The composition of the reference population of this study represents a distortion that stands out, especially compared to the social distribution in the city of Leipzig [35]. As it turned out, children from socially disadvantaged families were generally underrepresented in the LIFE-Child study, possibly due to a less pronounced health awareness. In comparison to well-off peers, these children show unfavorable distributions of serum lipids and their concentrations, and, therefore, they might run a higher risk of developing cardiovascular disease [35]. Consequently, it can be assumed that the prevalence of non-hereditary dyslipidemias in the population is greater as determined in this study.

8. Conclusion

By these investigations, current reference values for total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, ApoA1 and ApoB in children and young people were established, defined by modern analytical and statistical methods. In relation to previous (German) studies, data were completed and presented more specific about the age by means of a new methodological approach. With the exception of HDL cholesterol values <1 mmol/l, the prevalence of dyslipidemia in Leipzig, representative of Germany, showed similar distributions as in the US. This study corroborates age, gender and puberty-related courses of the parameters and underlines the need for current reference intervals.

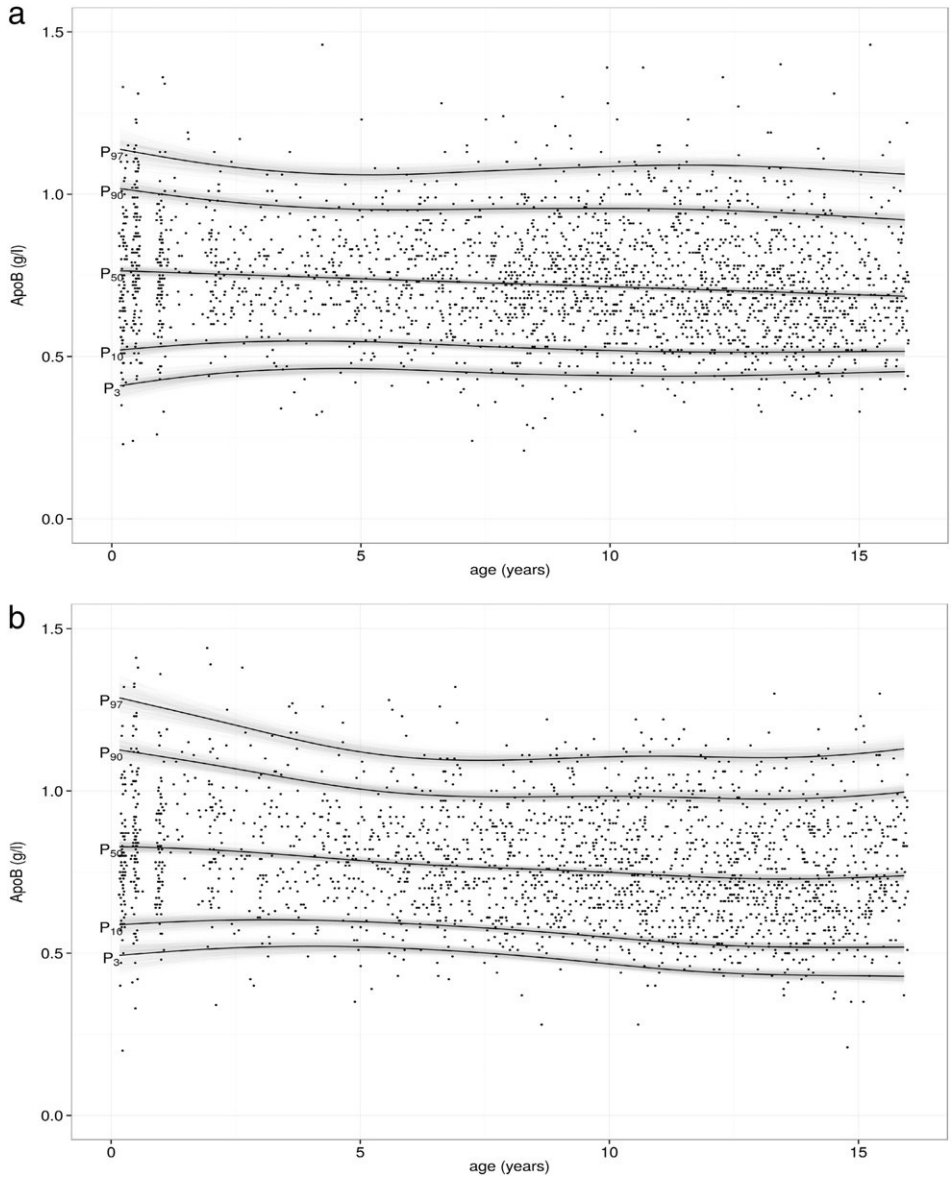

Fig. 8. Smoothed percentile curves for ApoB (g/l) in a) males/b) females over the age (0 to 16 years) based on the reference population of the LIFE-Child Cohort (total: n = 2571, n_{pers} = 1345, n_{meas} = 2546; females: n_{pers} = 1226, n_{meas} = 2329). Shown are the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles.

Table 13
Prevalence of dyslipidemia and familial hypercholesterolemia (LDL cholesterol >4.9 mmol/l) in the LIFE-Child cohort (n = 2571), as a representative example of Germany. Compared to the occurrence of dyslipidemia in the US similar prevalence are shown, with the exception of HDL cholesterol.

	Number of children	Prevalence	Prevalence in the US[b]
Total cholesterol >5.2 mmol/l	202	7.8%	8%
LDL cholesterol >3.4 mmol/l	158	6.1%	7%
HDL cholesterol <1 mmol/l	206	8.0%	13–15%
Triglycerides			
Children 0–9 years >1.1 mmol/l	583	22.1%	
Children 10–19 years >1.5 mmol/l	309	11.7%	12%
LDL > 3.4 mmol/l and TG > 1.5 mmol/l	32	1.2%	
LDL > 3.4 mmol/l and TC > 5.2 mmol/l	124	4.8%	
LDL cholesterol >4.9 mmol/l[a]	6	0.23% (1:500)	

[a] One of the criteria of familial hypercholesterolemia.
[b] Prevalence in the United States, according to the data from the National Health and Nutrition Examination Survey (NHANES) [31].

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Disclosure statement

The authors confirm that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.clinbiochem.2016.02.010.

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REGULAR ARTICLE

Serum lipid levels were related to socio-demographic characteristics in a German population-based child cohort

Anne Dathan-Stumpf[1,2,3], Mandy Vogel[1,3], Kristin Rieger[1,2,3], Joachim Thiery[1,4], Andreas Hiemisch[1,2,3], Wieland Kiess (wieland.kiess@medizin.uni-leipzig.de)[1,2,3]

1.LIFE-Child-Leipzig Research Center for Civilization Diseases, Leipzig University, Leipzig, Germany
2.Hospital for Children and Adolescents, University Hospital, Leipzig, Germany
3.Centre of Paediatric Research (CPL), Leipzig University, Leipzig, Germany
4.Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Leipzig University, Leipzig, Germany

Keywords
Family Affluence Scale, LIFE Child study, Serum lipids, Socio-demographics, Winkler index

Correspondence
Wieland Kiess, MD, Hospital for Children and Adolescents, University of Leipzig, Liebigstraße 20a, 04103 Leipzig, Germany.
Tel: 0049-341-9726000 |
Fax: 0049-341-9726009 |
Email: wieland.kiess@medizin.uni-leipzig.de

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ABSTRACT

Aim: Socio-demographic factors affect the development and lives of children and adolescents. We examined links between serum lipids and apolipoproteins and socio-demographic factors in the Leipzig Research Centre for Civilization Diseases Child (LIFE Child) study.

Methods: The Winkler index and the Family Affluence Scale were used to define characteristics of the social status of 938 boys and 860 girls aged from birth to 19 years. We then used univariate and multivariate regression analyses to examine the socio-demographic impact on total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL), cholesterol triglycerides and apolipoproteins A1 (ApoA1) and B (ApoB).

Results: No significant influences on the Winkler index or the Family Affluence Scale were observed regarding the concentrations of serum lipids for total cholesterol or LDL cholesterol. However, and most importantly, children and adolescents with high social status and high family affluence showed significantly higher HDL cholesterol and ApoA1 levels than those with lower individual totals. A higher Winkler index was associated with significantly lower values for triglycerides and ApoB.

Conclusion: Adolescents with higher family wealth and social status showed a lower cardiovascular risk profile, as measured by the concentrations of HDL cholesterol and triglycerides as well as ApoA1 and B.

INTRODUCTION

Socio-demographic factors, such as education, income and lifestyle affect the development and lives of children and adolescents in many ways. Poverty is synonymous with a lack of opportunities for fulfilment and can prevent equal participation in society (1). Various studies have shown that children from socially disadvantaged families had limited resources for education and were more likely to suffer from poorer health and show unfavourable behaviour patterns (2). This risky behaviour was manifested, for example, by above-average media consumption, eating irregular meals and early contact with addictive drugs such as alcohol and cigarettes (3). In addition, children from resource-poor families were often prone to social exclusion, emotional instability (4) and decreased academic performance, all of which were attributed to structural differences in the development of different areas of the brain (5). There also seemed to be an association between socio-demographic factors and obesity, but this has proved to be highly controversial in the literature. A German study stated that a low family income and a high degree of physical inactivity

Abbreviations

ANOVA, Analysis of variance; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; CHD, Coronary heart disease; FAS, Family Affluence Scale; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; LIFE, Leipzig Research Center of Civilization Diseases; SDS, Standard deviation score.

Key notes

- Socio-demographic factors have been shown to affect the development and lives of children and adolescents.
- We examined links between serum lipids and apolipoproteins and socio-demographic factors in 1798 subjects up to 19 years of age in the Leipzig Research Centre for Civilization Diseases Child study.
- Our study showed higher family wealth and social status were associated with a lower cardiovascular risk profile, measured by various laboratory tests.

were positively associated with obesity (6), while another clinical trial demonstrated that obesity, metabolic disorders and, therefore, the risk of type 2 diabetes were not typical of poorer children, but a problem for all social classes (7). Other studies have supported the statement that socioeconomic status has a negligible influence on risk factors such as obesity, blood pressure, cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol (8) and the resulting risk of coronary heart disease (CHD) (9). However, there have also been a lot of studies that have argued that this influence exists (10–13). They claimed that being overweight or obese correlated with an increased risk of cardiovascular and, or, metabolic diseases (14). Heart and circulatory diseases manifested after the fourth decade of life, while the formation of atherosclerosis started at an early age (15). Serum lipids were seen as crucial risk factors in the formation of atherosclerosis (16). There have been no adequate comparative studies that have examined the relationship between serum lipids, or rather apolipoproteins, and the specific socio-demographic characteristics of the Winkler index and the Family Affluence Scale (FAS).

The Leipzig Research Centre for Civilization Diseases Child (LIFE Child)cohort showed that the prevalence of dyslipidaemia in German children and adolescents from birth to 16 years of age was 6–22% (17). Therefore, the aim of this study was to assess the influence of social class and the family's wealth on the concentrations of serum lipids in this population-based cohort in Germany under present living conditions.

METHODS

Study population and design

The LIFE Child study was initiated in 2011 and its aim is to collect data on growth and development of newborn infants, children and adolescents as well as on environmental health determinants (18). The study population, recruited from 2011 until August 2015, consisted of 1798 children and adolescents, aged between birth and 19 years. There were 938 boys and 860 girls included in this analysis. Subjects qualified for this study if their serum lipid measurements were available, together with the socio-demographic findings of the Winkler index and FAS. Probands who were treated with medication due to familial dyslipidaemia would have been excluded, but none of the subjects met this criterion. Only the first examination of each subject was included in the study. To avoid violating the independence criteria, only one child per family was randomly selected. Figure 1 shows the composition of the reference population and Figure 2 illustrates the age and sex composition of the study population. The study was approved by the Ethical Committee of the University of Leipzig (reference number: Reg. No. 264-10-19042010). The LIFE Child study has been registered with the trial number: NCT02550236. Participants aged 12 years or older were required to actively consent to every examination and their parents had to give their written consent in advance.

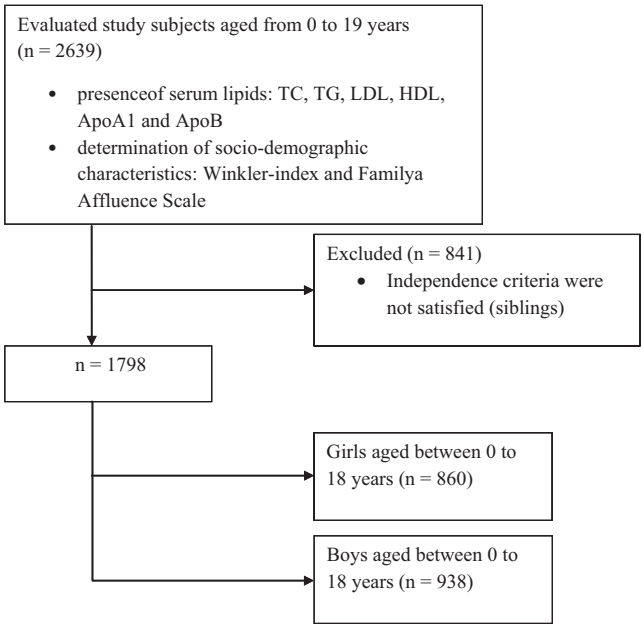

Figure 1 Composition of the study population from the LIFE Child cohort, Leipzig, Germany. The flowchart contains information about excluded subjects.

Measurement of socio-demographic characteristics

The data for socio-demographic factors were collected from the parents using questionnaires. The questionnaire on the Winkler index was answered exclusively by the parents, but the FAS questionnaires were answered by children aged 11 or over if the parents were not present or the parents' information was incomplete. If both the children and the parents completed the questionnaire for FAS, data provided by the parents were given higher priority and subsequently used for the analysis. However, this was only the case for <1% of the answered FAS questionnaires. In addition, the Winkler index could not be determined if the parents were not present but, again, this was only a small minority of cases. The focus of the Winkler questionnaire was education, professional qualifications, occupational status and the net household income per month. The latter was defined by the adjusted Winkler index as the monthly net household income after tax including child or social benefits (19). The multidimensional, aggregated Winkler index was formed by these parameters. This index resulted in values of three to 21 points and was characterised by the sum of the above-mentioned operationalised individual values. The following category values were applied: lower class at three to eight points, middle class at nine to 14 points and upper class at 15–21 points (19,20). In addition, the family wealth or FAS was determined, based on the self-completed questionnaires (21). This scale was considered to be an indirect measure of the socioeconomic status and included the following factors: whether the family owned a car, if the child had their own private room, the number of holidays taken in the last 12 months and the number of computers in the household. The total FAS score ranged

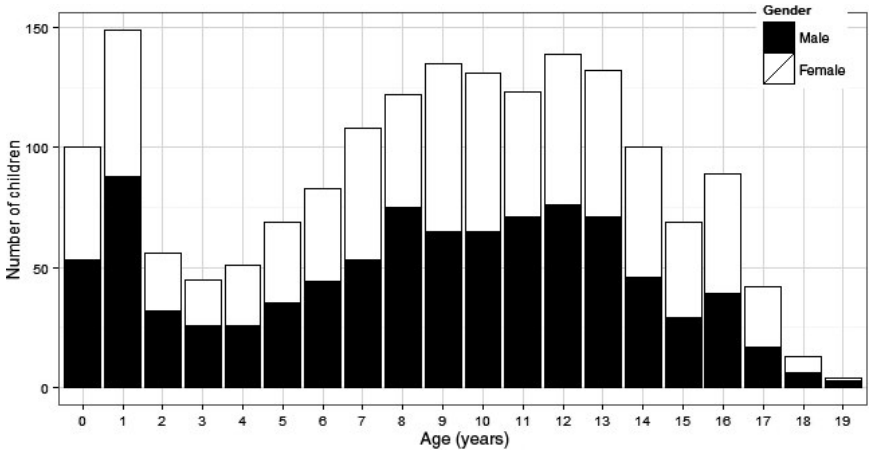

Figure 2 Age and sex distribution of the study population (n = 1798) from the LIFE Child cohort. The cohort comprised 938 males and 860 females.

from zero to seven points and was categorised as follows: low family affluence at zero to three points, average family wealth at four to five points and high family affluence at six to seven points (22). The different number of subjects who completed the Winkler index questionnaire (n = 1760) and the FAS questionnaire (n = 1798) was due to incomplete answers to the socio-demographic questionnaires.

Lipid measurements

Venous blood was taken from the fasting subjects in the LIFE Child study and it was documented if adequate fasting times had not been observed. Total fasting could not be assumed in children younger than seven years, but the values given in this age group did not lose their validity, because total fasting cannot be guaranteed in very young children in clinical practice either. However, this fact was only important for triglycerides and a relevant influence on the other serum lipids was not expected.

The measurement of laboratory parameters was carried out at the Institute for Laboratory Medicine of the University of Leipzig. Serum lipids were measured using a Cobas 8000 Clinical Chemistry Analyzer (Roche Diagnostics GmbH, Berlin, Germany). The total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol and triglycerides were determined using a validated specific homozygous enzymatic colour test. Apolipoproteins A1 (ApoA1) and B (ApoB) were determined by an immunological turbidity test.

Statistical analysis

The preparation and analysis of the data was carried out with the free statistical software R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) (23). The determinations, regression coefficients, confidence intervals and p values for univariate and multivariate regression analyses are presented as dependent variables for the laboratory parameters of serum lipids and apolipoproteins and as predictors for the socio-demographic characteristics, according to the Winkler index and FAS (Table 1). In addition to the age-adapted Z scores for the laboratory parameters, either gender or age (Table 2) was included as a possible third variable. The values of the lower class are given as the mean standard deviation scores (SDS). For middle and upper classes, the differences to the lower class values are stated, including the respective p values. Box-plots were created, showing the differences between the various categories of social status as well as the family wealth for age-adapted Z scores of the serum lipids and apolipoproteins. ANOVA was used to examine whether differences between the various socio-demographic

Table 1 Summary of the results of the regression models for serum lipids (TC, LDL, HDL, TG) and apolipoproteins (ApoA1, ApoB) as dependent variables and Winkler index and FAS as independent variables, based on the reference population of the LIFE Child cohort (n = 1798)

Regression models	B[a]	KI[b]	p[c]
Total cholesterol			
Winkler index	−0.0034	−0.0144; 0.0076	0.549
Family Affluence Scale	0.0258	−0.0082; 0.0597	0.137
HDL cholesterol			
Winkler index	0.0216	0.0102; 0.0329	<0.001*
Family Affluence Scale	0.0569	0.0219; 0.0919	0.0015*
LDL cholesterol			
Winkler index	−0.0093	−0.0202; 0.0016	0.0927
Family Affluence Scale	0.0068	−0.0268; 0.0404	0.691
Triglycerides			
Winkler index	−0.014	−0.0249; −0.0031	0.0118*
Family Affluence Scale	−0.0077	−0.0414; 0.0261	0.657
ApoA1			
Winkler index	0.01706	0.0055; 0.0287	0.0040*
Family Affluence Scale	0.0654	0.0297; 0.1011	<0.001*
ApoB			
Winkler index	−0.0137	−0.0247; −0.0028	0.0136*
Family Affluence Scale	−0.0088	−0.0426; 0.0249	0.607

The results correspond to age-adapted values. Shown are significant models (*) for Winkler index and FAS in HDL cholesterol and ApoA1 and only for Winkler index in triglycerides and ApoB.
[a]Regression coefficient; [b]95% -confidence interval forB; [c]Significance $p < 0.05$.

characteristics existed. Tukey's Honest Significant Difference method was used as a *post-hoc* test.

RESULTS

In this study, 1760 subjects (52% boys and 48% girls) were included in the investigation of social strata and 1798 subjects – 52% boys, 48% girls – in the investigation of family affluence.

Generally, the lower class was under-represented (n = 244, 14%), while the middle class (n = 761, 43%) was the most common, followed closely by the upper class (n = 755, 43%). The distribution according to family wealth showed a similar picture, but there were more families with a high wealth index, (n = 838, 46%). The under-representation was even more pronounced with respect to low family wealth with 229 subjects or 13%. There were 731 subjects (41%) who were classified as having medium family wealth.

No significant influences could be observed on total cholesterol levels by the Winkler index (p = 0.549) or the FAS (p = 0.137). Regression coefficients, confidence intervals and p values are given in Table 1 for all serum lipids and apolipoproteins. When we integrated age, as a possible third variable, into the regression analysis, no significant effect could be demonstrated on total cholesterol. Therefore, these results have not been included in Table 2. Children and young people from families with a high Winkler index had significantly higher values for HDL cholesterol than those with lower individual totals (p < 0.001) and there were significant differences between the lower and upper social classes (p = 0.001). A high value on the FAS was associated with significantly higher HDL cholesterol values (p = 0.0015) (Table 1). Again, the significance was restricted to the differences between the lower and upper classes (p = 0.0297). Figure 3 clarifies the differences between the various categories of social class, as well as the family wealth for age-adapted Z scores in HDL cholesterol.

LDL cholesterol showed no statistically significant correlations with respect to the Winkler index (p = 0.0927) or the FAS (p = 0.691) (Table 1). The inclusion of age as a predictor in the regression analysis revealed a growing effect of socioeconomic status on LDL cholesterol concentrations with age. While the SDS values of LDL increased by age in the lower class, we observed a reverse trend in the upper class SDS values. The difference between lower and upper class became statistically significant between the ages of 10 and 15 years. HDL showed decreasing SDS values with increasing age for the lower class and increasing SDS values for the upper class. The difference between the lower and upper classes became statistically significant around five years of age (Table 2). In the case of triglycerides, a

Table 2 Summary of effect sizes by integration of age as a third possible variable in the regression models of serum lipids (HDL, LDL) and apolipoproteins (ApoA1, ApoB) as dependent variables and the Winkler index as the independent variable, based on the reference population of the LIFE Child cohort (n = 1760)

	Age (years)				
	1	5	10	15	18
Effect in HDL-C (mmol/L)					
Lower class	−0.001	−0.1	−0.22	−0.34	−0.41
Middle class	0.15 (p = 0.34)	0.21 (p = 0.06)	0.27 (p < 0.001)*	0.34 (p < 0.001)*	0.38 (p = 0.02)*
Upper class	0.14 (p = 0.37)	0.24 (p = 0.03)*	0.35 (p < 0.001)*	0.47 (p < 0.001)*	0.54 (p = 0.001)*
Effect in LDL-C (mmol/L)					
Lower class	−0.30	−0.14	−0.05	0.25	0.36
Middle class	0.23 (p = 0.14)	0.13 (p = 0.22)	0.0007 (p = 0.99)	−0.13 (p = 0.28)	−0.21 (p = 0.19)
Upper class	0.26 (p = 0.08)	0.1 (p = 0.35)	−0.11 (p = 0.17)	−0.31 (p = 0.009)*	−0.44 (p = 0.007)*
Effect in ApoA1 (g/L)					
Lower class	0.01	−0.09	−0.21	−0.34	−0.41
Middle class	0.16 (p = 0.72)	0.17 (p = 0.13)	0.31 (p < 0.001)*	0.44 (p < 0.001)*	0.53 (p = 0.002)*
Upper class	0.18 (p = 0.64)	0.18 (p = 0.1) *	0.31 (p < 0.001)*	0.44 (p < 0.001)*	0.52 (p = 0.003)*
Effect in ApoB (g/L)					
Lower class	−0.28	−0.09	0.14	0.38	0.52
Middle class	0.21 (p = 0.17)	0.09 (p = 0.37)	−0.006 (p = 0.46)	−0.21 (p = 0.28)	−0.30 (p = 0.06)
Upper class	0.22 (p = 0.15)	0.05 (p = 0.67)	−0.17 (p = 0.03)*	−0.39 (p = 0.007)*	−0.53 (p = 0.001)*

The values of the lower class are given as the mean SDS values. For middle and upper class the differences to the lower class values are stated including the respective p-values. Shown are significant effects (*; significance p < 0.05) on HDL cholesterol, LDL cholesterol, ApoA1 and ApoB.

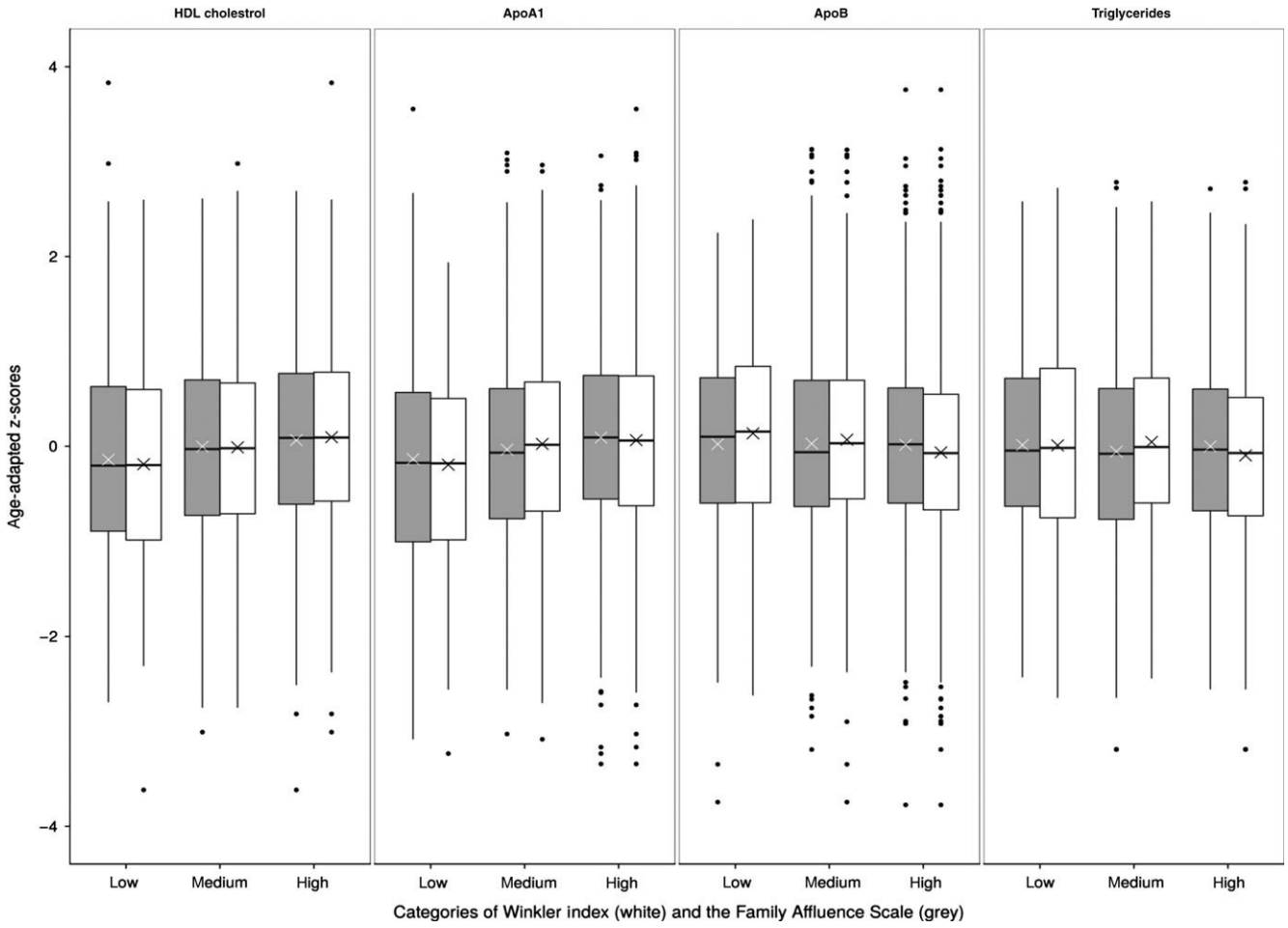

Figure 3 Boxplot to compare the sociodemographic characteristics with respect to the age-adapted z-scores of serum lipids (TC, LDL, HDL, TG) and apolipoproteins (ApoA1, ApoB). White: Representation of the comparison of the three forms of social status: lower class (n = 244), middle class (n = 761) and upper class (n = 755). Grey: Comparison of the three versions of familiar prosperity: low (n = 229), medium (n = 731) and high (n = 838). We have used conventional box-whisker plots. In the box, the dash marks the median (50% quantile), the lower limit of the box is characterized as the first quantile and the upper limit as the third quantile. The criss-cross represents the mean. The maximum length of the strokes up and down is 1.5 times of the interquartile ranges. The outliers are represented as points.

significant inverse relationship could only be detected for the Winkler index ($p = 0.0118$) and not for the FAS ($p = 0.657$) (Table 1). The significant difference between social classes could be identified between middle and upper classes ($p = 0.0172$). Categorical representations of the social status and the family wealth for age-adapted Z scores of the triglycerides can be found in Figure 3. After age was integrated into the regression analysis, no significant effect could be demonstrated with regards to triglycerides. Therefore, these results were not included in Table 2.

The controlled regression models for the Winkler index and ApoA1 were all significant, with the ApoA1 values rising as the Winkler index scores increased ($p = 0.004$). Significant differences between low and high socioeconomic status ($p = 0.006$) and between lower and middle classes ($p = 0.0152$) were found. Greater family wealth was associated with higher ApoA1 values ($p < 0.001$) (Table 1). Again, there were significant differences between low and high family wealth ($p = 0.0269$), as well as middle and high family affluence ($p = 0.0390$). In Figure 3 the differences between the various categories of social status as well as the family wealth for age-adapted Z scores of apolipoprotein A1 are illustrated.

Children and adolescents with a larger Winkler index score had significantly smaller apolipoprotein B levels than those with lower individual totals ($p = 0.0136$), with significant differences observed between the lower and upper classes ($p = 0.0193$) and middle and upper classes ($p = 0.0283$). The inverse dependency of the FAS to ApoB was not significant ($p = 0.607$) (Table 1). The corresponding categorical descriptions are shown in Figure 3. The inclusion of age as a predictor in the regression analysis revealed a growing effect of socioeconomic status on ApoB concentrations with age. Whereas the SDS values of ApoB increased by age in the lower class, the trend was reversed in the upper class SDS values. The difference between the lower and upper classes became statistically significant between five and 10 years of age. However, ApoA1 showed decreasing SDS values with increasing age for the lower class and increasing SDS values for the upper class. The

difference between the lower and upper classes became statistically significant at around five years of age (Table 2).

In general, no significant effect of gender was observed on the results of the regression analyses between serum lipids and social status or family wealth. Therefore, this factor was no longer included in the calculations.

DISCUSSION

Previously published results regarding the relationship between serum lipids and social status or family wealth have been highly controversial. It is difficult to find publications that have examined the association between lipids and, in particular, the Winkler index or the FAS in children and adolescents. The results of this study supported the influence of social factors on health.

In our study, no significant correlations between total cholesterol or LDL cholesterol and social class or family wealth could be detected. However, a study from Brazil, which only included young adults aged 23–25, found that social class had a significant ($p < 0.05$) influence on total cholesterol and LDL and HDL cholesterol: a low socioeconomic status was associated with lower concentrations (24). Thus, total cholesterol and LDL cholesterol represented more cardio-protective factors for individuals of lower social classes. This behaviour could also be observed in our values for children and adolescents, but without demonstrable significance. An investigation from Finland, which provided a good opportunity to compare the results of the LIFE Child study to similar subjects and statistics, such as the age limit, was also unable to prove a significant association between socioeconomic status and LDL cholesterol (10).

In our study, significantly higher HDL concentrations were recorded in children and adolescents with higher social status, meaning that children with lower social status would be exposed to a higher cardiovascular risk (25,26). This behaviour has been confirmed by other studies (12,24). Based on the mean statistics, we recorded effect sizes of 0.13 mmol/L, equivalent to 5.03 mg/dL, among boys and 0.29 mmol/L (11.21 mg/dL) in girls in the upper class compared to the lower class. Figueiredo et al. (24) listed effect sizes of 0.92 mg/dL in boys and 5.52 mg/dL among girls in the upper class compared to the lower class.

In the previously mentioned Finnish study no relationship between infantile socioeconomic status and triglycerides could be observed (10) and Dwyer et al. (8) came to the same conclusion. On the other hand, our analyses clearly demonstrated that children and young people from the lower social class had significantly higher triglyceride concentrations. This inverse relationship was also reported in the Andhra Pradesh Children and Parents Study (11) and by Gliksman et al. (12). The effect sizes determined for the lower class in our investigations were 0.03 mmol/L for the boys and 0.15 mmol/L for the girls. In comparison, Kinra et al. (11) reported an effect size of 0.1 mmol/L for boys in the lower class compared to the upper class, but did not detect any effect in the girls. Consequently, triglycerides were considered to be cardiovascular risk factors in individuals of lower social class.

Apolipoprotein B was one of the most important predictors for the development of hypercholesterolaemia within a five-year period (27). The LIFE Child study demonstrated that as the Winkler index increased, indicating higher social status, the concentrations of ApoB decreased and this was associated with a lower cardiovascular risk in these individuals. The increased risk of CHD in obesity was mediated, among other things, through increased concentrations of ApoB and decreased ApoA1 (28). The significantly higher ApoA1 concentrations in participants with higher socioeconomic status or higher family wealth underlined the cardio-protective advantages in this social stratum. However, poorer people with good education and access to good nutrition and physical exercise opportunities may have the same health prospects as wealthier people.

It can be assumed that these constituted effects were probably even more pronounced in our study population, because children and adolescents with lower social status were generally under-represented. Comparative studies could not be found for the influence of apolipoproteins or for the association of family wealth with serum lipids, as measured by the FAS.

In general, socio-demographic characteristics are determined by a number of factors, such as nutrition, physical activity, education and occupation, housing conditions, financial resources and social environment. The socio-demographic characteristics of the Winkler index and the FAS used in this study should not be interpreted as the sole explanation for the interaction between serum lipids and socio-demographic characteristics. They just represent a possible approach to answering this question.

The composition of the reference population of this study was distorted in comparison to the social class distribution in the city of Leipzig and one explanation for the under-representation of the lower social stratum was lower health awareness. In terms of monthly net income, the proportion of families with an income of at least €2000 per month was more than twice as high as the corresponding proportion of households in the city of Leipzig (29). It can, therefore, be concluded that children from families with a particularly good income participated in the LIFE Child study. Therefore, it is necessary to develop strategies that recruit under-represented, lower social classes and integrate them into the concept of LIFE Child, to be able to generate greater data on children from lower social class families. However, our cohort was indeed representative of the situation in the affluent city of Leipzig: children and young people from the LIFE Child Health cohort and the LIFE Child Obesity cohort were included in this investigation. The prevalence of obesity and of low income and lower education families in this entire LIFE Child cohort was comparable to the prevalence of obesity and social disparities in the German population, as measured by Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS) (30). We hypothesised that the effect of social class would

actually be underestimated if the data were compared with data from poorer countries.

CONCLUSION

This study illustrated the importance of socio-demographic factors in health development, especially for cardiovascular risk, of children and adolescents. Children and adolescents with higher family wealth and social status showed a lower cardiovascular risk profile, measured by the concentrations of HDL cholesterol and triglycerides, as well as apolipoproteins A1 and B. It can be concluded that these children had better health prospects. Therefore, action needs to be taken to minimise social differences and thus counteract the development of subsequent risk factors. This preventive approach should be implemented through joint policy initiatives by various institutions related to, and responsible for, health, family issues and education.

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CONFLICTS OF INTEREST

The authors confirm that there are no conflicts of interest.

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4 ZUSAMMENFASSUNG DER ARBEIT

Dissertation zur Erlangung des akademischen Grades Dr. med.

Pädiatrische Referenzintervalle und Zusammenhänge soziodemographischer Kenngrößen zu Serumkonzentrationen von Lipoproteinen

eingereicht von: Anne Dathan-Stumpf

angefertigt an der Universität Leipzig / Klinik und Poliklinik für Kinder und Jugendliche der Universität Leipzig in Zusammenarbeit mit LIFE-Child / Leipziger Forschungszentrum für Zivilisationserkrankungen (LIFE)

betreut von Prof. Dr. med. Wieland Kiess
Mandy Vogel

Eingereicht 07/ 2016

Da die Erhebung von Referenzintervallen abhängig ist von der zugrunde gelegten Population sowie der laboranalytischen und statistischen Methode, empfiehlt die IFCC die Ermittlung dieser unter Verwendung sich weiterentwickelnder, modernisierter Verfahren. Hiermit stehen aktuelle alters- und geschlechtsabhängige Referenzintervalle und Perzentilenkurven für Gesamtcholesterol, Triglyceriden, LDL- und HDL-Cholesterol sowie ApoA1 und ApoB für Kinder und Jugendliche, basierend auf heutigen modernen analytischen und statistischen Methoden, zur Verfügung. Die Erstellung der Referenzwerte erfolgte hierbei kontinuierlich über das Alter (in Jahren), das heißt, eine Einteilung in willkürliche Altersgruppen wurde vermieden, wodurch eine präzisere Darstelllung der physiologischen Verläufe der Laborparameter gegeben war. Zu diesem Zweck wurde die LMS-Methode nach Cole verwendet, welche in das „gamlss“-Paket der Statistiksoftware R eingearbeitet ist. Die Methode ermöglicht die Vermeidung zufälliger Schwankungen in den Perzentilen, wobei die Daten einem Glättungsverfahren unterzogen werden. Durch die kombinierte Verwendung einer angepassten Resampling-Technik konnten neben mehreren Probanden einer Familie

auch „Follow up“-Messungen berücksichtigt werden, ohne das sich daraus eine Verletzung der Unabhängigkeitskriterien ergab. Die LMS-Methode nach Cole wurden ebenfalls in der groß angelegten KiGGS-Studie, in der Referenzintervalle für Gesamtcholesterin, HDL- und LDL-Cholesterol erstellte wurden und die damit eine gute Vergleichsstudie darstellt, verwendet, ist aber generell ein bislang in der Labormedizin eher selten angewandtes Verfahren. Die Bestimmung der Konzentrationen der Laborparameter erfolgte nach den aktuellen analytischen Standards des Zentrallabors. Die Ermittlung der Referenzwerte sowie der Perzentilenverläufe für die Apolipoproteine A1 und B nach dem oben geschilderten Vorgehen stellt eine komplette Neuerung dar. Auf Grundlage der hier ermittelten Untersuchungsergebnisse konnten die in bisherigen Studien beschriebenen alters- und geschlechtsspezifischen Verteilungen der Serumlipide zum Großteil bestätigt und ergänzt werden. Mögliche Abweichungen sind, wie eingangs erläutert, auf Unterschiede in der Zusammensetzung und Größe der Referenzpopulation, dem laboranalytischen Vorgehen oder den statistischen Berechnungsmethoden zurückzuführen. Generell decken sich die Angaben der Prävalenz von Dyslipidämien in der LIFE-Child Studie mit den amerikanischen Daten. Da in unserer Studie jedoch gut situierte Kinder und Jugendliche, bei denen Dyslipidämien statistisch seltener vorkommen, überrepräsentiert waren, lässt sich vermuten, dass die Prävalenz von Fettstoffwechselstörungen in der Leipziger Bevölkerung sogar noch höher liegt.

Sowohl für Gesamtcholesterin als auch für LDL-Cholesterol konnte kein signifikanter Zusammenhang zum Winkler Index bzw. der Family Affluence Scale beobachtet werden. Kinder und Jugendliche mit hohem Sozialstatus bzw. hohem familiären Wohlstand wiesen signifikant höhere HDL-Cholesterol und ApoA1-Konzentrationen auf als jene mit niedrigeren Einzelsummen. Zudem war ein höherer Winkler Index mit signifikant niedrigeren Konzentrationen für Triglyceride und ApoB assoziiert. Generell konnte kein signifikanter Einfluss des Geschlechts in den Regressionsanalysen zwischen Serumlipiden und sozialem Status bzw. familiärem Wohlstand beobachtet werden. Allerdings zeigte sich, dass das Alter, als mögliche dritte unabhängige Variable, durchaus einen Einfluss auf die Entwicklung der Serumkonzentrationen von LDL- und HDL-Cholesterol, ApoA1 und ApoB und den sozialen Status nimmt.

Gemessen an den Konzentrationen für HDL-Cholesterol und Triglyceride sowie für die Apolipoproteine A1 und B, weisen Kinder und Jugendliche mit höherem familiärem Wohlstand und Sozialstatus ein niedrigeres kardiovaskuläres Risikoprofil auf und verfügen somit über größere Gesundheitschancen. Auch hier lässt sich vermuten, dass die Effekte in der Bevölkerung noch viel stärker ausgeprägt sind als hier kalkuliert, aufgrund der Überrepräsentierung wohl situierter Probanden.

Die in dieser Arbeit herangezogenen soziodemographischen Charakteristika des Winkler Index und der Family Affluence Scale dürfen nicht als einziges Erklärungskonzept der Wechselwirkung zwischen Serumlipiden und soziodemographische Kenngrößen gedeutet werden. Vielmehr stellen sie eine mögliche Herangehensweise an die hier diskutierte Problematik dar und sollen verdeutlichen, welchen vielfältigen Einflüssen die Serumlipide und Apolipoproteine schon im Kindesalter unterlegen sind. Die Arbeit liefert neue Erkenntnisse und Ergänzungen von Einflüssen auf die kardiovaskuläre Gesundheit von Kindern und Jugendlichen und wird damit dem Ziel der LIFE-Child Studie gerecht. Alle eingangs gesetzten Ziele konnte realisiert und alle Fragen beantwortet werden.

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II ANHANG

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Pediatric reference data of serum lipids and prevalence of dyslipidemia: results from a population-based cohort in Germany

Anne Dathan-Stumpf, Mandy Vogel, Andreas Hiemisch, Joachim Thiery, Ralph Burkhardt, Jürgen Kratzsch, Wieland Kiess

12 Tabellen

[1] veröffentlicht nur in der Onlineversion

Tab. 1 Reference values for total cholesterol (mmol/l) by age (0 to 16 years) and gender, based on the reference population of the LIFE-Child cohort (n= 2504). The table shows the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th percentile (P97) as well as their 95% - confidence intervals (*KI*). The values correspond to interpolated calculations at the exact time.

	males (n=1311)														
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	2.48	*2.32*	*2.61*	2.88	*2.80*	*3.00*	3.76	*3.68*	*3.84*	4.69	*4.54*	*4.80*	5.14	*4.98*	*5.37*
1	2.55	*2.41*	*2.66*	2.93	*2.86*	*3.04*	3.79	*3.72*	*3.86*	4.70	*4.57*	*4.80*	5.14	*5.00*	*5.34*
1.5	2.62	*2.48*	*2.72*	2.99	*2.92*	*3.08*	3.82	*3.76*	*3.88*	4.71	*4.59*	*4.80*	5.15	*5.01*	*5.34*
2	2.68	*2.54*	*2.77*	3.04	*2.97*	*3.13*	3.85	*3.79*	*3.91*	4.73	*4.61*	*4.81*	5.16	*5.02*	*5.35*
2.5	2.74	*2.60*	*2.83*	3.09	*3.02*	*3.18*	3.89	*3.82*	*3.95*	4.75	*4.63*	*4.84*	5.18	*5.05*	*5.37*
3	2.79	*2.65*	*2.88*	3.13	*3.06*	*3.23*	3.92	*3.85*	*3.98*	4.78	*4.65*	*4.87*	5.21	*5.07*	*5.39*
3.5	2.84	*2.70*	*2.94*	3.18	*3.10*	*3.28*	3.96	*3.89*	*4.02*	4.82	*4.69*	*4.91*	5.25	*5.10*	*5.43*
4	2.88	*2.75*	*2.98*	3.22	*3.15*	*3.32*	4.00	*3.93*	*4.06*	4.86	*4.72*	*4.95*	5.29	*5.14*	*5.47*
4.5	2.92	*2.80*	*3.02*	3.26	*3.19*	*3.35*	4.04	*3.97*	*4.10*	4.90	*4.77*	*4.99*	5.34	*5.18*	*5.52*
5	2.96	*2.84*	*3.05*	3.29	*3.22*	*3.39*	4.07	*4.01*	*4.13*	4.94	*4.82*	*5.03*	5.38	*5.22*	*5.56*
5.5	2.99	*2.87*	*3.08*	3.32	*3.26*	*3.41*	4.10	*4.04*	*4.17*	4.98	*4.86*	*5.07*	5.43	*5.28*	*5.61*
6	3.02	*2.91*	*3.10*	3.35	*3.29*	*3.43*	4.13	*4.07*	*4.19*	5.02	*4.90*	*5.10*	5.47	*5.33*	*5.65*
6.5	3.04	*2.93*	*3.12*	3.37	*3.32*	*3.45*	4.16	*4.09*	*4.22*	5.06	*4.94*	*5.13*	5.52	*5.38*	*5.69*
7	3.06	*2.95*	*3.14*	3.39	*3.34*	*3.47*	4.18	*4.12*	*4.23*	5.09	*4.98*	*5.16*	5.56	*5.43*	*5.73*
7.5	3.07	*2.97*	*3.15*	3.40	*3.35*	*3.49*	4.20	*4.14*	*4.25*	5.12	*5.01*	*5.20*	5.60	*5.48*	*5.76*
8	3.09	*2.99*	*3.16*	3.42	*3.37*	*3.49*	4.21	*4.16*	*4.27*	5.15	*5.04*	*5.23*	5.64	*5.52*	*5.79*
8.5	3.09	*3.00*	*3.17*	3.42	*3.38*	*3.50*	4.23	*4.18*	*4.28*	5.18	*5.08*	*5.25*	5.68	*5.56*	*5.84*
9	3.10	*3.01*	*3.17*	3.43	*3.38*	*3.51*	4.24	*4.19*	*4.30*	5.21	*5.10*	*5.28*	5.72	*5.60*	*5.88*
9.5	3.09	*3.01*	*3.17*	3.43	*3.37*	*3.51*	4.24	*4.19*	*4.31*	5.23	*5.12*	*5.31*	5.75	*5.64*	*5.93*
10	3.09	*3.00*	*3.16*	3.42	*3.36*	*3.50*	4.24	*4.18*	*4.32*	5.24	*5.13*	*5.33*	5.78	*5.66*	*5.95*
10.5	3.07	*2.98*	*3.15*	3.40	*3.35*	*3.49*	4.23	*4.17*	*4.31*	5.24	*5.13*	*5.33*	5.79	*5.66*	*5.97*
11	3.05	*2.96*	*3.12*	3.38	*3.33*	*3.46*	4.20	*4.14*	*4.28*	5.22	*5.11*	*5.31*	5.78	*5.66*	*5.97*
11.5	3.03	*2.94*	*3.10*	3.35	*3.30*	*3.43*	4.17	*4.11*	*4.24*	5.19	*5.08*	*5.28*	5.76	*5.63*	*5.94*
12	3.00	*2.92*	*3.07*	3.32	*3.27*	*3.39*	4.13	*4.07*	*4.19*	5.15	*5.04*	*5.23*	5.72	*5.59*	*5.90*
12.5	2.97	*2.85*	*3.01*	3.28	*3.20*	*3.32*	4.08	*3.98*	*4.09*	5.10	*4.92*	*5.12*	5.66	*5.46*	*5.79*
13	2.94	*2.82*	*2.98*	3.25	*3.16*	*3.29*	4.04	*3.92*	*4.05*	5.04	*4.85*	*5.07*	5.61	*5.38*	*5.74*
13.5	2.91	*2.79*	*2.96*	3.21	*3.12*	*3.26*	3.99	*3.87*	*4.01*	4.99	*4.79*	*5.02*	5.55	*5.32*	*5.68*
14	2.89	*2.77*	*2.95*	3.18	*3.09*	*3.24*	3.95	*3.83*	*3.97*	4.93	*4.73*	*4.98*	5.49	*5.25*	*5.65*
14.5	2.87	*2.74*	*2.93*	3.16	*3.07*	*3.22*	3.91	*3.80*	*3.94*	4.88	*4.69*	*4.93*	5.44	*5.20*	*5.62*
15	2.85	*2.72*	*2.93*	3.13	*3.04*	*3.21*	3.87	*3.77*	*3.91*	4.84	*4.66*	*4.90*	5.40	*5.16*	*5.60*
15.5	2.83	*2.69*	*2.92*	3.11	*3.02*	*3.20*	3.84	*3.75*	*3.89*	4.81	*4.61*	*4.89*	5.36	*5.12*	*5.61*
16	2.82	*2.67*	*2.92*	3.09	*2.99*	*3.19*	3.82	*3.71*	*3.88*	4.78	*4.57*	*4.88*	5.33	*5.08*	*5.61*

	females (n=1193)											
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	2.81	*2.67*	*2.97*	3.20	*3.10*	*3.30*	4.13	*4.02*	*4.23*	5.19	*5.04*	*5.36*	5.73	*5.50*	*5.98*
1	2.84	*2.71*	*2.99*	3.23	*3.13*	*3.32*	4.14	*4.05*	*4.23*	5.18	*5.05*	*5.33*	5.72	*5.52*	*5.94*
1.5	2.88	*2.75*	*3.01*	3.25	*3.17*	*3.34*	4.15	*4.08*	*4.23*	5.18	*5.07*	*5.30*	5.71	*5.53*	*5.90*
2	2.91	*2.78*	*3.03*	3.28	*3.20*	*3.36*	4.17	*4.10*	*4.23*	5.18	*5.07*	*5.28*	5.69	*5.53*	*5.86*
2.5	2.94	*2.80*	*3.06*	3.30	*3.23*	*3.39*	4.18	*4.12*	*4.24*	5.17	*5.06*	*5.27*	5.68	*5.52*	*5.84*
3	2.96	*2.84*	*3.08*	3.33	*3.25*	*3.42*	4.19	*4.13*	*4.25*	5.16	*5.06*	*5.25*	5.66	*5.50*	*5.83*
3.5	2.99	*2.87*	*3.10*	3.35	*3.28*	*3.44*	4.20	*4.14*	*4.26*	5.15	*5.05*	*5.24*	5.64	*5.48*	*5.81*
4	3.02	*2.89*	*3.13*	3.37	*3.30*	*3.46*	4.20	*4.15*	*4.27*	5.14	*5.04*	*5.23*	5.62	*5.47*	*5.80*
4.5	3.04	*2.92*	*3.15*	3.39	*3.32*	*3.48*	4.21	*4.16*	*4.27*	5.13	*5.03*	*5.22*	5.60	*5.45*	*5.78*
5	3.06	*2.95*	*3.16*	3.41	*3.34*	*3.49*	4.22	*4.16*	*4.27*	5.13	*5.03*	*5.22*	5.59	*5.44*	*5.77*
5.5	3.08	*2.98*	*3.17*	3.42	*3.35*	*3.50*	4.22	*4.17*	*4.28*	5.13	*5.02*	*5.22*	5.58	*5.44*	*5.76*
6	3.09	*3.00*	*3.18*	3.43	*3.37*	*3.51*	4.23	*4.17*	*4.29*	5.13	*5.03*	*5.22*	5.58	*5.44*	*5.75*
6.5	3.10	*3.02*	*3.19*	3.44	*3.37*	*3.52*	4.24	*4.18*	*4.30*	5.13	*5.04*	*5.22*	5.59	*5.45*	*5.74*
7	3.11	*3.03*	*3.20*	3.45	*3.38*	*3.53*	4.25	*4.18*	*4.31*	5.14	*5.05*	*5.23*	5.60	*5.46*	*5.74*
7.5	3.12	*3.04*	*3.21*	3.46	*3.38*	*3.54*	4.25	*4.19*	*4.32*	5.15	*5.06*	*5.25*	5.61	*5.47*	*5.74*
8	3.13	*3.04*	*3.21*	3.46	*3.38*	*3.54*	4.26	*4.19*	*4.33*	5.16	*5.06*	*5.25*	5.62	*5.48*	*5.75*
8.5	3.13	*3.05*	*3.22*	3.46	*3.38*	*3.54*	4.26	*4.19*	*4.34*	5.16	*5.07*	*5.26*	5.62	*5.49*	*5.75*
9	3.12	*3.05*	*3.22*	3.46	*3.38*	*3.54*	4.26	*4.19*	*4.34*	5.17	*5.08*	*5.27*	5.63	*5.50*	*5.75*
9.5	3.12	*3.04*	*3.21*	3.45	*3.38*	*3.53*	4.26	*4.19*	*4.34*	5.17	*5.09*	*5.28*	5.63	*5.50*	*5.75*
10	3.10	*3.04*	*3.19*	3.44	*3.38*	*3.51*	4.25	*4.19*	*4.32*	5.17	*5.10*	*5.27*	5.64	*5.51*	*5.74*
10.5	3.09	*3.03*	*3.17*	3.43	*3.37*	*3.49*	4.24	*4.19*	*4.30*	5.16	*5.11*	*5.25*	5.64	*5.52*	*5.73*
11	3.07	*3.02*	*3.15*	3.41	*3.36*	*3.46*	4.23	*4.19*	*4.28*	5.16	*5.10*	*5.23*	5.63	*5.52*	*5.72*
11.5	3.05	*3.00*	*3.12*	3.39	*3.34*	*3.43*	4.21	*4.16*	*4.26*	5.15	*5.08*	*5.23*	5.63	*5.51*	*5.72*
12	3.03	*2.98*	*3.11*	3.37	*3.31*	*3.42*	4.20	*4.14*	*4.25*	5.14	*5.05*	*5.24*	5.63	*5.49*	*5.73*
12.5	3.01	*2.95*	*3.10*	3.36	*3.29*	*3.41*	4.18	*4.11*	*4.25*	5.14	*5.03*	*5.25*	5.63	*5.47*	*5.75*
13	3.00	*2.92*	*3.09*	3.34	*3.26*	*3.41*	4.18	*4.09*	*4.26*	5.14	*5.02*	*5.27*	5.63	*5.47*	*5.77*
13.5	2.98	*2.90*	*3.08*	3.33	*3.25*	*3.40*	4.17	*4.08*	*4.26*	5.14	*5.02*	*5.29*	5.65	*5.48*	*5.80*
14	2.97	*2.89*	*3.07*	3.33	*3.24*	*3.39*	4.17	*4.08*	*4.26*	5.16	*5.03*	*5.31*	5.67	*5.50*	*5.83*
14.5	2.96	*2.89*	*3.06*	3.32	*3.24*	*3.39*	4.18	*4.09*	*4.27*	5.18	*5.06*	*5.33*	5.70	*5.53*	*5.86*
15	2.96	*2.88*	*3.06*	3.32	*3.24*	*3.38*	4.19	*4.11*	*4.27*	5.21	*5.10*	*5.34*	5.74	*5.57*	*5.90*
15.5	2.95	*2.87*	*3.05*	3.32	*3.25*	*3.38*	4.20	*4.13*	*4.27*	5.24	*5.14*	*5.37*	5.79	*5.62*	*5.95*
16	2.95	*2.85*	*3.05*	3.32	*3.25*	*3.38*	4.22	*4.15*	*4.28*	5.28	*5.18*	*5.41*	5.84	*5.67*	*6.03*

Tab. 2 Reference values for LDL-cholesterol (mmol/l) by age (0 to 16 years) and gender, based on the reference population of the LIFE-Child cohort (n = 2503). The table shows the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th percentile (P97) as well as their 95% - confidence intervals (*KI*). The values correspond to interpolated calculations at the exact time.

	males (n=1311)														
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	1.09	*0.96*	*1.21*	1.41	*1.34*	*1.51*	2.14	*2.06*	*2.22*	2.94	*2.78*	*3.06*	3.34	*3.18*	*3.57*
1	1.13	*1.00*	*1.23*	1.44	*1.39*	*1.54*	2.16	*2.10*	*2.23*	2.96	*2.83*	*3.05*	3.36	*3.22*	*3.57*
1.5	1.17	*1.05*	*1.25*	1.47	*1.43*	*1.57*	2.19	*2.14*	*2.25*	2.99	*2.87*	*3.06*	3.38	*3.25*	*3.57*
2	1.21	*1.09*	*1.28*	1.50	*1.46*	*1.60*	2.21	*2.16*	*2.27*	3.01	*2.90*	*3.07*	3.40	*3.28*	*3.58*
2.5	1.24	*1.12*	*1.31*	1.53	*1.49*	*1.62*	2.23	*2.19*	*2.29*	3.03	*2.92*	*3.09*	3.43	*3.30*	*3.61*
3	1.26	*1.15*	*1.33*	1.55	*1.51*	*1.65*	2.25	*2.21*	*2.32*	3.05	*2.94*	*3.11*	3.45	*3.32*	*3.63*
3.5	1.29	*1.17*	*1.35*	1.57	*1.53*	*1.67*	2.27	*2.23*	*2.34*	3.07	*2.95*	*3.14*	3.47	*3.34*	*3.66*
4	1.30	*1.19*	*1.37*	1.59	*1.54*	*1.69*	2.28	*2.24*	*2.35*	3.08	*2.97*	*3.16*	3.49	*3.36*	*3.68*
4.5	1.32	*1.21*	*1.39*	1.60	*1.56*	*1.69*	2.30	*2.25*	*2.35*	3.10	*2.98*	*3.17*	3.51	*3.38*	*3.70*
5	1.33	*1.22*	*1.40*	1.61	*1.57*	*1.70*	2.31	*2.26*	*2.36*	3.11	*3.00*	*3.18*	3.53	*3.40*	*3.72*
5.5	1.34	*1.24*	*1.40*	1.62	*1.58*	*1.70*	2.31	*2.27*	*2.37*	3.13	*3.02*	*3.20*	3.55	*3.42*	*3.73*
6	1.35	*1.25*	*1.41*	1.63	*1.59*	*1.71*	2.32	*2.28*	*2.37*	3.14	*3.03*	*3.21*	3.57	*3.45*	*3.74*
6.5	1.36	*1.26*	*1.41*	1.63	*1.59*	*1.71*	2.32	*2.27*	*2.37*	3.15	*3.04*	*3.22*	3.59	*3.46*	*3.76*
7	1.36	*1.27*	*1.42*	1.64	*1.60*	*1.71*	2.33	*2.27*	*2.37*	3.16	*3.04*	*3.23*	3.61	*3.48*	*3.77*
7.5	1.37	*1.27*	*1.42*	1.64	*1.60*	*1.71*	2.33	*2.27*	*2.38*	3.17	*3.06*	*3.24*	3.62	*3.50*	*3.78*
8	1.37	*1.28*	*1.43*	1.64	*1.60*	*1.71*	2.33	*2.28*	*2.38*	3.18	*3.08*	*3.24*	3.64	*3.53*	*3.80*
8.5	1.38	*1.29*	*1.43*	1.65	*1.61*	*1.71*	2.34	*2.29*	*2.38*	3.20	*3.10*	*3.25*	3.66	*3.55*	*3.81*
9	1.38	*1.30*	*1.44*	1.65	*1.61*	*1.72*	2.34	*2.30*	*2.39*	3.21	*3.11*	*3.26*	3.68	*3.58*	*3.83*
9.5	1.38	*1.30*	*1.44*	1.65	*1.61*	*1.72*	2.34	*2.30*	*2.39*	3.22	*3.12*	*3.28*	3.70	*3.60*	*3.85*
10	1.38	*1.31*	*1.44*	1.65	*1.61*	*1.72*	2.34	*2.29*	*2.40*	3.22	*3.13*	*3.30*	3.71	*3.60*	*3.88*
10.5	1.38	*1.31*	*1.44*	1.64	*1.61*	*1.72*	2.33	*2.29*	*2.40*	3.23	*3.13*	*3.31*	3.72	*3.62*	*3.89*
11	1.38	*1.31*	*1.43*	1.64	*1.60*	*1.71*	2.33	*2.28*	*2.40*	3.22	*3.12*	*3.30*	3.73	*3.62*	*3.89*
11.5	1.37	*1.30*	*1.42*	1.63	*1.60*	*1.69*	2.31	*2.27*	*2.38*	3.21	*3.12*	*3.28*	3.72	*3.61*	*3.88*
12	1.37	*1.30*	*1.41*	1.62	*1.59*	*1.68*	2.30	*2.26*	*2.35*	3.19	*3.10*	*3.26*	3.70	*3.59*	*3.86*
12.5	1.36	*1.30*	*1.41*	1.61	*1.58*	*1.66*	2.28	*2.24*	*2.32*	3.17	*3.08*	*3.23*	3.68	*3.56*	*3.83*
13	1.36	*1.30*	*1.41*	1.60	*1.57*	*1.66*	2.26	*2.21*	*2.30*	3.14	*3.05*	*3.21*	3.65	*3.52*	*3.81*
13.5	1.36	*1.30*	*1.41*	1.60	*1.56*	*1.65*	2.24	*2.19*	*2.28*	3.11	*3.01*	*3.18*	3.62	*3.48*	*3.78*
14	1.36	*1.29*	*1.41*	1.59	*1.55*	*1.65*	2.22	*2.16*	*2.27*	3.08	*2.97*	*3.16*	3.59	*3.45*	*3.75*
14.5	1.36	*1.29*	*1.42*	1.59	*1.54*	*1.64*	2.21	*2.15*	*2.26*	3.06	*2.94*	*3.14*	3.56	*3.41*	*3.73*
15	1.36	*1.29*	*1.42*	1.58	*1.54*	*1.65*	2.19	*2.13*	*2.25*	3.04	*2.91*	*3.13*	3.53	*3.38*	*3.72*
15.5	1.36	*1.29*	*1.43*	1.58	*1.53*	*1.65*	2.18	*2.12*	*2.24*	3.02	*2.89*	*3.12*	3.52	*3.35*	*3.71*
16	1.37	*1.29*	*1.44*	1.58	*1.52*	*1.65*	2.18	*2.12*	*2.24*	3.00	*2.87*	*3.11*	3.50	*3.33*	*3.71*

	females (n=1192)														
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	1.29	*1.18*	*1.38*	1.59	*1.50*	*1.67*	2.37	*2.25*	*2.48*	3.35	*3.14*	*3.56*	3.88	*3.63*	*4.20*
1	1.32	*1.23*	*1.40*	1.62	*1.55*	*1.69*	2.40	*2.32*	*2.48*	3.38	*3.22*	*3.53*	3.91	*3.71*	*4.15*
1.5	1.35	*1.26*	*1.43*	1.65	*1.59*	*1.74*	2.43	*2.36*	*2.52*	3.40	*3.28*	*3.51*	3.92	*3.77*	*4.10*
2	1.38	*1.29*	*1.48*	1.68	*1.61*	*1.80*	2.45	*2.38*	*2.59*	3.41	*3.30*	*3.55*	3.93	*3.77*	*4.13*
2.5	1.40	*1.31*	*1.53*	1.70	*1.63*	*1.85*	2.47	*2.40*	*2.63*	3.41	*3.29*	*3.58*	3.92	*3.75*	*4.15*
3	1.43	*1.33*	*1.55*	1.72	*1.65*	*1.86*	2.48	*2.40*	*2.64*	3.40	*3.27*	*3.58*	3.90	*3.73*	*4.13*
3.5	1.45	*1.35*	*1.57*	1.74	*1.66*	*1.87*	2.48	*2.40*	*2.62*	3.38	*3.25*	*3.54*	3.86	*3.70*	*4.08*
4	1.46	*1.37*	*1.57*	1.75	*1.68*	*1.86*	2.48	*2.40*	*2.59*	3.36	*3.23*	*3.49*	3.82	*3.66*	*4.02*
4.5	1.47	*1.39*	*1.57*	1.76	*1.69*	*1.85*	2.47	*2.40*	*2.56*	3.33	*3.21*	*3.45*	3.78	*3.64*	*3.96*
5	1.48	*1.41*	*1.57*	1.76	*1.70*	*1.84*	2.46	*2.40*	*2.54*	3.30	*3.19*	*3.41*	3.75	*3.60*	*3.91*
5.5	1.49	*1.42*	*1.57*	1.77	*1.71*	*1.84*	2.46	*2.40*	*2.52*	3.28	*3.18*	*3.39*	3.71	*3.58*	*3.87*
6	1.49	*1.43*	*1.56*	1.77	*1.71*	*1.83*	2.45	*2.40*	*2.52*	3.26	*3.17*	*3.37*	3.69	*3.56*	*3.84*
6.5	1.50	*1.43*	*1.56*	1.77	*1.71*	*1.83*	2.45	*2.39*	*2.51*	3.25	*3.16*	*3.36*	3.67	*3.55*	*3.81*
7	1.50	*1.44*	*1.56*	1.77	*1.72*	*1.82*	2.44	*2.40*	*2.51*	3.24	*3.17*	*3.34*	3.66	*3.54*	*3.79*
7.5	1.50	*1.44*	*1.57*	1.77	*1.71*	*1.82*	2.44	*2.40*	*2.50*	3.24	*3.17*	*3.33*	3.66	*3.54*	*3.78*
8	1.50	*1.44*	*1.57*	1.77	*1.71*	*1.82*	2.44	*2.40*	*2.50*	3.24	*3.17*	*3.33*	3.66	*3.54*	*3.76*
8.5	1.49	*1.44*	*1.57*	1.77	*1.71*	*1.82*	2.44	*2.39*	*2.50*	3.24	*3.17*	*3.32*	3.66	*3.54*	*3.75*
9	1.48	*1.43*	*1.56*	1.76	*1.71*	*1.81*	2.44	*2.39*	*2.50*	3.24	*3.18*	*3.33*	3.66	*3.54*	*3.75*
9.5	1.47	*1.43*	*1.55*	1.75	*1.70*	*1.80*	2.43	*2.39*	*2.49*	3.24	*3.18*	*3.32*	3.66	*3.54*	*3.76*
10	1.46	*1.42*	*1.54*	1.74	*1.69*	*1.79*	2.43	*2.39*	*2.48*	3.24	*3.18*	*3.32*	3.66	*3.55*	*3.74*
10.5	1.45	*1.41*	*1.52*	1.73	*1.68*	*1.77*	2.42	*2.38*	*2.47*	3.23	*3.18*	*3.31*	3.66	*3.55*	*3.73*
11	1.43	*1.39*	*1.50*	1.71	*1.67*	*1.75*	2.40	*2.36*	*2.45*	3.22	*3.17*	*3.30*	3.65	*3.55*	*3.72*
11.5	1.41	*1.37*	*1.48*	1.70	*1.65*	*1.73*	2.39	*2.34*	*2.43*	3.22	*3.15*	*3.30*	3.65	*3.54*	*3.72*
12	1.39	*1.35*	*1.46*	1.68	*1.63*	*1.71*	2.38	*2.33*	*2.43*	3.21	*3.13*	*3.30*	3.64	*3.53*	*3.73*
12.5	1.38	*1.33*	*1.45*	1.66	*1.61*	*1.71*	2.37	*2.30*	*2.42*	3.20	*3.12*	*3.31*	3.64	*3.51*	*3.74*
13	1.36	*1.31*	*1.43*	1.65	*1.59*	*1.70*	2.36	*2.29*	*2.42*	3.20	*3.10*	*3.31*	3.64	*3.50*	*3.76*
13.5	1.35	*1.29*	*1.42*	1.64	*1.57*	*1.69*	2.36	*2.28*	*2.42*	3.21	*3.10*	*3.32*	3.65	*3.50*	*3.78*
14	1.33	*1.28*	*1.41*	1.63	*1.57*	*1.68*	2.35	*2.28*	*2.42*	3.22	*3.11*	*3.33*	3.66	*3.53*	*3.80*
14.5	1.32	*1.27*	*1.40*	1.62	*1.56*	*1.68*	2.36	*2.28*	*2.42*	3.23	*3.13*	*3.34*	3.68	*3.54*	*3.83*
15	1.31	*1.26*	*1.39*	1.61	*1.56*	*1.67*	2.36	*2.29*	*2.42*	3.24	*3.14*	*3.35*	3.70	*3.56*	*3.85*
15.5	1.30	*1.24*	*1.38*	1.61	*1.55*	*1.66*	2.36	*2.30*	*2.42*	3.26	*3.15*	*3.36*	3.73	*3.58*	*3.88*
16	1.30	*1.23*	*1.37*	1.60	*1.55*	*1.66*	2.37	*2.31*	*2.42*	3.28	*3.17*	*3.38*	3.75	*3.61*	*3.92*

Tab. 3 Reference values for HDL cholesterol (mmol/l) by age (0 to 16 years) and gender, based on the reference population of the LIFE-Child cohort (n = 2504). The table shows the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th percentile (P97) as well as their 95% - confidence intervals (*KI*). The values correspond to interpolated calculations at the exact time.

	males (n=1311)											
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.62	*0.56*	*0.68*	0.76	*0.72*	*0.81*	1.11	*1.08*	*1.15*	1.56	*1.49*	*1.63*	1.80	*1.69*	*1.95*
1	0.65	*0.60*	*0.70*	0.79	*0.75*	*0.83*	1.14	*1.10*	*1.18*	1.58	*1.51*	*1.65*	1.82	*1.70*	*1.95*
1.5	0.69	*0.63*	*0.73*	0.82	*0.78*	*0.87*	1.18	*1.12*	*1.22*	1.62	*1.53*	*1.67*	1.85	*1.72*	*1.97*
2	0.72	*0.67*	*0.77*	0.87	*0.82*	*0.91*	1.22	*1.16*	*1.26*	1.66	*1.57*	*1.72*	1.90	*1.77*	*2.00*
2.5	0.77	*0.72*	*0.82*	0.91	*0.87*	*0.95*	1.27	*1.22*	*1.31*	1.72	*1.64*	*1.77*	1.95	*1.84*	*2.04*
3	0.81	*0.76*	*0.86*	0.96	*0.92*	*1.00*	1.33	*1.29*	*1.37*	1.78	*1.71*	*1.83*	2.01	*1.92*	*2.10*
3.5	0.86	*0.81*	*0.91*	1.01	*0.97*	*1.06*	1.39	*1.35*	*1.43*	1.84	*1.78*	*1.89*	2.08	*2.00*	*2.16*
4	0.91	*0.86*	*0.96*	1.06	*1.02*	*1.11*	1.44	*1.40*	*1.49*	1.90	*1.84*	*1.96*	2.14	*2.06*	*2.22*
4.5	0.95	*0.90*	*1.00*	1.10	*1.06*	*1.15*	1.49	*1.45*	*1.53*	1.96	*1.90*	*2.02*	2.21	*2.13*	*2.28*
5	0.98	*0.93*	*1.03*	1.14	*1.10*	*1.18*	1.54	*1.50*	*1.58*	2.01	*1.95*	*2.07*	2.26	*2.19*	*2.34*
5.5	1.01	*0.97*	*1.06*	1.17	*1.14*	*1.22*	1.58	*1.54*	*1.62*	2.06	*2.00*	*2.11*	2.32	*2.24*	*2.39*
6	1.04	*0.99*	*1.09*	1.20	*1.16*	*1.24*	1.61	*1.58*	*1.65*	2.11	*2.05*	*2.16*	2.37	*2.30*	*2.44*
6.5	1.06	*1.01*	*1.11*	1.23	*1.19*	*1.27*	1.64	*1.61*	*1.68*	2.15	*2.10*	*2.21*	2.42	*2.35*	*2.49*
7	1.07	*1.02*	*1.12*	1.24	*1.20*	*1.28*	1.67	*1.63*	*1.71*	2.19	*2.13*	*2.24*	2.46	*2.39*	*2.54*
7.5	1.08	*1.03*	*1.13*	1.25	*1.21*	*1.29*	1.68	*1.65*	*1.72*	2.21	*2.16*	*2.27*	2.50	*2.42*	*2.57*
8	1.08	*1.03*	*1.12*	1.25	*1.22*	*1.29*	1.69	*1.66*	*1.73*	2.23	*2.18*	*2.30*	2.52	*2.44*	*2.60*
8.5	1.07	*1.03*	*1.12*	1.25	*1.21*	*1.28*	1.69	*1.66*	*1.73*	2.24	*2.19*	*2.31*	2.54	*2.46*	*2.62*
9	1.06	*1.02*	*1.11*	1.24	*1.20*	*1.27*	1.69	*1.65*	*1.72*	2.25	*2.19*	*2.31*	2.55	*2.46*	*2.63*
9.5	1.04	*1.01*	*1.09*	1.22	*1.19*	*1.26*	1.67	*1.63*	*1.71*	2.24	*2.18*	*2.30*	2.55	*2.46*	*2.63*
10	1.03	*0.99*	*1.08*	1.20	*1.17*	*1.24*	1.66	*1.62*	*1.69*	2.23	*2.17*	*2.29*	2.54	*2.45*	*2.61*
10.5	1.01	*0.98*	*1.06*	1.19	*1.15*	*1.22*	1.64	*1.60*	*1.67*	2.21	*2.15*	*2.27*	2.52	*2.43*	*2.60*
11	0.99	*0.96*	*1.04*	1.17	*1.13*	*1.20*	1.61	*1.57*	*1.65*	2.18	*2.13*	*2.24*	2.50	*2.41*	*2.57*
11.5	0.97	*0.94*	*1.02*	1.14	*1.11*	*1.17*	1.58	*1.55*	*1.62*	2.15	*2.09*	*2.21*	2.46	*2.38*	*2.54*
12	0.95	*0.92*	*1.00*	1.12	*1.08*	*1.15*	1.55	*1.51*	*1.59*	2.11	*2.06*	*2.17*	2.42	*2.34*	*2.49*
12.5	0.93	*0.91*	*0.98*	1.10	*1.06*	*1.12*	1.52	*1.48*	*1.55*	2.07	*2.02*	*2.13*	2.38	*2.29*	*2.45*
13	0.92	*0.89*	*0.96*	1.07	*1.04*	*1.10*	1.49	*1.45*	*1.52*	2.03	*1.98*	*2.09*	2.34	*2.25*	*2.40*
13.5	0.90	*0.88*	*0.95*	1.06	*1.02*	*1.08*	1.46	*1.42*	*1.50*	1.99	*1.94*	*2.05*	2.30	*2.20*	*2.36*
14	0.90	*0.86*	*0.94*	1.04	*1.01*	*1.07*	1.44	*1.40*	*1.47*	1.96	*1.91*	*2.02*	2.26	*2.16*	*2.32*
14.5	0.89	*0.86*	*0.94*	1.04	*1.00*	*1.06*	1.42	*1.38*	*1.46*	1.93	*1.88*	*1.99*	2.23	*2.13*	*2.28*
15	0.89	*0.85*	*0.95*	1.03	*1.00*	*1.06*	1.41	*1.37*	*1.44*	1.91	*1.86*	*1.97*	2.20	*2.10*	*2.25*
15.5	0.89	*0.83*	*0.96*	1.03	*0.99*	*1.07*	1.40	*1.35*	*1.44*	1.89	*1.83*	*1.96*	2.17	*2.07*	*2.23*
16	0.90	*0.82*	*0.98*	1.03	*0.98*	*1.07*	1.39	*1.34*	*1.43*	1.87	*1.80*	*1.95*	2.15	*2.03*	*2.22*

	females (n=1193)														
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.64	*0.50*	*0.72*	0.79	*0.73*	*0.84*	1.17	*1.13*	*1.22*	1.65	*1.57*	*1.72*	1.90	*1.80*	*2.03*
1	0.66	*0.54*	*0.72*	0.80	*0.75*	*0.85*	1.17	*1.13*	*1.21*	1.62	*1.54*	*1.68*	1.86	*1.73*	*1.98*
1.5	0.68	*0.57*	*0.74*	0.82	*0.77*	*0.87*	1.18	*1.12*	*1.23*	1.61	*1.51*	*1.68*	1.84	*1.68*	*1.97*
2	0.71	*0.61*	*0.77*	0.85	*0.79*	*0.91*	1.21	*1.14*	*1.26*	1.62	*1.52*	*1.70*	1.84	*1.69*	*1.97*
2.5	0.75	*0.65*	*0.81*	0.89	*0.84*	*0.94*	1.25	*1.19*	*1.30*	1.66	*1.57*	*1.73*	1.87	*1.73*	*1.99*
3	0.79	*0.70*	*0.85*	0.94	*0.89*	*0.99*	1.29	*1.24*	*1.34*	1.70	*1.63*	*1.76*	1.91	*1.79*	*2.02*
3.5	0.84	*0.75*	*0.89*	0.99	*0.94*	*1.03*	1.35	*1.30*	*1.39*	1.76	*1.70*	*1.81*	1.97	*1.87*	*2.06*
4	0.88	*0.80*	*0.94*	1.03	*0.99*	*1.08*	1.40	*1.36*	*1.44*	1.82	*1.76*	*1.87*	2.03	*1.95*	*2.11*
4.5	0.92	*0.84*	*0.98*	1.08	*1.04*	*1.12*	1.45	*1.41*	*1.49*	1.87	*1.82*	*1.93*	2.08	*2.01*	*2.16*
5	0.96	*0.87*	*1.02*	1.12	*1.08*	*1.16*	1.49	*1.46*	*1.54*	1.92	*1.87*	*1.97*	2.13	*2.07*	*2.20*
5.5	0.99	*0.90*	*1.05*	1.15	*1.10*	*1.19*	1.53	*1.49*	*1.57*	1.96	*1.91*	*2.01*	2.17	*2.10*	*2.24*
6	1.01	*0.92*	*1.07*	1.17	*1.13*	*1.21*	1.56	*1.52*	*1.59*	1.99	*1.94*	*2.04*	2.21	*2.14*	*2.27*
6.5	1.03	*0.94*	*1.09*	1.19	*1.15*	*1.23*	1.58	*1.54*	*1.61*	2.01	*1.96*	*2.06*	2.23	*2.16*	*2.30*
7	1.04	*0.96*	*1.10*	1.20	*1.16*	*1.24*	1.59	*1.55*	*1.63*	2.02	*1.97*	*2.08*	2.24	*2.17*	*2.31*
7.5	1.05	*0.96*	*1.10*	1.21	*1.17*	*1.25*	1.60	*1.56*	*1.64*	2.03	*1.98*	*2.09*	2.25	*2.18*	*2.32*
8	1.05	*0.97*	*1.10*	1.21	*1.17*	*1.25*	1.60	*1.56*	*1.64*	2.03	*1.99*	*2.09*	2.25	*2.18*	*2.32*
8.5	1.04	*0.98*	*1.10*	1.21	*1.17*	*1.24*	1.59	*1.56*	*1.63*	2.03	*1.98*	*2.08*	2.24	*2.17*	*2.30*
9	1.03	*0.97*	*1.08*	1.20	*1.16*	*1.23*	1.58	*1.55*	*1.62*	2.02	*1.97*	*2.06*	2.23	*2.16*	*2.29*
9.5	1.02	*0.97*	*1.06*	1.19	*1.16*	*1.21*	1.57	*1.55*	*1.60*	2.00	*1.97*	*2.05*	2.22	*2.15*	*2.28*
10	1.00	*0.96*	*1.04*	1.17	*1.14*	*1.20*	1.56	*1.53*	*1.59*	1.99	*1.96*	*2.04*	2.21	*2.14*	*2.26*
10.5	0.99	*0.95*	*1.03*	1.15	*1.12*	*1.18*	1.55	*1.52*	*1.58*	1.98	*1.95*	*2.03*	2.20	*2.13*	*2.25*
11	0.97	*0.93*	*1.01*	1.14	*1.10*	*1.16*	1.53	*1.50*	*1.56*	1.97	*1.94*	*2.02*	2.19	*2.12*	*2.24*
11.5	0.95	*0.92*	*0.99*	1.12	*1.09*	*1.14*	1.52	*1.49*	*1.55*	1.96	*1.93*	*2.01*	2.19	*2.11*	*2.24*
12	0.93	*0.90*	*0.97*	1.10	*1.07*	*1.13*	1.51	*1.48*	*1.54*	1.96	*1.92*	*2.01*	2.18	*2.11*	*2.24*
12.5	0.92	*0.89*	*0.96*	1.09	*1.06*	*1.12*	1.50	*1.47*	*1.54*	1.96	*1.92*	*2.01*	2.18	*2.10*	*2.24*
13	0.91	*0.88*	*0.95*	1.09	*1.05*	*1.11*	1.50	*1.46*	*1.54*	1.96	*1.91*	*2.01*	2.19	*2.10*	*2.24*
13.5	0.90	*0.88*	*0.95*	1.08	*1.04*	*1.11*	1.50	*1.46*	*1.54*	1.97	*1.92*	*2.02*	2.20	*2.12*	*2.25*
14	0.90	*0.88*	*0.95*	1.09	*1.05*	*1.11*	1.51	*1.47*	*1.55*	1.98	*1.94*	*2.04*	2.22	*2.14*	*2.26*
14.5	0.91	*0.89*	*0.96*	1.10	*1.06*	*1.12*	1.53	*1.49*	*1.56*	2.01	*1.96*	*2.06*	2.24	*2.17*	*2.29*
15	0.93	*0.90*	*0.98*	1.11	*1.08*	*1.14*	1.55	*1.52*	*1.58*	2.03	*2.00*	*2.09*	2.27	*2.20*	*2.32*
15.5	0.95	*0.92*	*1.01*	1.14	*1.09*	*1.17*	1.58	*1.54*	*1.61*	2.06	*2.03*	*2.12*	2.31	*2.23*	*2.36*
16	0.97	*0.94*	*1.04*	1.16	*1.11*	*1.20*	1.60	*1.56*	*1.65*	2.09	*2.05*	*2.16*	2.34	*2.25*	*2.41*

Tab. 4 Reference values for triglycerides (mmol/l) by age (0 to 16 years) and gender, based on the reference population of the LIFE-Child cohort (n = 2504). The table shows the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th percentile (P97) as well as their 95% - confidence intervals (*KI*). The values correspond to interpolated calculations at the exact time.

	males (n=1311)											
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.61	*0.55*	*0.70*	0.8	*0.73*	*0.87*	1.5	*1.39*	*1.61*	3.14	*2.84*	*3.47*	4.66	*3.98*	*5.43*
1	0.52	*0.47*	*0.58*	0.67	*0.63*	*0.72*	1.25	*1.17*	*1.34*	2.6	*2.36*	*2.85*	3.83	*3.34*	*4.42*
1.5	0.45	*0.40*	*0.49*	0.58	*0.54*	*0.62*	1.06	*0.98*	*1.14*	2.17	*1.94*	*2.40*	3.18	*2.77*	*3.65*
2	0.39	*0.35*	*0.43*	0.5	*0.46*	*0.54*	0.91	*0.83*	*0.98*	1.83	*1.62*	*2.05*	2.67	*2.29*	*3.07*
2.5	0.35	*0.31*	*0.39*	0.45	*0.41*	*0.49*	0.8	*0.72*	*0.87*	1.59	*1.39*	*1.78*	2.29	*1.95*	*2.64*
3	0.32	*0.28*	*0.36*	0.41	*0.37*	*0.45*	0.72	*0.66*	*0.78*	1.4	*1.24*	*1.58*	2.01	*1.73*	*2.32*
3.5	0.3	*0.27*	*0.34*	0.38	*0.36*	*0.42*	0.67	*0.61*	*0.72*	1.27	*1.13*	*1.42*	1.81	*1.58*	*2.10*
4	0.29	*0.26*	*0.33*	0.37	*0.34*	*0.40*	0.63	*0.58*	*0.67*	1.18	*1.05*	*1.31*	1.66	*1.47*	*1.92*
4.5	0.28	*0.25*	*0.32*	0.36	*0.33*	*0.39*	0.6	*0.57*	*0.64*	1.12	*1.00*	*1.22*	1.56	*1.39*	*1.79*
5	0.28	*0.25*	*0.31*	0.35	*0.33*	*0.38*	0.58	*0.55*	*0.62*	1.07	*0.96*	*1.16*	1.48	*1.33*	*1.70*
5.5	0.28	*0.24*	*0.31*	0.34	*0.32*	*0.37*	0.57	*0.54*	*0.60*	1.04	*0.94*	*1.12*	1.43	*1.29*	*1.64*
6	0.27	*0.24*	*0.31*	0.34	*0.32*	*0.37*	0.56	*0.53*	*0.59*	1.02	*0.92*	*1.08*	1.4	*1.27*	*1.60*
6.5	0.27	*0.24*	*0.31*	0.34	*0.32*	*0.37*	0.56	*0.53*	*0.59*	1.01	*0.92*	*1.07*	1.39	*1.26*	*1.58*
7	0.27	*0.24*	*0.30*	0.34	*0.32*	*0.36*	0.56	*0.53*	*0.59*	1.01	*0.93*	*1.08*	1.4	*1.28*	*1.59*
7.5	0.28	*0.25*	*0.30*	0.34	*0.32*	*0.37*	0.56	*0.54*	*0.59*	1.03	*0.95*	*1.10*	1.42	*1.30*	*1.61*
8	0.28	*0.26*	*0.31*	0.35	*0.33*	*0.37*	0.58	*0.55*	*0.60*	1.06	*0.98*	*1.12*	1.47	*1.35*	*1.66*
8.5	0.29	*0.26*	*0.31*	0.36	*0.34*	*0.38*	0.59	*0.57*	*0.62*	1.1	*1.02*	*1.17*	1.54	*1.42*	*1.73*
9	0.29	*0.27*	*0.32*	0.37	*0.35*	*0.39*	0.61	*0.58*	*0.64*	1.15	*1.06*	*1.22*	1.63	*1.50*	*1.82*
9.5	0.3	*0.28*	*0.32*	0.37	*0.36*	*0.39*	0.63	*0.60*	*0.66*	1.2	*1.11*	*1.28*	1.72	*1.58*	*1.91*
10	0.3	*0.28*	*0.33*	0.38	*0.36*	*0.40*	0.65	*0.61*	*0.68*	1.25	*1.15*	*1.34*	1.8	*1.65*	*2.00*
10.5	0.31	*0.29*	*0.33*	0.39	*0.37*	*0.41*	0.66	*0.63*	*0.70*	1.29	*1.19*	*1.38*	1.88	*1.71*	*2.09*
11	0.31	*0.29*	*0.33*	0.39	*0.37*	*0.41*	0.67	*0.64*	*0.71*	1.32	*1.23*	*1.42*	1.94	*1.76*	*2.16*
11.5	0.32	*0.30*	*0.34*	0.4	*0.38*	*0.42*	0.69	*0.65*	*0.72*	1.35	*1.25*	*1.45*	1.99	*1.80*	*2.22*
12	0.32	*0.31*	*0.34*	0.4	*0.38*	*0.43*	0.7	*0.66*	*0.73*	1.37	*1.28*	*1.46*	2.02	*1.83*	*2.25*
12.5	0.33	*0.31*	*0.35*	0.41	*0.39*	*0.44*	0.71	*0.67*	*0.74*	1.38	*1.29*	*1.48*	2.03	*1.82*	*2.26*
13	0.34	*0.32*	*0.36*	0.42	*0.40*	*0.44*	0.71	*0.68*	*0.75*	1.39	*1.30*	*1.48*	2.03	*1.82*	*2.25*
13.5	0.35	*0.33*	*0.37*	0.43	*0.41*	*0.45*	0.72	*0.69*	*0.76*	1.39	*1.30*	*1.48*	2.02	*1.81*	*2.23*
14	0.35	*0.33*	*0.38*	0.44	*0.41*	*0.46*	0.73	*0.69*	*0.76*	1.39	*1.30*	*1.48*	2	*1.78*	*2.20*
14.5	0.36	*0.34*	*0.39*	0.44	*0.42*	*0.47*	0.73	*0.70*	*0.77*	1.38	*1.29*	*1.48*	1.97	*1.75*	*2.17*
15	0.36	*0.34*	*0.39*	0.45	*0.42*	*0.47*	0.73	*0.70*	*0.77*	1.37	*1.27*	*1.48*	1.94	*1.72*	*2.15*
15.5	0.37	*0.35*	*0.40*	0.45	*0.42*	*0.48*	0.74	*0.70*	*0.77*	1.36	*1.25*	*1.49*	1.92	*1.69*	*2.12*
16	0.37	*0.35*	*0.41*	0.46	*0.43*	*0.48*	0.74	*0.70*	*0.78*	1.36	*1.23*	*1.50*	1.91	*1.67*	*2.12*

	females (n=1193)													
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.69	*0.63*	*0.76*	0.89	*0.82*	*0.96*	1.59	*1.49*	*1.70*	3.21	*2.90*	*3.46*	4.69	*4.11*	*5.62*
1	0.61	*0.56*	*0.66*	0.77	*0.72*	*0.84*	1.38	*1.30*	*1.46*	2.75	*2.51*	*2.93*	4	*3.58*	*4.64*
1.5	0.53	*0.49*	*0.57*	0.67	*0.63*	*0.73*	1.19	*1.12*	*1.26*	2.35	*2.16*	*2.49*	3.41	*3.09*	*3.88*
2	0.47	*0.43*	*0.50*	0.59	*0.55*	*0.63*	1.03	*0.98*	*1.09*	2.01	*1.86*	*2.14*	2.91	*2.66*	*3.26*
2.5	0.42	*0.38*	*0.45*	0.52	*0.49*	*0.56*	0.9	*0.85*	*0.95*	1.75	*1.61*	*1.86*	2.51	*2.32*	*2.79*
3	0.38	*0.35*	*0.40*	0.47	*0.44*	*0.50*	0.8	*0.76*	*0.85*	1.54	*1.41*	*1.64*	2.2	*2.02*	*2.42*
3.5	0.35	*0.32*	*0.37*	0.43	*0.41*	*0.46*	0.73	*0.69*	*0.77*	1.38	*1.26*	*1.48*	1.97	*1.81*	*2.16*
4	0.33	*0.30*	*0.35*	0.4	*0.38*	*0.43*	0.67	*0.64*	*0.71*	1.27	*1.16*	*1.36*	1.8	*1.64*	*1.97*
4.5	0.31	*0.29*	*0.34*	0.39	*0.37*	*0.41*	0.64	*0.61*	*0.67*	1.19	*1.09*	*1.28*	1.67	*1.54*	*1.84*
5	0.31	*0.28*	*0.33*	0.38	*0.36*	*0.40*	0.62	*0.59*	*0.65*	1.14	*1.05*	*1.22*	1.59	*1.47*	*1.76*
5.5	0.31	*0.28*	*0.33*	0.37	*0.36*	*0.39*	0.61	*0.58*	*0.64*	1.11	*1.03*	*1.19*	1.55	*1.42*	*1.70*
6	0.31	*0.28*	*0.33*	0.38	*0.36*	*0.40*	0.61	*0.58*	*0.64*	1.1	*1.02*	*1.18*	1.53	*1.40*	*1.69*
6.5	0.31	*0.28*	*0.34*	0.38	*0.36*	*0.40*	0.61	*0.59*	*0.64*	1.1	*1.02*	*1.18*	1.52	*1.40*	*1.68*
7	0.32	*0.29*	*0.35*	0.39	*0.37*	*0.41*	0.62	*0.60*	*0.65*	1.11	*1.03*	*1.19*	1.53	*1.41*	*1.69*
7.5	0.32	*0.29*	*0.35*	0.39	*0.37*	*0.42*	0.63	*0.61*	*0.66*	1.13	*1.05*	*1.21*	1.56	*1.43*	*1.72*
8	0.33	*0.29*	*0.36*	0.4	*0.38*	*0.42*	0.64	*0.62*	*0.67*	1.15	*1.07*	*1.23*	1.6	*1.47*	*1.76*
8.5	0.34	*0.30*	*0.37*	0.41	*0.38*	*0.43*	0.66	*0.63*	*0.69*	1.19	*1.11*	*1.27*	1.66	*1.53*	*1.82*
9	0.35	*0.31*	*0.38*	0.42	*0.39*	*0.45*	0.68	*0.66*	*0.72*	1.24	*1.17*	*1.32*	1.74	*1.61*	*1.89*
9.5	0.36	*0.31*	*0.39*	0.43	*0.41*	*0.46*	0.71	*0.68*	*0.74*	1.3	*1.23*	*1.38*	1.83	*1.69*	*1.97*
10	0.37	*0.32*	*0.40*	0.45	*0.42*	*0.47*	0.74	*0.71*	*0.77*	1.36	*1.28*	*1.44*	1.91	*1.77*	*2.06*
10.5	0.38	*0.32*	*0.41*	0.46	*0.44*	*0.49*	0.76	*0.73*	*0.79*	1.42	*1.34*	*1.49*	1.99	*1.85*	*2.15*
11	0.39	*0.33*	*0.42*	0.47	*0.45*	*0.50*	0.79	*0.76*	*0.82*	1.46	*1.39*	*1.54*	2.06	*1.91*	*2.21*
11.5	0.39	*0.33*	*0.42*	0.49	*0.45*	*0.51*	0.81	*0.77*	*0.85*	1.5	*1.42*	*1.58*	2.11	*1.96*	*2.25*
12	0.4	*0.34*	*0.43*	0.49	*0.46*	*0.52*	0.82	*0.79*	*0.87*	1.53	*1.44*	*1.61*	2.14	*1.98*	*2.29*
12.5	0.4	*0.34*	*0.43*	0.5	*0.47*	*0.52*	0.83	*0.79*	*0.87*	1.53	*1.45*	*1.62*	2.14	*1.98*	*2.29*
13	0.4	*0.34*	*0.43*	0.5	*0.47*	*0.52*	0.83	*0.80*	*0.87*	1.53	*1.45*	*1.61*	2.12	*1.96*	*2.27*
13.5	0.4	*0.34*	*0.43*	0.5	*0.47*	*0.52*	0.83	*0.80*	*0.87*	1.51	*1.43*	*1.60*	2.08	*1.92*	*2.23*
14	0.4	*0.35*	*0.43*	0.5	*0.47*	*0.52*	0.83	*0.80*	*0.86*	1.49	*1.42*	*1.58*	2.04	*1.88*	*2.19*
14.5	0.4	*0.35*	*0.43*	0.5	*0.47*	*0.52*	0.83	*0.80*	*0.86*	1.48	*1.40*	*1.57*	2	*1.84*	*2.16*
15	0.4	*0.35*	*0.43*	0.5	*0.48*	*0.52*	0.83	*0.80*	*0.86*	1.47	*1.39*	*1.56*	1.97	*1.81*	*2.15*
15.5	0.4	*0.36*	*0.43*	0.5	*0.48*	*0.52*	0.83	*0.80*	*0.87*	1.46	*1.39*	*1.55*	1.95	*1.78*	*2.14*
16	0.4	*0.36*	*0.43*	0.5	*0.48*	*0.53*	0.84	*0.80*	*0.87*	1.46	*1.39*	*1.56*	1.94	*1.77*	*2.15*

Tab. 5 Reference values for apolipoprotein A1 (g/l) by age (0 to 16 years) and gender, based on the reference population of the LIFE-Child cohort (n = 2569). The table shows the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th percentile (P97) as well as their 95% - confidence intervals (*KI*). The values correspond to interpolated calculations at the exact time.

	males (n=1345)											
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.96	*0.87*	*1.02*	1.07	*1.03*	*1.11*	1.31	*1.28*	*1.34*	1.57	*1.52*	*1.61*	1.7	*1.64*	*1.78*
1	0.92	*0.85*	*0.96*	1.02	*0.98*	*1.06*	1.25	*1.21*	*1.28*	1.5	*1.44*	*1.54*	1.62	*1.55*	*1.70*
1.5	0.9	*0.83*	*0.94*	1.00	*0.96*	*1.04*	1.22	*1.17*	*1.27*	1.46	*1.40*	*1.51*	1.58	*1.51*	*1.67*
2	0.9	*0.83*	*0.94*	1.00	*0.96*	*1.04*	1.22	*1.18*	*1.27*	1.46	*1.40*	*1.51*	1.58	*1.51*	*1.66*
2.5	0.92	*0.85*	*0.96*	1.02	*0.99*	*1.06*	1.25	*1.22*	*1.28*	1.49	*1.45*	*1.53*	1.61	*1.56*	*1.68*
3	0.95	*0.88*	*1.00*	1.06	*1.02*	*1.10*	1.29	*1.26*	*1.32*	1.54	*1.50*	*1.58*	1.66	*1.61*	*1.72*
3.5	0.99	*0.91*	*1.04*	1.1	*1.05*	*1.15*	1.34	*1.30*	*1.38*	1.59	*1.55*	*1.64*	1.72	*1.67*	*1.78*
4	1.02	*0.94*	*1.08*	1.13	*1.09*	*1.18*	1.38	*1.34*	*1.42*	1.64	*1.59*	*1.69*	1.77	*1.72*	*1.84*
4.5	1.05	*0.98*	*1.09*	1.16	*1.12*	*1.20*	1.41	*1.37*	*1.45*	1.68	*1.63*	*1.72*	1.81	*1.77*	*1.87*
5	1.07	*1.01*	*1.11*	1.18	*1.14*	*1.22*	1.43	*1.40*	*1.47*	1.71	*1.67*	*1.74*	1.84	*1.80*	*1.90*
5.5	1.09	*1.04*	*1.13*	1.2	*1.17*	*1.23*	1.46	*1.42*	*1.49*	1.74	*1.69*	*1.77*	1.87	*1.83*	*1.93*
6	1.11	*1.06*	*1.15*	1.22	*1.19*	*1.26*	1.48	*1.45*	*1.51*	1.76	*1.72*	*1.80*	1.91	*1.86*	*1.96*
6.5	1.13	*1.08*	*1.17*	1.24	*1.21*	*1.28*	1.5	*1.47*	*1.53*	1.79	*1.75*	*1.83*	1.94	*1.89*	*1.98*
7	1.14	*1.10*	*1.18*	1.25	*1.22*	*1.29*	1.52	*1.49*	*1.55*	1.81	*1.77*	*1.84*	1.96	*1.91*	*2.00*
7.5	1.15	*1.11*	*1.18*	1.26	*1.23*	*1.29*	1.53	*1.50*	*1.55*	1.82	*1.78*	*1.86*	1.97	*1.93*	*2.02*
8	1.15	*1.12*	*1.19*	1.27	*1.24*	*1.30*	1.53	*1.50*	*1.56*	1.83	*1.79*	*1.86*	1.98	*1.94*	*2.03*
8.5	1.16	*1.13*	*1.19*	1.27	*1.24*	*1.30*	1.54	*1.51*	*1.56*	1.84	*1.80*	*1.87*	1.99	*1.94*	*2.04*
9	1.16	*1.13*	*1.20*	1.27	*1.25*	*1.30*	1.54	*1.51*	*1.57*	1.84	*1.81*	*1.88*	2.00	*1.95*	*2.04*
9.5	1.16	*1.13*	*1.20*	1.28	*1.25*	*1.30*	1.54	*1.52*	*1.57*	1.85	*1.81*	*1.89*	2.01	*1.96*	*2.05*
10	1.16	*1.13*	*1.20*	1.27	*1.25*	*1.30*	1.54	*1.52*	*1.57*	1.85	*1.81*	*1.89*	2.01	*1.96*	*2.05*
10.5	1.15	*1.13*	*1.19*	1.26	*1.24*	*1.29*	1.53	*1.50*	*1.56*	1.84	*1.80*	*1.87*	2.00	*1.95*	*2.04*
11	1.14	*1.11*	*1.17*	1.25	*1.22*	*1.27*	1.51	*1.48*	*1.53*	1.81	*1.78*	*1.85*	1.97	*1.93*	*2.01*
11.5	1.11	*1.09*	*1.15*	1.22	*1.19*	*1.24*	1.48	*1.45*	*1.50*	1.78	*1.75*	*1.82*	1.94	*1.89*	*1.98*
12	1.09	*1.06*	*1.12*	1.19	*1.16*	*1.21*	1.44	*1.42*	*1.47*	1.74	*1.71*	*1.78*	1.9	*1.85*	*1.94*
12.5	1.06	*1.04*	*1.09*	1.16	*1.13*	*1.18*	1.41	*1.38*	*1.43*	1.7	*1.67*	*1.74*	1.86	*1.81*	*1.90*
13	1.03	*1.01*	*1.06*	1.13	*1.11*	*1.15*	1.38	*1.35*	*1.40*	1.67	*1.64*	*1.71*	1.83	*1.78*	*1.86*
13.5	1.01	*0.99*	*1.04*	1.11	*1.08*	*1.13*	1.35	*1.32*	*1.38*	1.64	*1.61*	*1.68*	1.8	*1.75*	*1.83*
14	1.00	*0.98*	*1.04*	1.1	*1.07*	*1.12*	1.34	*1.31*	*1.36*	1.63	*1.60*	*1.67*	1.79	*1.73*	*1.82*
14.5	1.00	*0.98*	*1.03*	1.1	*1.07*	*1.12*	1.33	*1.30*	*1.36*	1.63	*1.59*	*1.67*	1.79	*1.73*	*1.82*
15	1.00	*0.98*	*1.04*	1.1	*1.07*	*1.12*	1.33	*1.30*	*1.37*	1.63	*1.59*	*1.67*	1.79	*1.73*	*1.82*
15.5	1.01	*0.98*	*1.05*	1.1	*1.07*	*1.13*	1.33	*1.30*	*1.37*	1.63	*1.59*	*1.68*	1.79	*1.73*	*1.83*
16	1.01	*0.98*	*1.05*	1.1	*1.07*	*1.13*	1.33	*1.30*	*1.37*	1.63	*1.58*	*1.68*	1.79	*1.72*	*1.83*

	females (n=1224)														
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.96	*0.84*	*1.03*	1.08	*1.05*	*1.14*	1.35	*1.33*	*1.37*	1.62	*1.57*	*1.64*	1.75	*1.71*	*1.84*
1	0.93	*0.83*	*0.99*	1.04	*1.01*	*1.09*	1.29	*1.26*	*1.32*	1.55	*1.49*	*1.57*	1.67	*1.62*	*1.75*
1.5	0.92	*0.83*	*0.97*	1.02	*0.99*	*1.07*	1.26	*1.22*	*1.29*	1.51	*1.45*	*1.54*	1.62	*1.57*	*1.71*
2	0.92	*0.85*	*0.97*	1.02	*1.00*	*1.07*	1.25	*1.22*	*1.29*	1.49	*1.44*	*1.53*	1.61	*1.56*	*1.69*
2.5	0.94	*0.87*	*0.98*	1.04	*1.02*	*1.08*	1.27	*1.24*	*1.29*	1.51	*1.46*	*1.54*	1.62	*1.58*	*1.69*
3	0.96	*0.91*	*1.00*	1.07	*1.04*	*1.10*	1.29	*1.27*	*1.32*	1.54	*1.49*	*1.56*	1.65	*1.61*	*1.72*
3.5	1.00	*0.94*	*1.03*	1.1	*1.07*	*1.13*	1.33	*1.30*	*1.36*	1.57	*1.53*	*1.60*	1.69	*1.66*	*1.75*
4	1.03	*0.98*	*1.06*	1.13	*1.11*	*1.17*	1.36	*1.34*	*1.39*	1.61	*1.57*	*1.64*	1.73	*1.70*	*1.79*
4.5	1.05	*1.01*	*1.09*	1.16	*1.13*	*1.19*	1.39	*1.36*	*1.42*	1.64	*1.60*	*1.68*	1.77	*1.73*	*1.83*
5	1.08	*1.03*	*1.11*	1.18	*1.16*	*1.21*	1.41	*1.39*	*1.44*	1.67	*1.63*	*1.70*	1.79	*1.76*	*1.85*
5.5	1.09	*1.05*	*1.12*	1.19	*1.17*	*1.22*	1.43	*1.40*	*1.45*	1.68	*1.65*	*1.71*	1.81	*1.77*	*1.86*
6	1.1	*1.06*	*1.13*	1.21	*1.19*	*1.23*	1.44	*1.41*	*1.46*	1.69	*1.66*	*1.72*	1.82	*1.78*	*1.87*
6.5	1.11	*1.08*	*1.14*	1.21	*1.19*	*1.24*	1.44	*1.42*	*1.47*	1.7	*1.66*	*1.73*	1.82	*1.78*	*1.87*
7	1.12	*1.09*	*1.15*	1.22	*1.20*	*1.25*	1.45	*1.43*	*1.48*	1.7	*1.67*	*1.74*	1.83	*1.79*	*1.88*
7.5	1.14	*1.10*	*1.16*	1.24	*1.21*	*1.26*	1.46	*1.44*	*1.49*	1.72	*1.68*	*1.75*	1.84	*1.80*	*1.89*
8	1.15	*1.12*	*1.17*	1.25	*1.22*	*1.27*	1.47	*1.45*	*1.50*	1.73	*1.69*	*1.76*	1.85	*1.81*	*1.89*
8.5	1.15	*1.13*	*1.18*	1.25	*1.23*	*1.27*	1.48	*1.46*	*1.50*	1.73	*1.70*	*1.76*	1.86	*1.82*	*1.90*
9	1.16	*1.13*	*1.18*	1.26	*1.24*	*1.27*	1.48	*1.47*	*1.50*	1.74	*1.71*	*1.76*	1.86	*1.83*	*1.90*
9.5	1.16	*1.14*	*1.18*	1.26	*1.24*	*1.27*	1.48	*1.47*	*1.50*	1.74	*1.72*	*1.77*	1.87	*1.83*	*1.90*
10	1.15	*1.13*	*1.18*	1.25	*1.23*	*1.27*	1.48	*1.46*	*1.50*	1.73	*1.71*	*1.76*	1.86	*1.83*	*1.90*
10.5	1.14	*1.12*	*1.17*	1.24	*1.21*	*1.25*	1.47	*1.45*	*1.48*	1.72	*1.70*	*1.75*	1.85	*1.82*	*1.89*
11	1.12	*1.10*	*1.15*	1.22	*1.19*	*1.24*	1.45	*1.43*	*1.47*	1.71	*1.68*	*1.73*	1.84	*1.80*	*1.87*
11.5	1.1	*1.08*	*1.12*	1.19	*1.17*	*1.21*	1.42	*1.40*	*1.44*	1.69	*1.66*	*1.72*	1.82	*1.78*	*1.85*
12	1.07	*1.06*	*1.10*	1.17	*1.15*	*1.19*	1.4	*1.38*	*1.43*	1.67	*1.65*	*1.71*	1.81	*1.76*	*1.84*
12.5	1.05	*1.04*	*1.08*	1.15	*1.13*	*1.17*	1.39	*1.37*	*1.41*	1.66	*1.64*	*1.70*	1.8	*1.76*	*1.83*
13	1.04	*1.02*	*1.07*	1.14	*1.12*	*1.15*	1.38	*1.36*	*1.40*	1.66	*1.64*	*1.70*	1.81	*1.76*	*1.84*
13.5	1.02	*1.01*	*1.05*	1.13	*1.10*	*1.14*	1.38	*1.36*	*1.40*	1.67	*1.65*	*1.71*	1.83	*1.77*	*1.86*
14	1.02	*1.01*	*1.05*	1.13	*1.10*	*1.14*	1.39	*1.36*	*1.41*	1.7	*1.67*	*1.74*	1.86	*1.80*	*1.89*
14.5	1.02	*1.01*	*1.05*	1.13	*1.10*	*1.15*	1.41	*1.38*	*1.43*	1.74	*1.71*	*1.78*	1.91	*1.85*	*1.95*
15	1.03	*1.02*	*1.07*	1.15	*1.12*	*1.17*	1.44	*1.41*	*1.47*	1.79	*1.77*	*1.84*	1.98	*1.91*	*2.01*
15.5	1.05	*1.04*	*1.09*	1.17	*1.14*	*1.19*	1.48	*1.45*	*1.52*	1.86	*1.84*	*1.91*	2.07	*1.99*	*2.09*
16	1.07	*1.05*	*1.12*	1.2	*1.16*	*1.22*	1.53	*1.49*	*1.57*	1.93	*1.90*	*1.99*	2.15	*2.06*	*2.19*

Tab. 6 Reference values for apolipoprotein B (g/l) by age (0 to 16 years) and gender, based on the reference population of the LIFE-Child cohort (n = 2571). The table shows the 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th percentile (P97) as well as their 95% - confidence intervals (*KI*). The values correspond to interpolated calculations at the exact time.

	males (n=1345)											
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.42	*0.37*	*0.46*	0.52	*0.51*	*0.56*	0.76	*0.74*	*0.78*	1.01	*0.97*	*1.04*	1.13	*1.08*	*1.19*
1	0.43	*0.39*	*0.46*	0.53	*0.52*	*0.56*	0.76	*0.74*	*0.78*	1	*0.96*	*1.02*	1.12	*1.08*	*1.17*
1.5	0.44	*0.40*	*0.46*	0.54	*0.52*	*0.56*	0.76	*0.74*	*0.77*	0.99	*0.96*	*1.01*	1.1	*1.07*	*1.15*
2	0.45	*0.41*	*0.47*	0.54	*0.53*	*0.57*	0.75	*0.74*	*0.77*	0.98	*0.95*	*1.00*	1.09	*1.06*	*1.14*
2.5	0.45	*0.42*	*0.47*	0.54	*0.53*	*0.57*	0.75	*0.74*	*0.77*	0.97	*0.94*	*0.99*	1.08	*1.05*	*1.13*
3	0.46	*0.42*	*0.48*	0.55	*0.53*	*0.57*	0.75	*0.74*	*0.76*	0.97	*0.94*	*0.98*	1.07	*1.04*	*1.12*
3.5	0.46	*0.43*	*0.48*	0.55	*0.54*	*0.57*	0.75	*0.74*	*0.76*	0.96	*0.93*	*0.98*	1.07	*1.04*	*1.11*
4	0.46	*0.43*	*0.48*	0.55	*0.54*	*0.57*	0.74	*0.73*	*0.76*	0.96	*0.93*	*0.97*	1.06	*1.03*	*1.11*
4.5	0.46	*0.43*	*0.48*	0.55	*0.54*	*0.57*	0.74	*0.73*	*0.75*	0.96	*0.93*	*0.97*	1.06	*1.03*	*1.11*
5	0.46	*0.43*	*0.48*	0.55	*0.53*	*0.57*	0.74	*0.73*	*0.75*	0.95	*0.93*	*0.97*	1.06	*1.03*	*1.10*
5.5	0.46	*0.43*	*0.48*	0.54	*0.53*	*0.56*	0.74	*0.73*	*0.75*	0.95	*0.93*	*0.97*	1.06	*1.03*	*1.10*
6	0.46	*0.43*	*0.48*	0.54	*0.53*	*0.56*	0.73	*0.73*	*0.74*	0.95	*0.93*	*0.97*	1.06	*1.03*	*1.10*
6.5	0.46	*0.43*	*0.47*	0.54	*0.53*	*0.56*	0.73	*0.72*	*0.74*	0.95	*0.93*	*0.97*	1.06	*1.03*	*1.11*
7	0.45	*0.43*	*0.47*	0.53	*0.52*	*0.55*	0.73	*0.72*	*0.74*	0.95	*0.93*	*0.97*	1.07	*1.04*	*1.11*
7.5	0.45	*0.42*	*0.47*	0.53	*0.52*	*0.55*	0.73	*0.72*	*0.74*	0.95	*0.93*	*0.97*	1.07	*1.04*	*1.11*
8	0.45	*0.42*	*0.46*	0.53	*0.52*	*0.55*	0.72	*0.72*	*0.73*	0.96	*0.93*	*0.97*	1.07	*1.05*	*1.12*
8.5	0.45	*0.42*	*0.46*	0.53	*0.52*	*0.54*	0.72	*0.72*	*0.73*	0.96	*0.93*	*0.97*	1.08	*1.05*	*1.12*
9	0.44	*0.42*	*0.46*	0.52	*0.51*	*0.54*	0.72	*0.71*	*0.73*	0.96	*0.93*	*0.97*	1.08	*1.05*	*1.12*
9.5	0.44	*0.42*	*0.46*	0.52	*0.51*	*0.54*	0.72	*0.71*	*0.73*	0.96	*0.93*	*0.97*	1.08	*1.06*	*1.13*
10	0.44	*0.42*	*0.46*	0.52	*0.51*	*0.53*	0.72	*0.71*	*0.72*	0.96	*0.93*	*0.97*	1.09	*1.06*	*1.13*
10.5	0.44	*0.42*	*0.46*	0.52	*0.51*	*0.53*	0.71	*0.70*	*0.72*	0.96	*0.93*	*0.97*	1.09	*1.06*	*1.13*
11	0.44	*0.42*	*0.45*	0.52	*0.51*	*0.53*	0.71	*0.70*	*0.72*	0.95	*0.93*	*0.97*	1.09	*1.06*	*1.13*
11.5	0.44	*0.42*	*0.45*	0.51	*0.51*	*0.53*	0.71	*0.70*	*0.72*	0.95	*0.93*	*0.97*	1.09	*1.06*	*1.13*
12	0.44	*0.42*	*0.45*	0.51	*0.50*	*0.53*	0.71	*0.70*	*0.71*	0.95	*0.93*	*0.97*	1.09	*1.06*	*1.13*
12.5	0.44	*0.42*	*0.45*	0.51	*0.50*	*0.53*	0.7	*0.69*	*0.71*	0.95	*0.92*	*0.96*	1.09	*1.06*	*1.13*
13	0.44	*0.42*	*0.46*	0.51	*0.50*	*0.53*	0.7	*0.69*	*0.71*	0.95	*0.92*	*0.96*	1.09	*1.06*	*1.13*
13.5	0.44	*0.43*	*0.46*	0.51	*0.50*	*0.53*	0.7	*0.69*	*0.71*	0.94	*0.92*	*0.96*	1.08	*1.05*	*1.13*
14	0.45	*0.43*	*0.46*	0.51	*0.50*	*0.53*	0.7	*0.68*	*0.71*	0.94	*0.91*	*0.96*	1.08	*1.05*	*1.12*
14.5	0.45	*0.43*	*0.46*	0.51	*0.50*	*0.53*	0.69	*0.68*	*0.70*	0.93	*0.90*	*0.95*	1.07	*1.04*	*1.12*
15	0.45	*0.43*	*0.47*	0.52	*0.50*	*0.53*	0.69	*0.68*	*0.70*	0.93	*0.90*	*0.95*	1.07	*1.03*	*1.12*
15.5	0.45	*0.43*	*0.47*	0.52	*0.50*	*0.53*	0.69	*0.68*	*0.70*	0.92	*0.89*	*0.95*	1.07	*1.02*	*1.12*
16	0.45	*0.43*	*0.48*	0.52	*0.50*	*0.54*	0.69	*0.67*	*0.70*	0.92	*0.88*	*0.95*	1.06	*1.01*	*1.12*

	females (n=1226)														
age (years)	P3	*KI*		P10	*KI*		P50	*KI*		P90	*KI*		P97	*KI*	
0.5	0.5	*0.44*	*0.53*	0.59	*0.56*	*0.62*	0.83	*0.81*	*0.85*	1.12	*1.07*	*1.15*	1.27	*1.23*	*1.34*
1	0.5	*0.45*	*0.54*	0.59	*0.57*	*0.62*	0.82	*0.81*	*0.84*	1.11	*1.07*	*1.13*	1.26	*1.22*	*1.31*
1.5	0.51	*0.46*	*0.54*	0.6	*0.58*	*0.63*	0.82	*0.80*	*0.84*	1.09	*1.06*	*1.12*	1.24	*1.20*	*1.29*
2	0.51	*0.47*	*0.54*	0.6	*0.58*	*0.63*	0.82	*0.80*	*0.85*	1.08	*1.05*	*1.11*	1.22	*1.19*	*1.27*
2.5	0.52	*0.48*	*0.55*	0.6	*0.58*	*0.63*	0.81	*0.80*	*0.84*	1.07	*1.04*	*1.10*	1.2	*1.17*	*1.25*
3	0.52	*0.49*	*0.55*	0.6	*0.59*	*0.63*	0.81	*0.79*	*0.84*	1.05	*1.03*	*1.08*	1.18	*1.15*	*1.24*
3.5	0.52	*0.49*	*0.55*	0.6	*0.59*	*0.63*	0.8	*0.79*	*0.82*	1.04	*1.01*	*1.07*	1.17	*1.14*	*1.21*
4	0.52	*0.49*	*0.54*	0.6	*0.59*	*0.62*	0.8	*0.79*	*0.81*	1.03	*1.00*	*1.05*	1.15	*1.12*	*1.19*
4.5	0.52	*0.49*	*0.54*	0.6	*0.59*	*0.62*	0.79	*0.78*	*0.80*	1.02	*0.99*	*1.04*	1.13	*1.10*	*1.17*
5	0.52	*0.50*	*0.54*	0.6	*0.58*	*0.61*	0.79	*0.77*	*0.80*	1.01	*0.98*	*1.03*	1.12	*1.09*	*1.16*
5.5	0.52	*0.49*	*0.53*	0.59	*0.58*	*0.61*	0.78	*0.77*	*0.79*	1.00	*0.97*	*1.02*	1.11	*1.08*	*1.15*
6	0.51	*0.49*	*0.53*	0.59	*0.58*	*0.61*	0.78	*0.76*	*0.79*	0.99	*0.96*	*1.01*	1.1	*1.07*	*1.14*
6.5	0.51	*0.49*	*0.53*	0.59	*0.57*	*0.60*	0.77	*0.76*	*0.78*	0.99	*0.96*	*1.00*	1.1	*1.07*	*1.13*
7	0.51	*0.49*	*0.52*	0.58	*0.57*	*0.60*	0.77	*0.76*	*0.78*	0.98	*0.96*	*1.00*	1.09	*1.07*	*1.13*
7.5	0.5	*0.48*	*0.52*	0.58	*0.57*	*0.59*	0.76	*0.75*	*0.77*	0.98	*0.96*	*1.00*	1.09	*1.07*	*1.13*
8	0.49	*0.48*	*0.51*	0.57	*0.56*	*0.59*	0.76	*0.75*	*0.77*	0.98	*0.96*	*1.00*	1.1	*1.07*	*1.12*
8.5	0.49	*0.47*	*0.50*	0.57	*0.56*	*0.58*	0.76	*0.75*	*0.77*	0.98	*0.96*	*1.00*	1.1	*1.07*	*1.13*
9	0.48	*0.46*	*0.50*	0.56	*0.55*	*0.58*	0.76	*0.75*	*0.77*	0.98	*0.96*	*1.00*	1.1	*1.08*	*1.13*
9.5	0.47	*0.46*	*0.49*	0.56	*0.55*	*0.57*	0.75	*0.74*	*0.77*	0.98	*0.96*	*1.00*	1.1	*1.08*	*1.13*
10	0.47	*0.45*	*0.48*	0.55	*0.54*	*0.56*	0.75	*0.74*	*0.76*	0.98	*0.97*	*1.00*	1.11	*1.08*	*1.13*
10.5	0.46	*0.44*	*0.47*	0.54	*0.53*	*0.56*	0.74	*0.73*	*0.76*	0.98	*0.97*	*1.00*	1.11	*1.08*	*1.13*
11	0.45	*0.44*	*0.47*	0.54	*0.53*	*0.55*	0.74	*0.73*	*0.75*	0.98	*0.96*	*1.00*	1.11	*1.08*	*1.13*
11.5	0.45	*0.43*	*0.46*	0.53	*0.52*	*0.54*	0.74	*0.72*	*0.75*	0.98	*0.96*	*1.00*	1.11	*1.08*	*1.13*
12	0.44	*0.42*	*0.46*	0.53	*0.52*	*0.54*	0.73	*0.72*	*0.75*	0.98	*0.95*	*1.00*	1.1	*1.08*	*1.14*
12.5	0.44	*0.42*	*0.45*	0.52	*0.51*	*0.54*	0.73	*0.71*	*0.75*	0.98	*0.95*	*1.00*	1.1	*1.07*	*1.14*
13	0.44	*0.42*	*0.45*	0.52	*0.51*	*0.54*	0.73	*0.71*	*0.74*	0.97	*0.94*	*1.00*	1.1	*1.07*	*1.14*
13.5	0.43	*0.41*	*0.45*	0.52	*0.50*	*0.53*	0.73	*0.71*	*0.74*	0.98	*0.94*	*1.00*	1.1	*1.07*	*1.14*
14	0.43	*0.41*	*0.45*	0.52	*0.50*	*0.53*	0.73	*0.71*	*0.74*	0.98	*0.95*	*1.00*	1.11	*1.07*	*1.14*
14.5	0.43	*0.41*	*0.45*	0.52	*0.51*	*0.53*	0.73	*0.71*	*0.74*	0.98	*0.95*	*1.00*	1.11	*1.08*	*1.15*
15	0.43	*0.41*	*0.45*	0.52	*0.51*	*0.53*	0.73	*0.72*	*0.75*	0.98	*0.96*	*1.00*	1.11	*1.08*	*1.16*
15.5	0.43	*0.41*	*0.45*	0.52	*0.51*	*0.54*	0.74	*0.72*	*0.75*	0.99	*0.97*	*1.01*	1.12	*1.09*	*1.17*
16	0.43	*0.40*	*0.45*	0.52	*0.50*	*0.54*	0.74	*0.72*	*0.75*	1.00	*0.97*	*1.02*	1.13	*1.10*	*1.18*

Tab. 7: Lower (P3) and upper (P97) limit and lambda, mu, sigma for total cholesterol (mmol/l) in males (n = 1311) and females (n = 1193)

age	males (n= 1311)					females (n= 1193)				
(years)	P3	P97	L	M	S	P3	P97	L	M	S
0.5	2.48	5.14	0.79	3.76	0.19	2.81	5.73	0.44	4.13	0.19
1	2.55	5.14	0.75	3.79	0.18	2.84	5.72	0.43	4.14	0.18
1.5	2.62	5.15	0.71	3.82	0.18	2.88	5.71	0.43	4.15	0.18
2	2.68	5.16	0.67	3.85	0.17	2.91	5.69	0.43	4.17	0.18
2.5	2.74	5.18	0.63	3.89	0.17	2.94	5.68	0.43	4.18	0.17
3	2.79	5.21	0.59	3.92	0.16	2.96	5.66	0.43	4.19	0.17
3.5	2.84	5.25	0.55	3.96	0.16	2.99	5.64	0.43	4.20	0.17
4	2.88	5.29	0.52	4.00	0.16	3.02	5.62	0.42	4.20	0.16
4.5	2.92	5.34	0.48	4.04	0.16	3.04	5.60	0.42	4.21	0.16
5	2.96	5.38	0.44	4.07	0.16	3.06	5.59	0.42	4.22	0.16
5.5	2.99	5.43	0.41	4.10	0.16	3.08	5.58	0.41	4.22	0.16
6	3.02	5.47	0.37	4.13	0.16	3.09	5.58	0.41	4.23	0.16
6.5	3.04	5.52	0.33	4.16	0.16	3.10	5.59	0.40	4.24	0.16
7	3.06	5.56	0.30	4.18	0.16	3.11	5.60	0.40	4.25	0.16
7.5	3.07	5.60	0.26	4.20	0.16	3.12	5.61	0.39	4.25	0.16
8	3.09	5.64	0.23	4.21	0.16	3.13	5.62	0.38	4.26	0.16
8.5	3.09	5.68	0.19	4.23	0.16	3.13	5.62	0.38	4.26	0.16
9	3.10	5.72	0.16	4.24	0.16	3.12	5.63	0.37	4.26	0.16
9.5	3.09	5.75	0.12	4.24	0.16	3.12	5.63	0.37	4.26	0.16
10	3.09	5.78	0.09	4.24	0.17	3.10	5.64	0.36	4.25	0.16
10.5	3.07	5.79	0.06	4.23	0.17	3.09	5.64	0.35	4.24	0.16
11	3.05	5.78	0.02	4.20	0.17	3.07	5.63	0.35	4.23	0.16
11.5	3.03	5.76	-0.01	4.17	0.17	3.05	5.63	0.34	4.21	0.16
12	3.00	5.72	-0.04	4.13	0.17	3.03	5.63	0.34	4.20	0.16
12.5	2.97	5.66	-0.08	4.08	0.17	3.01	5.63	0.33	4.18	0.17
13	2.94	5.61	-0.11	4.04	0.17	3.00	5.63	0.33	4.18	0.17
13.5	2.91	5.55	-0.14	3.99	0.17	2.98	5.65	0.32	4.17	0.17
14	2.89	5.49	-0.17	3.95	0.17	2.97	5.67	0.31	4.17	0.17
14.5	2.87	5.44	-0.20	3.91	0.17	2.96	5.70	0.31	4.18	0.17
15	2.85	5.40	-0.23	3.87	0.17	2.96	5.74	0.30	4.19	0.18
15.5	2.83	5.36	-0.26	3.84	0.17	2.95	5.79	0.29	4.20	0.18
16	2.82	5.33	-0.30	3.82	0.17	2.95	5.84	0.29	4.22	0.18

Tab. 8: Lower (P3) and upper (P97) limit and lambda, mu, sigma for LDL cholesterol (mmol/l) in males (n = 1311) and females (n = 1192)

age	males (n= 1311)					females (n= 1192)				
(years)	P3	P97	L	M	S	P3	P97	L	M	S
0.5	1.09	3.34	0.74	2.14	0.28	1.29	3.88	0.38	2.37	0.29
1	1.13	3.36	0.71	2.16	0.28	1.32	3.91	0.39	2.40	0.28
1.5	1.17	3.38	0.69	2.19	0.27	1.35	3.92	0.39	2.43	0.28
2	1.21	3.40	0.66	2.21	0.27	1.38	3.93	0.39	2.45	0.27
2.5	1.24	3.43	0.64	2.23	0.26	1.40	3.92	0.40	2.47	0.27
3	1.26	3.45	0.62	2.25	0.26	1.43	3.90	0.40	2.48	0.26
3.5	1.29	3.47	0.59	2.27	0.26	1.45	3.86	0.40	2.48	0.26
4	1.30	3.49	0.57	2.28	0.26	1.46	3.82	0.41	2.48	0.25
4.5	1.32	3.51	0.54	2.30	0.25	1.47	3.78	0.41	2.47	0.25
5	1.33	3.53	0.52	2.31	0.25	1.48	3.75	0.42	2.46	0.24
5.5	1.34	3.55	0.49	2.31	0.25	1.49	3.71	0.42	2.46	0.24
6	1.35	3.57	0.47	2.32	0.25	1.49	3.69	0.42	2.45	0.24
6.5	1.36	3.59	0.44	2.32	0.25	1.50	3.67	0.43	2.45	0.24
7	1.36	3.61	0.42	2.33	0.26	1.50	3.66	0.43	2.44	0.23
7.5	1.37	3.62	0.39	2.33	0.26	1.50	3.66	0.44	2.44	0.23
8	1.37	3.64	0.37	2.33	0.26	1.50	3.66	0.44	2.44	0.23
8.5	1.38	3.66	0.34	2.34	0.26	1.49	3.66	0.44	2.44	0.24
9	1.38	3.68	0.32	2.34	0.26	1.48	3.66	0.45	2.44	0.24
9.5	1.38	3.70	0.29	2.34	0.26	1.47	3.66	0.45	2.43	0.24
10	1.38	3.71	0.27	2.34	0.26	1.46	3.66	0.46	2.43	0.24
10.5	1.38	3.72	0.24	2.33	0.26	1.45	3.66	0.46	2.42	0.24
11	1.38	3.73	0.22	2.33	0.26	1.43	3.65	0.47	2.40	0.25
11.5	1.37	3.72	0.19	2.31	0.26	1.41	3.65	0.47	2.39	0.25
12	1.37	3.70	0.16	2.30	0.26	1.39	3.64	0.48	2.38	0.25
12.5	1.36	3.68	0.14	2.28	0.26	1.38	3.64	0.48	2.37	0.25
13	1.36	3.65	0.11	2.26	0.26	1.36	3.64	0.49	2.36	0.26
13.5	1.36	3.62	0.09	2.24	0.26	1.35	3.65	0.49	2.36	0.26
14	1.36	3.59	0.06	2.22	0.26	1.33	3.66	0.50	2.35	0.26
14.5	1.36	3.56	0.04	2.21	0.26	1.32	3.68	0.50	2.36	0.27
15	1.36	3.53	0.01	2.19	0.25	1.31	3.70	0.51	2.36	0.27
15.5	1.36	3.52	-0.02	2.18	0.25	1.30	3.73	0.51	2.36	0.27
16	1.37	3.50	-0.04	2.18	0.25	1.30	3.75	0.52	2.37	0.28

Tab. 9: Lower (P3) and upper (P97) limit and lambda, mu, sigma for HDL cholesterol (mmol/l) in males (n = 1311) and females (n = 1193)

age	males (n= 1311)					females (n=1193)				
(years)	P3	P97	L	M	S	P3	P97	L	M	S
0.5	0.62	1.80	0.35	1.11	0.28	0.64	1.90	0.43	1.17	0.28
1	0.65	1.82	0.36	1.14	0.27	0.66	1.86	0.45	1.17	0.27
1.5	0.69	1.85	0.37	1.18	0.26	0.68	1.84	0.48	1.18	0.26
2	0.72	1.90	0.37	1.22	0.25	0.71	1.84	0.50	1.21	0.25
2.5	0.77	1.95	0.37	1.27	0.25	0.75	1.87	0.51	1.25	0.24
3	0.81	2.01	0.37	1.33	0.24	0.79	1.91	0.53	1.29	0.23
3.5	0.86	2.08	0.36	1.39	0.23	0.84	1.97	0.53	1.35	0.22
4	0.91	2.14	0.36	1.44	0.23	0.88	2.03	0.54	1.40	0.22
4.5	0.95	2.21	0.35	1.49	0.22	0.92	2.08	0.54	1.45	0.21
5	0.98	2.26	0.34	1.54	0.22	0.96	2.13	0.54	1.49	0.21
5.5	1.01	2.32	0.34	1.58	0.22	0.99	2.17	0.54	1.53	0.21
6	1.04	2.37	0.33	1.61	0.22	1.01	2.21	0.54	1.56	0.20
6.5	1.06	2.42	0.32	1.64	0.22	1.03	2.23	0.54	1.58	0.20
7	1.07	2.46	0.31	1.67	0.22	1.04	2.24	0.55	1.59	0.20
7.5	1.08	2.50	0.30	1.68	0.22	1.05	2.25	0.55	1.60	0.20
8	1.08	2.52	0.29	1.69	0.23	1.05	2.25	0.56	1.60	0.20
8.5	1.07	2.54	0.27	1.69	0.23	1.04	2.24	0.57	1.59	0.20
9	1.06	2.55	0.26	1.69	0.23	1.03	2.23	0.58	1.58	0.20
9.5	1.04	2.55	0.25	1.67	0.24	1.02	2.22	0.59	1.57	0.20
10	1.03	2.54	0.23	1.66	0.24	1.00	2.21	0.60	1.56	0.21
10.5	1.01	2.52	0.22	1.64	0.24	0.99	2.20	0.61	1.55	0.21
11	0.99	2.50	0.21	1.61	0.24	0.97	2.19	0.62	1.53	0.21
11.5	0.97	2.46	0.19	1.58	0.25	0.95	2.19	0.63	1.52	0.22
12	0.95	2.42	0.18	1.55	0.25	0.93	2.18	0.64	1.51	0.22
12.5	0.93	2.38	0.16	1.52	0.25	0.92	2.18	0.64	1.50	0.22
13	0.92	2.34	0.14	1.49	0.25	0.91	2.19	0.65	1.50	0.23
13.5	0.90	2.30	0.12	1.46	0.25	0.90	2.20	0.66	1.50	0.23
14	0.90	2.26	0.10	1.44	0.25	0.90	2.22	0.66	1.51	0.23
14.5	0.89	2.23	0.07	1.42	0.24	0.91	2.24	0.66	1.53	0.23
15	0.89	2.20	0.04	1.41	0.24	0.93	2.27	0.66	1.55	0.23
15.5	0.89	2.17	0.01	1.40	0.24	0.95	2.31	0.66	1.58	0.23
16	0.90	2.15	-0.02	1.39	0.23	0.97	2.34	0.65	1.60	0.23

Tab. 10: Lower (P3) and upper (P97) limit and lambda, mu, sigma for triglycerides (mmol/l) in males (n = 1311) and females (n = 1193)

age	males (n= 1311)					females (n=1193)				
(years)	P3	P97	L	M	S	P3	P97	L	M	S
0.5	0.61	4.66	-0.23	1.50	0.53	0.69	4.69	-0.27	1.59	0.50
1	0.52	3.83	-0.24	1.25	0.52	0.61	4.00	-0.29	1.38	0.49
1.5	0.45	3.18	-0.25	1.06	0.51	0.53	3.41	-0.30	1.19	0.48
2	0.39	2.67	-0.25	0.91	0.50	0.47	2.91	-0.31	1.03	0.47
2.5	0.35	2.29	-0.26	0.80	0.49	0.42	2.51	-0.32	0.90	0.47
3	0.32	2.01	-0.27	0.72	0.48	0.38	2.20	-0.33	0.80	0.46
3.5	0.30	1.81	-0.28	0.67	0.46	0.35	1.97	-0.34	0.73	0.45
4	0.29	1.66	-0.28	0.63	0.45	0.33	1.80	-0.35	0.67	0.44
4.5	0.28	1.56	-0.29	0.60	0.44	0.31	1.67	-0.36	0.64	0.43
5	0.28	1.48	-0.30	0.58	0.43	0.31	1.59	-0.37	0.62	0.43
5.5	0.28	1.43	-0.30	0.57	0.43	0.31	1.55	-0.38	0.61	0.42
6	0.27	1.40	-0.31	0.56	0.42	0.31	1.53	-0.38	0.61	0.41
6.5	0.27	1.39	-0.31	0.56	0.42	0.31	1.52	-0.39	0.61	0.41
7	0.27	1.40	-0.32	0.56	0.42	0.32	1.53	-0.39	0.62	0.41
7.5	0.28	1.42	-0.32	0.56	0.42	0.32	1.56	-0.39	0.63	0.41
8	0.28	1.47	-0.33	0.58	0.43	0.33	1.60	-0.39	0.64	0.41
8.5	0.29	1.54	-0.33	0.59	0.43	0.34	1.66	-0.39	0.66	0.41
9	0.29	1.63	-0.34	0.61	0.44	0.35	1.74	-0.39	0.68	0.42
9.5	0.30	1.72	-0.34	0.63	0.45	0.36	1.83	-0.38	0.71	0.42
10	0.30	1.80	-0.35	0.65	0.46	0.37	1.91	-0.37	0.74	0.43
10.5	0.31	1.88	-0.35	0.66	0.46	0.38	1.99	-0.36	0.76	0.43
11	0.31	1.94	-0.36	0.67	0.47	0.39	2.06	-0.35	0.79	0.43
11.5	0.32	1.99	-0.36	0.69	0.47	0.39	2.11	-0.34	0.81	0.44
12	0.32	2.02	-0.37	0.70	0.47	0.40	2.14	-0.33	0.82	0.44
12.5	0.33	2.03	-0.37	0.71	0.46	0.40	2.14	-0.31	0.83	0.43
13	0.34	2.03	-0.38	0.71	0.46	0.40	2.12	-0.30	0.83	0.43
13.5	0.35	2.02	-0.38	0.72	0.45	0.40	2.08	-0.28	0.83	0.43
14	0.35	2.00	-0.39	0.73	0.44	0.40	2.04	-0.26	0.83	0.43
14.5	0.36	1.97	-0.39	0.73	0.44	0.40	2.00	-0.24	0.83	0.42
15	0.36	1.94	-0.40	0.73	0.43	0.40	1.97	-0.22	0.83	0.42
15.5	0.37	1.92	-0.41	0.74	0.42	0.40	1.95	-0.20	0.83	0.42
16	0.37	1.91	-0.41	0.74	0.42	0.40	1.94	-0.18	0.84	0.41

Tab. 11: Lower (P3) and upper (P97) limit and lambda, mu, sigma for ApoA1 (g/l) in males (n = 1345) and females (n = 1224)

age (years)	males (n= 1345)					females (n=1224)				
	P3	P97	L	M	S	P3	P97	L	M	S
0.5	0.96	1.70	0.57	1.31	0.15	0.96	1.75	0.88	1.35	0.16
1	0.92	1.62	0.59	1.25	0.15	0.93	1.67	0.84	1.29	0.15
1.5	0.90	1.58	0.61	1.22	0.15	0.92	1.62	0.80	1.26	0.15
2	0.90	1.58	0.62	1.22	0.15	0.92	1.61	0.76	1.25	0.15
2.5	0.92	1.61	0.62	1.25	0.15	0.94	1.62	0.72	1.27	0.14
3	0.95	1.66	0.62	1.29	0.15	0.96	1.65	0.68	1.29	0.14
3.5	0.99	1.72	0.60	1.34	0.15	1.00	1.69	0.65	1.33	0.14
4	1.02	1.77	0.58	1.38	0.14	1.03	1.73	0.61	1.36	0.14
4.5	1.05	1.81	0.55	1.41	0.14	1.05	1.77	0.57	1.39	0.14
5	1.07	1.84	0.52	1.43	0.14	1.08	1.79	0.54	1.41	0.13
5.5	1.09	1.87	0.50	1.46	0.14	1.09	1.81	0.51	1.43	0.13
6	1.11	1.91	0.47	1.48	0.14	1.10	1.82	0.48	1.44	0.13
6.5	1.13	1.94	0.44	1.50	0.14	1.11	1.82	0.45	1.44	0.13
7	1.14	1.96	0.41	1.52	0.14	1.12	1.83	0.42	1.45	0.13
7.5	1.15	1.97	0.38	1.53	0.14	1.14	1.84	0.40	1.46	0.13
8	1.15	1.98	0.35	1.53	0.14	1.15	1.85	0.37	1.47	0.13
8.5	1.16	1.99	0.31	1.54	0.14	1.15	1.86	0.35	1.48	0.13
9	1.16	2.00	0.28	1.54	0.14	1.16	1.86	0.33	1.48	0.13
9.5	1.16	2.01	0.25	1.54	0.14	1.16	1.87	0.31	1.48	0.13
10	1.16	2.01	0.22	1.54	0.14	1.15	1.86	0.30	1.48	0.13
10.5	1.15	2.00	0.18	1.53	0.15	1.14	1.85	0.28	1.47	0.13
11	1.14	1.97	0.15	1.51	0.15	1.12	1.84	0.26	1.45	0.13
11.5	1.11	1.94	0.12	1.48	0.15	1.10	1.82	0.25	1.42	0.13
12	1.09	1.90	0.09	1.44	0.15	1.07	1.81	0.23	1.40	0.14
12.5	1.06	1.86	0.06	1.41	0.15	1.05	1.80	0.22	1.39	0.14
13	1.03	1.83	0.03	1.38	0.15	1.04	1.81	0.20	1.38	0.15
13.5	1.01	1.80	-0.01	1.35	0.15	1.02	1.83	0.19	1.38	0.15
14	1.00	1.79	-0.04	1.34	0.15	1.02	1.86	0.18	1.39	0.16
14.5	1.00	1.79	-0.08	1.33	0.15	1.02	1.91	0.16	1.41	0.17
15	1.00	1.79	-0.12	1.33	0.15	1.03	1.98	0.14	1.44	0.17
15.5	1.01	1.79	-0.16	1.33	0.15	1.05	2.07	0.13	1.48	0.18
16	1.01	1.79	-0.20	1.33	0.15	1.07	2.15	0.11	1.53	0.19

Tab. 12: Lower (P3) and upper (P97) limit and lambda, mu, sigma for ApoB (g/l) in males (n= 1345) and females (n= 1226)

age (years)	males (n= 1345)					females (n=1226)				
	P3	P97	L	M	S	P3	P97	L	M	S
0.5	0.42	1.13	0.87	0.76	0.25	0.50	1.27	0.34	0.83	0.25
1	0.43	1.12	0.85	0.76	0.24	0.50	1.26	0.35	0.82	0.24
1.5	0.44	1.10	0.82	0.76	0.23	0.51	1.24	0.35	0.82	0.23
2	0.45	1.09	0.80	0.75	0.23	0.51	1.22	0.36	0.82	0.23
2.5	0.45	1.08	0.77	0.75	0.22	0.52	1.20	0.36	0.81	0.22
3	0.46	1.07	0.75	0.75	0.22	0.52	1.18	0.37	0.81	0.22
3.5	0.46	1.07	0.72	0.75	0.22	0.52	1.17	0.38	0.80	0.21
4	0.46	1.06	0.70	0.74	0.22	0.52	1.15	0.38	0.80	0.21
4.5	0.46	1.06	0.67	0.74	0.21	0.52	1.13	0.39	0.79	0.20
5	0.46	1.06	0.65	0.74	0.22	0.52	1.12	0.39	0.79	0.20
5.5	0.46	1.06	0.62	0.74	0.22	0.52	1.11	0.40	0.78	0.20
6	0.46	1.06	0.59	0.73	0.22	0.51	1.10	0.41	0.78	0.20
6.5	0.46	1.06	0.56	0.73	0.22	0.51	1.10	0.41	0.77	0.20
7	0.45	1.07	0.53	0.73	0.22	0.51	1.09	0.42	0.77	0.20
7.5	0.45	1.07	0.50	0.73	0.23	0.50	1.09	0.42	0.76	0.21
8	0.45	1.07	0.47	0.72	0.23	0.49	1.10	0.43	0.76	0.21
8.5	0.45	1.08	0.43	0.72	0.23	0.49	1.10	0.43	0.76	0.21
9	0.44	1.08	0.40	0.72	0.23	0.48	1.10	0.44	0.76	0.22
9.5	0.44	1.08	0.36	0.72	0.24	0.47	1.10	0.44	0.75	0.22
10	0.44	1.09	0.33	0.72	0.24	0.47	1.11	0.45	0.75	0.23
10.5	0.44	1.09	0.29	0.71	0.24	0.46	1.11	0.46	0.74	0.23
11	0.44	1.09	0.25	0.71	0.24	0.45	1.11	0.46	0.74	0.23
11.5	0.44	1.09	0.21	0.71	0.24	0.45	1.11	0.47	0.74	0.24
12	0.44	1.09	0.18	0.71	0.24	0.44	1.10	0.47	0.73	0.24
12.5	0.44	1.09	0.14	0.70	0.24	0.44	1.10	0.48	0.73	0.24
13	0.44	1.09	0.10	0.70	0.24	0.44	1.10	0.48	0.73	0.24
13.5	0.44	1.08	0.06	0.70	0.24	0.43	1.10	0.49	0.73	0.24
14	0.45	1.08	0.02	0.70	0.23	0.43	1.11	0.49	0.73	0.25
14.5	0.45	1.07	-0.02	0.69	0.23	0.43	1.11	0.50	0.73	0.25
15	0.45	1.07	-0.06	0.69	0.23	0.43	1.11	0.50	0.73	0.25
15.5	0.45	1.07	-0.10	0.69	0.23	0.43	1.12	0.51	0.74	0.25
16	0.45	1.06	-0.14	0.69	0.23	0.43	1.13	0.51	0.74	0.25

III ERKLÄRUNG ÜBER DIE EIGENSTÄNDIGE ABFASSUNG DER ARBEIT

Hiermit erkläre ich, Anne Dathan-Stumpf, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren.

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Datum Unterschrift

IV CURRICULUM VITAE

Persönliche Daten

Name: Anne Dathan-Stumpf, geb. Dathan

Geburtsdatum: 16.04.1990

Geburtsort: Karl-Marx-Stadt

Nationalität: deutsch

Familienstand: verheiratet, 1 Kind

Medizinische Ausbildung

Seit 05/ 2016	Praktisches Jahr im Rahmen des Studiums der Humanmedizin, Medizinische Fakultät der Universität Leipzig
2012 - 2016	Klinischer Abschnitt des Studiums der Humanmedizin, Medizinische Fakultät der Universität Leipzig (Abschlussnote der zweiten ärztlichen Prüfung: 2,0)
2010 - 2012	Vorklinischer Abschnitt des Studiums der Humanmedizin, Medizinische Fakultät der Universität Leipzig (Abschlussnote der ersten ärztlichen Prüfung: 2,0)

Praktische Erfahrungen

03/ 2015	Famulatur, pädiatrischen Praxis auf der Holzhäuser Str. 81, Dr. med. André Braun, Leipzig
09/ 2013 - 10/ 2013	Famulatur, gynäkologische Praxis am Johannisplatz 1, Dr. med. Arnd Besser, Leipzig
07/ 2013 - 08/ 2013	Famulatur, Universitätsklinikum Leipzig, Klinik und Poliklinik für Augenheilkunde
03/ 2013 - 04/ 2013	Famulatur, Universitätsklinikum Leipzig, Gastroenterologie
07/ 2011 - 09/ 2011	Krankenpflegepraktikum, Klinikum Chemnitz, kardiologische und internistische Intensivstation
02/ 2011 - 03/ 2011	Krankenpflegepraktikum, Klinikum Chemnitz, gastroenterologische und internistische Intensivstation
02/ 2011	Praktikum im OP-Saal, Klinikum Chemnitz

Dissertation

Seit 01/2013	Mitarbeit am LIFE-Child Projekt im Bereich der Datennacherfassung und Bereinigung

Schulische Ausbildung

06/ 2010	Allgemeine Hochschulreife, Sportgymnasium Chemnitz (Abschlussnote: 1,3)
2001 - 2010	Sportgymnasium Chemnitz, Sportart: Schwimmen
1997 - 2001	Seeber Grundschule Niederwiesa

Sonstige Tätigkeiten

2011 - 2016	Tätigkeit im gastronomischen Dienstleistungsbereich
2010 - 2011	Tätigkeit als Hostess auf verschiedenen Messen und Großveranstaltungen
2009 - 2010	einjährige Trainerarbeit im Nachwuchskader des SCC v. 1892 e.V.

Sprach- und EDV-Kenntnisse

Deutsch (Muttersprache)
Englisch
Latein (kleines Latinum)
Microsoft-Office 2013 (Grundkenntnisse)
Statistiksoftware R (Grundkenntnisse)

V DANKSAGUNG

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