JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń

Cite as: MAJCHRZAK, Mateusz, GRACZYK, Natalia, GRACZYK, Martyna, WISOKY, Wiktor, CZAPLA, Natalia, ZIÓŁKOWSKA, Weronika, STRÓŻYŃSKA, Ewelina, ŁOPIŃSKA, Joanna, MAJCHRZYCKA, Marta and IGNYŚ, Piotr. Sexual Dimorphism and Aging as Determinants of Serum Lipid Profiles and Cardiovascular Risk. Journal of Education, Health and Sport. 2026;91:70887. https://doi.org/10.12775/JEHS.2026.91.70887

ARTICLE TIMELINE
Received: 14.04.2026 Revised: 15.05.2026
Accepted: 16.05.2026 Published: 23.05.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Title: Sexual Dimorphism and Aging as Determinants of Serum Lipid Profiles and Cardiovascular Risk

Authors:

Mateusz Majchrzak, ORCID http://orcid.org/0009-0008-4775-7525
E-mail: majchrzak.lekarz@gmail.com
University Clinical Hospital in Poznań,
49 Przybyszewskiego Street, 60-355 Poznań, Poland

Natalia Graczyk, ORCID https://orcid.org/0009-0000-1140-6004
E-mail nataliagraczyk09@gmail.com
University Clinical Hospital in Poznań,
49 Przybyszewskiego Street, 60-355 Poznań, Poland

Martyna Graczyk, ORCID https://orcid.org/0009-0000-3646-6441
E-mail: martynagraczyk8@gmail.com
MSWiA Hospital in Opole,
44 Krakowska Street, 45-075 Opole, Poland

Wiktor Wisoky, ORCID http://orcid.org/0009-0009-7226-9133
E-mail: ww.wiktor.wisoky@gmail.com
University Clinical Hospital in Poznań,
49 Przybyszewskiego Street, 60-355 Poznań, Poland

Natalia Czapla ,ORCID http://orcid.org/0009-0001-9029-5759
E-mail: nataliaczaplapoczta@gmail.com
University Clinical Hospital in Poznań,
49 Przybyszewskiego Street, 60-355 Poznań, Poland

Weronika Ziółkowska, ORCID http://orcid.org/0009-0003-1896-7877
E-mail: weronika.ziolkowskaa@gmail.com
Karol Marcinkowski University Hospital in Zielona Góra,
26 Zyty Street, 65-046 Zielona Góra, Poland

Ewelina Strużyńska, ORCID http://orcid.org/0009-0003-7749-0052
E-mail: ewelinastruzynskaa@gmail.com
University of Zielona Góra: Zielona Góra, Lubusz, Poland

Joanna Łopińska, ORCID http://orcid.org/0009-0009-7554-8023
E-mail: joanna.lopinska96@gmail.com
University Clinical Hospital in Poznan,
49 Przybyszewskiego Street, 60-355 Poznań, Poland

Marta Majchrzycka, ORCID http://orcid.org/0009-0009-1359-1253
E-mail: marta.majchrzycka@onet.pl
1University Clinical Hospital in Poznan,
49 Przybyszewskiego Street, 60-355 Poznań, Poland

Piotr Ignyś, ORCID http://orcid.org/0009-0009-5938-5412
E-mail: ignyspiotr88@gmail.com
4University of Zielona Góra: Zielona Góra, Lubusz, PL

Corresponding Author
Mateusz Majchrzak,e-mail: majchrzak.lekarz@gmail.com

Abstract
The complex variability of circulating blood lipid profiles serves as a fundamental physiological indicator for the onset and progression of numerous metabolic and chronic conditions. It is clinically well-established that dyslipidemia—a multifaceted metabolic state characterized by pathologically elevated lipid concentrations—functions as a primary driver in the pathogenesis of atherosclerosis and subsequent cardiovascular disease. Given that the systematic reduction of these lipid fractions, whether through pharmacological intervention or lifestyle modification, can drastically improve a patient's long-term cardiovascular prognosis, a nuanced understanding of lipid distribution is critical for effective clinical management.
This review provides a comprehensive analysis of the various biological determinants that govern these fluctuations, with a particular emphasis on the distinct roles of sex-based hormonal profiles and age-related physiological shifts. By examining the interplay between these factors, we aim to elucidate how they independently and synergistically influence the serum concentrations of triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Furthermore, the discussion explores how these demographic variables modulate the metabolic pathways responsible for both the accumulation of pro-atherogenic particles and the efficiency of reverse cholesterol transport, ultimately shaping an individual's overall cardiovascular risk profile.
Methods:
This study was conducted as a comprehensive review of existing scientific literature and clinical guidelines (including AHA, ACC, and ESC/EAS) regarding lipoprotein metabolism. We analyzed the pathophysiological mechanisms through which non-modifiable risk factors—specifically age and biological sex—influence lipid profiles. The research focused on synthesizing data from biochemical studies (e.g., enzyme activity like CYP7A1, LPL, and PCSK9), genetic expression and epidemiological observations. By integrating findings on hormonal regulation and age-related cellular changes, we aimed to provide a holistic overview of how these determinants dictate long-term cardiovascular risk and influence clinical diagnostic criteria.

Key words: Lipoprotein metabolism, Cardiovascular disease risk, Dyslipidemia, Aging, Sexual dimorphism, Estrogen and Testosterone, LDL, Adipose tissue distribution

Introduction

Lipoprotein metabolism involves a sophisticated array of biochemical processes that engage various tissues across the human organism [1]. It is well-documented that abnormal serum lipoprotein levels constitute an essential risk factor for cardiovascular diseases (CVD), which remain the leading global cause of mortality among adults [2]. Specifically, dyslipidemias characterized by elevated triglycerides (TG) and reduced high-density lipoprotein (HDL) concentrations serve as direct contributors to metabolic instability and are intrinsically interconnected with all five diagnostic criteria for metabolic syndrome [3].
Furthermore, the clinical significance of these lipids is underscored by the inclusion of high total cholesterol (TC) in Systematic Coronary Risk Estimation (SCORE) models, highlighting their role as the pathophysiological foundation of modern civilization diseases [4]. Beyond these standard metrics, lipoprotein concentrations represent the majority of biochemical markers used to assess the risk of atherosclerotic cardiovascular disease (ASCVD) [5].

Numerous studies in the literature emphasize the profound connection between lipid profiles and individual demographic factors. Age and sex serve as the unmodifiable baselines for all comprehensive CVD risk assessments [4]. Critical transitions in lipoprotein metabolism predominantly occur at biological aging breakthrough points, suggesting that identical CVD risk factors may carry different clinical relevance depending on an individual's age and sex [6,7,8,9]. Understanding these nuances is therefore vital for tailoring preventive strategies and improving long-term patient outcomes.

Age

Aging was proven to be a principal unmodifiable risk factor in various atherosclerotic cardiovascular diseases. Age is described as an independent risk factor due to its role in ASCVD development in the elderly. The aging process constitutes a liability for every group of people, regardless of the presence of other risk factors and unhealthy habits.[10] However, the modifiable risk factors can be changed by specific treatment and behavior, contradistinctively to age. Obsolescence causes a higher risk of ASCVD in the elderly affected by modifiable factors than in the healthy and unaffected. [11]

Advanced age predisposes to alterations of lipoprotein metabolism pathways, which leads to many changes in lipoprotein concentration and function.

The activity of lipoprotein lipase decreases with age. The research conducted on the soleus muscles of rats corroborates this statement.[12] The rate at which LPS enzyme activity decreases is between 55 and 60 percent, being one of the reasons for age-induced lipoprotein metabolism alterations. This process is presumably a result of age-related changes in the function of hormones that influence lipid metabolism, including leptin, epinephrine, and somatropin.[13]

Age-caused increase in reactive oxygen species (ROS) affects the accumulation of hepatic cholesterol in the liver. Elevated ROS levels increase synthesis de novo of hepatic cholesterol by boosting expression of SREBP-2 protein and intensify cholesterol and glucose uptake in the hepatic cells.

It leads to a higher accumulation of cholesterol in the liver, its concentration in hepatic cells, and an overall increase of hepatic cholesterol level with age.[14]

Various studies have shown that getting older results in an increase of LDL-C despite the sex of examined subjects. Although there is not any known mechanism, scientific researches made on that topic lead to hypothetical reasons for LDL-C concentration alterations.

Intensified intestinal cholesterol absorption and lowered number of hepatic LDL receptors (LDLRr) lead to LDL-C increase up to +34mg/dL. Framingham Study shows that LDL-C rises respectively from 97.08 - 100.44mg/dL at the age of 15-19, to 132.25 - 156.91mg/dL in 75-79 aged adults of both sexes.[15] Furthermore, the rate of LDL-C clearance from the blood system is reduced during the lifetime. As a result of the reduction of hepatic LDLr number caused by the aging process.[16,17] LDLr takes part in the process of removing apo B-100 from the plasma, additionally VLDL and LDL particles from the bloodstream. Furthermore, decreased levels of LDLr is the cause of elevated concentration of LDL-C VLDL-C and apo B-100 lipoproteins in the elderly.[18]

Advanced age leads to bile acid synthesis decrease, caused directly by the deadening of Cholesterol 7 alpha-hydroxylase (CYP7AI) enzyme activity. CYP7AI is responsible for converting cholesterol to 7-alpha-hydroxycholesterol, which can result in age-related dysregulation of lipoprotein metabolism.[19] There is a significant role of aberrations in proprotein convertase subtilisin kexin-9 (PSCK9). This enzyme binds the A-domain of LDLr, which causes the LDLr degradation

process. PCSK9 is regulated by SREBP-2 and its levels seem to rise with age, which is the reason for low LDLr level and high LDL-C concentration in the elderly.[20]
HDL-C concentration is also dependent on aging.[25] HDL-C levels tend to rise in adults, until the age of 50-55, then it starts to diminish. The age-caused reduction of the atheroprotective HDL-C leads to the pathogenesis of ASCVD.[21] The rate at which HDL-C concentrations decrease per year in people aged 50-93 is a 1% average decrease in males and an 0,8% average decrease in females [22].
Age-induced changes in levels of specific lipoprotein fraction alter overall lipoprotein balance and cause changes in Total Cholesterol level. Through various studies, a particular trend has been observed. The average level of TC gets higher during the first 50 years of life, and after reaching its peak, decreases in both elderly men and women. The depletion starts between 50 and 55 years of age, and parallelly the decrease of HDL-C concentration occurs at the same age period. [23] However, a reduction in TC level is lower in women than in men. Nevertheless, a small amount of scientific research suggests an increase of TC level after 50-55 years, although these statements rely on small trials of humble representativeness [24].
Changes induced by advancing age in the lipoprotein metabolism and lipoprotein levels include an increase in the concentration of LDL-C, VLDL-C, and apo B-100 lipoprotein fractions. Additionally, a decrease in HDL-C concentration and TC levels. Getting older is also the reason for increased hepatic cholesterol accumulation. Those changes directly lead to alterations in lipoprotein fractions in the elderly, and because of that, different recommendations for lipid values are proposed for both children and adults by the American Heart Association and the American College of Cardiology. Their purpose is to minimize the risk of ASCVD and clarify the effects of abnormal lipid concentration treatment [25].

Comparison of desirable, acceptable and abnormal blood lipoprotein fraction concentration of children and adult* [mg/dl]

	children			adult		
	desirable	acceptable	abnormal	desirable	acceptable	abnormal
TC	<170	170-199	>199	<200	200-239	>239
LDL-C	<110	110-129	>129	<100	130-159	>159
HDL-C	>45	40-45	<40	>60	40-60	<40

*According to Grundy et al. 2019

Those recommendations are not included in the European Society of Cardiology and the European Atherosclerosis Society guidelines for the treatment of dyslipidaemias [3]. However, European guidelines include a recommendation for specific supervision of dyslipidaemias in people over 65 years old. The statins treatment is especially advised because it helps achieve a healthy and desired LDL-C concentration, which results in lowered ASCVD risk. The presence of individual references

for people at an advanced age in both American and European guidelines indicates the importance of age as an individual risk factor of ASCVD. The determinant is directly related to age-induced alteration of lipoprotein metabolism.

Sex

Sex hormones' levels are pivotal factors, which determine lipoprotein levels, which correlate with atherosclerotic cardiovascular disease (ASCVD) risk. High levels of estrogens (primarily estradiol and progesterone) induce mechanisms responsible for advantageous (in comparison to men that are generally more prone to hyperlipidemias and ASCVD [26]) differences in triglyceride, free fatty acid, and cholesterol metabolism. Additionally, statistically more women than men present healthy lifestyle behaviors, such as acknowledging the risk of being overweight and expressing a desire to lose weight or actively trying to [27] The distribution of body fat plays a crucial role in lipoprotein, fatty acids, and triglyceride blood levels. Estrogen is responsible for the sex-bias expression of the liver genes that code lipid metabolism enzymes, which results in significant differences in serum cholesterol fraction levels and lipid metabolism. It is crucial to indicate the noteworthy decrease in sex hormones' levels after menopause hence postmenopausal women will be distinguished from women prior to menopause in this chapter. Postmenopausal women show a higher predisposition to hyperlipidemias comparable to that typical of men. Wherethrough, data shows that before the age of 75 primarily men die from ASCVD (twice as much before 65), but cardiovascular disease (CVD) accounts for a higher percentage in causes of death in women, probably because the risk increases with age [28] and women tend to live longer [29]. That ultimately results in more women dying of cardiovascular disease [30]. The impact of sex hormones' levels on lipoproteins levels and ASCVD risk is still under-researched.

Distribution of adipocytes and lipid storage

Women customarily have a higher body fat percentage than men. Moreover, there are essential differences in adipocytes and lipid distribution. Women generally store body fat in subcutaneous depots of gluteal-femoral regions, whereas men accumulate adipocytes in the visceral area [31]. This discrepancy is attributable to estrogen regulating pre-adipocytes maturation, promoting white adipogenic lineage through estrogen receptor alpha (Erα). Estrogen promotes insulin sensitivity and activates adiponectin- mediators of subcutaneous body fat distribution [32]. Additionally, ectopic body fat is stored in muscles (more typical for women) and liver (storage more prominent in men) [33]. The differences are caused by sex hormone signaling in adipocytes. Women after menopause tend to have their body fat redistributed to visceral depots, which comes with losing the favorable body fat distribution and increasing the risk of metabolic and cardiovascular diseases [34]. Both women and men with central obesity independently present an adverse CVD risk profile, enhanced insulin resistance, increased low-density lipoprotein (LDL) and triglycerides (TG), additionally a decline in size, concentration, and function of high-density lipoprotein (HDL) [35,36]. Evidence indicates that catecholamine-induced lipolysis profoundly differs between upper and lower body fat in women, simultaneously being relatively consistent in men. There are indications that oxidation of fatty acids occurs more efficiently in men than in women [37]. All of these factors are directly connected to estrogen signaling, which furthermore corroborates the hypothesis of sex hormones induced metabolic pathways, therefore specific lipid distribution.

Estrogen

Women primarily produce estrogens in ovaries, although after menopause, the hormone level significantly decreases. Inversely, the ASCVD risk abruptly increases. Therefore, it is believed that

estrogen is preventative of ASCVD by having advantageous effects on lipid liver metabolism and serum lipoprotein levels. The proposed pathway of regulation is via estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), or G-protein coupled estrogen receptor (GPER) [38]. There are around one thousand liver genes upregulated by sex hormones. Estrogen seems to activate genes related to favorable lipid metabolism. Differences include enhanced very low-density lipoprotein (VLDL) secretion in response to fatty acid delivery that prevents liver fat accumulation [39] and further accelerated TG-rich VLDL clearance [40]. Additionally, estrogen is responsible for reducing the transcytosis of LDL in endothelial cells. Moreover, it enhances macrophage cholesterol efflux potential and mediates primary steps in reverse cholesterol transport. All of the mentioned estrogen effects will be further explicated in the following chapters.

LDL

Estrogens display antioxidant effects on LDL and the arterial wall, protecting the body from atherosclerosis. Additionally, estrogen is responsible for reducing the transcytosis of LDL in endothelial cells. It does so by impacting the SR-B1 pathway, which is activated by estrogen binding to the G protein-coupled estrogen receptor [41]. It lessens the risk of atherosclerosis for women prior to menopause in comparison with women post-menopause and men. Surprisingly, treatment of arterial endothelial cells with estrogen gave satisfactory results in men but turned out to be a failure in postmenopausal women. The basis on which the discrepancy occurs is yet to be discovered.

HDL

There are pronounced differences in HDL levels between sexes, especially in the concentration of large HDL particles [42]. The divergence of methylation profile in the liver between women's (higher average methylation in the X-chromosome) and men's (higher average methylation in autosomes) genes are believed to be the cause. On this account, females display higher expression of the KDM6A gene, silencing of which in cultured cells was associated with decreased HDL levels and apolipoprotein A1 (APOA1) production. APOA1 is a primary component of HDL particles and could have an anti-clotting effect, counteracting atheroma formation [43]. Therefore, there is a systematic distinction between medical norms of HDL levels for women (>50 mg/d) and men (>40 mg/d). Evidence shows that derivatives of estradiol, primarily 17β-estradiol fatty acyl esters, enhance macrophage cholesterol efflux potential and mediate primary steps in reverse cholesterol transport. Scavenger receptor class B type 1 (SR-BI) and estrogen receptors are responsible for the regulation of this pathway. Consequently, HDLs ability to remove excess cholesterol from foam cells and its portage to the liver, where excretion occurs, results in lowering the risk of cardiovascular events [44]. Nonetheless, there is some research contradicting these findings and stating that there are no differences in the cholesterol efflux capacity of HDL between men and women, either pre- or postmenopause [34]. Elevated levels of HDL in women translate to intensified amount and activity of paraoxonase-1 (PON1)- an essential antioxidant enzyme of HDL, which also seems to co-active the cholesterol efflux from macrophages . Studies show that PON1 may be upregulated by estradiol, but menopause does not correlate with a relevant decrease of PON1 activity [35]. Therefore, PON1 has been associated with reducing ASCVD risk in some works [45], while being contradicted in others [46]. Obesity in women is associated with a decrease in the activity of PON1, proving that its levels correlate with anthropometric measures, including BMI and waist circumference [47]. There is evidence that HDL promotes endothelial protection and is associated with increased release of nitric oxide from endothelial cells although the biological functions of HDL are altered in patients with coronary disease or diabetes [48].

However, HDL-associated estradiol therapy stimulates endothelial NO synthase and consequently vasodilation in postmenopausal women, lessening unfavorable effects of HDL alterations [49]. Thus it might also be effective in men, but there is not enough data to corroborate this statement.

TG and VLDL

During the fasted state, triglycerides are packed into VLDL, which are more profoundly produced by women. Females present excess activity of LPL in response to VLDL particles, resulting in better clearance of TG and overall contributes to lower blood TG levels. Parallelly in the fed state TGs circulate in the form of chylomicrons that women have a better clearing of than men [50]. Increased blood levels seem to correlate more strictly to increased ASCVD risk in females, but the cause remains unknown. Estrogen signaling appears to play a crucial role in preventing non-alcoholic fatty liver disease (NAFLD), insulin resistance, fatty liver, weight gain, and dyslipidemias. Therefore those disease entities become significantly more occurrent in postmenopausal women and gradually with age are instanced in men [51]. Estrogens act directly in the liver via hepatocyte estrogen receptor alpha in metabolizing of TGs [52]. Conducted tests advocate that loss of Erα in hepatocytes manifests itself by increased expression of lipid synthesis genes, additionally genes involved in the inflammatory process and collagen deposition. Hepatocyte Erα deprivation also results in decreased expression of genes that encode PL transfer protein and hepatic lipase- vital to cyclic liver lipid metabolism [53]. A particular mechanism of this regulation is under research, but the impact of liver X receptor α, nuclear receptor Small Heterodimer Partner (SHP), or microRNA mir-125b are suggested to participate in the process [50]. Additionally, estrogen possibly promotes fatty acid oxidation in the liver by enhancing the production of fibroblast growth factor 21 (FGF21) [54].

Lp A

Here is a negligible correlation between biological sex and lipoprotein(a) concentrations. [55].

Testosterone

Testosterone tends to have a different impact on ASCVD risk under specific circumstances. Generally, in men, low levels of testosterone and sex hormone-binding globulin (SHBG) are associated with insulin resistance and related diseases like type 2 diabetes, NAFLD, and metabolic syndrome [56]. Metabolic syndrome plays a crucial role in the hypothesized mechanism of increased ASCVD risk with testosterone deficiency because it constitutes a risk factor [57]. Reduced testosterone levels correlate with increased fasting glucose and insulin, which can be treated with the intake of testosterone, which improves muscle glucose metabolism and insulin sensitivity [58]. However, there are some studies with contradicting results, stating that there is no incontrovertible connection between testosterone levels and ASCVD risk [59]. Furthermore, some indicate that high androgens levels increase susceptibility [60]. Experiments regarding the role of the Androgen Receptor suggest that it curtails ASCVD risk and lowers glucose and lipid risk factors [61].

Conclusions

The primary objective of this review is to provide a holistic synthesis of the multifaceted influence exerted by non-modifiable determinants on specific lipoprotein concentrations. Such an analytical undertaking is imperative in the current clinical landscape, given that suboptimal lipid profiles—collectively termed dyslipidemia—remain the predominant and most pervasive risk factor for cardiovascular diseases (CVD), which continue to stand as the leading cause of global mortality. Within the complex interplay of factors contributing to lipid variability, biological aging and sexual dimorphism emerge as foundational, non-modifiable pillars that dictate a patient's long-term cardiovascular trajectory.

The most significant and well-documented impact of senescence on the lipidic landscape is the progressive elevation of low-density lipoprotein (LDL) cholesterol. This phenomenon is primarily driven by a mechanistic decline in the expression and activity of hepatic LDL receptors (LDL-R), which impairs the liver's capacity to clear pro-atherogenic particles from systemic circulation. However, contemporary research is increasingly pivoting toward auxiliary but equally critical mechanisms. These include the exacerbation of systemic oxidative stress, age-dependent alterations in key enzyme activities (such as CETP or LCAT), and the pathological sequestration of cholesterol within hepatic tissues. Collectively, these physiological shifts do not merely alter blood chemistry but contribute to a cumulative and progressive escalation of cardiovascular risk over the human lifespan.

Furthermore, the sexual dimorphism observed in lipid profiles is largely mediated by the complex physiological influence of sex hormones, most notably estrogen. Estrogen plays a cardioprotective role by modulating the metabolic pathways that govern lipid synthesis and clearance. The most prominent mechanisms underlying these sex-based differences involve distinct, hormonally-driven patterns of adipocyte distribution—specifically the variance between android and gynoid fat deposition—as well as significant fluctuations in high-density lipoprotein (HDL) concentrations. By elucidating these biological nuances, this review seeks to bridge the gap between basic lipidology and personalized clinical risk assessment, emphasizing that "normal" lipid values must always be interpreted through the prism of an individual's biological age and sex.

Disclosures:

Author's contribution:
Conceptualization: Mateusz Majchrzak, Natalia Graczyk
Methodology: Wiktor Wisoky, Ewelina Strużyńska, Mateusz Majchrzak
Formal analysis: Natalia Graczyk, Joanna Łopińska, Natalia Czapla
Investigation: Wiktor Wisoky, Piotr Ignyś
Resources: Joanna Łopińska, Weronika Ziółkowska
Writing-rough preparation: Martyna Graczyk, Marta Majchrzycka, Piotr Ignyś
Writing-review and editing: Natalia Graczyk, Martyna Graczyk, Mateusz Majchrzak
Visualization: Ewelina Strużyńska, Marta Majchrzycka, Weronika Ziółkowska
Supervision: Mateusz Majchrzak, Natalia Graczyk, Natalia Czapla
Project administration: Mateusz Majchrzak

All authors have read and agreed to the published version of the manuscript.

Disclosure: Authors do not report any disclosures.
Funding Statement: No funding was received.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Acknowledgments: Not applicable.
Conflict of Interest Statement: Authors have declared no conflict of interest.

Declaration on the use of AI: In preparing this work, the authors used Grammarly for the purpose of improving language and readability, text formatting, and verification of bibliographic styles. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

Bibliography:

1. Kwan, Bonnie C. H., Florian Kronenberg, Srinivasan Beddhu, and Alfred K. Cheung. "Lipoprotein Metabolism and Lipid Management in Chronic Kidney Disease." *Journal of the American Society of Nephrology* 18, no. 4 (April 1, 2007): 1246–61. https://doi.org/10.1681/ASN.2006091006.
2. Virani, Salim S., Alvaro Alonso, Hugo J. Aparicio, Emelia J. Benjamin, Marcio S. Bittencourt, Clifton W. Callaway, April P. Carson, et al. "Heart Disease and Stroke Statistics—2021 Update." *Circulation* 143, no. 8 (February 23, 2021): e254–743. https://doi.org/10.1161/CIR.0000000000000950.
3. Mach, François, Colin Baigent, Alberico L Catapano, Konstantinos C Koskinas, Manuela Casula, Lina Badimon, M John Chapman, et al. "2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)." *European Heart Journal* 41, no. 1 (January 1, 2020): 111–88. https://doi.org/10.1093/eurheartj/ehz455.
4. Huang, Paul L. "A Comprehensive Definition for Metabolic Syndrome." *Disease Models & Mechanisms* 2, no. 5–6 (April 30, 2009): 231–37. https://doi.org/10.1242/dmm.001180.
5. Saklayen, Mohammad G. "The Global Epidemic of the Metabolic Syndrome." *Current Hypertension Reports* 20, no. 2 (February 26, 2018): 12. https://doi.org/10.1007/s11906-018-0812-z.
6. Appelman, Yolande, Bas B. van Rijn, Monique E. ten Haaf, Eric Boersma, and Sanne A. E. Peters. "Sex Differences in Cardiovascular Risk Factors and Disease Prevention." *Atherosclerosis* 241, no. 1 (July 1, 2015): 211–18. https://doi.org/10.1016/j.atherosclerosis.2015.01.027.
7. Pinhas-Hamiel, Orit, Liat Lerner-Geva, Nancy M. Copperman, and Marc S. Jacobson. "Lipid and Insulin Levels in Obese Children: Changes with Age and Puberty." *Obesity* 15, no. 11 (2007): 2825–31. https://doi.org/10.1038/oby.2007.335.
8. Swapnali, R K, Ravikiran Kisan, and D S Jayaprakash Murthy. "Effect of Menopause on Lipid Profile and Apolipoproteins" 4 (2011): 8.
9. Mainous, Arch G., Rebecca J. Tanner, Kiarash P. Rahmanian, Ara Jo, and Peter J. Carek. "Effect of Sedentary Lifestyle on Cardiovascular Disease Risk Among Healthy Adults With Body Mass Indexes 18.5 to 29.9 Kg/M2." *American Journal of Cardiology* 123, no. 5 (March 1, 2019): 764–68. https://doi.org/10.1016/j.amjcard.2018.11.043.

10. Dhingra, Ravi, and Ramachandran S. Vasan. "Age as a Cardiovascular Risk Factor." *The Medical Clinics of North America* 96, no. 1 (January 2012): 87–91. https://doi.org/10.1016/j.mcna.2011.11.003.

11. Lee, Whanhee, Sung-Hee Hwang, Hayoung Choi, and Ho Kim. "The Association between Smoking or Passive Smoking and Cardiovascular Diseases Using a Bayesian Hierarchical Model: Based on the 2008-2013 Korea Community Health Survey." *Epidemiology and Health* 39 (June 22, 2017). https://doi.org/10.4178/epih.e2017026.
12. Bey, Lionel, Enas Areiqat, Andrea Sano, and Marc T. Hamilton. "Reduced Lipoprotein Lipase Activity in Postural Skeletal Muscle during Aging." *Journal of Applied Physiology* 91, no. 2 (August 1, 2001): 687–92. https://doi.org/10.1152/jappl.2001.91.2.687.
13. Mc Auley, Mark T., and Kathleen M. Mooney. "Lipid Metabolism and Hormonal Interactions: Impact on Cardiovascular Disease and Healthy Aging." *Expert Review of Endocrinology & Metabolism* 9, no. 4 (July 2014): 357–67. https://doi.org/10.1586/17446651.2014.921569.

14. Seo, Eunhui, Hwansu Kang, Hojung Choi, Woohyuk Choi, and Hee-Sook Jun. "Reactive Oxygen Species-induced Changes in Glucose and Lipid Metabolism Contribute to the Accumulation of Cholesterol in the Liver during Aging." *Aging Cell* 18, no. 2 (April 2019). https://doi.org/10.1111/acel.12895.

15. Abbott, R D, R J Garrison, P W Wilson, F H Epstein, W P Castelli, M Feinleib, and C LaRue. "Joint Distribution of Lipoprotein Cholesterol Classes. The Framingham Study." *Arteriosclerosis: An Official Journal of the American Heart Association, Inc.* 3, no. 3 (May 1983): 260–72. https://doi.org/10.1161/01.ATV.3.3.260.
16. Millar, J. S., A. H. Lichtenstein, M. Cuchel, G. G. Dolnikowski, D. L. Hachey, J. S. Cohn, and E. J. Schaefer. "Impact of Age on the Metabolism of VLDL, IDL, and LDL Apolipoprotein B-100 in Men." *Journal of Lipid Research* 36, no. 6 (June 1995): 1155–67.
17. Mahley, Robert W., and Thomas L. Innerarity. "Lipoprotein Receptors and Cholesterol Homeostasis." *Biochimica et Biophysica Acta (BBA) - Reviews on Biomembranes* 737, no. 2 (May 24, 1983): 197–222. https://doi.org/10.1016/0304-4157(83)90001-1.
18. Véniant, M M, C H Zlot, R L Walzem, V Pierotti, R Driscoll, D Dichek, J Herz, and S G Young. "Lipoprotein Clearance Mechanisms in LDL Receptor-Deficient 'Apo-B48-Only' and 'Apo-B100-Only' Mice." *Journal of Clinical Investigation* 102, no. 8 (October 15, 1998): 1559–68.
19. Bertolotti, M., C. Gabbi, C. Anzivino, M. Crestani, N. Mitro, M. Del Puppo, C. Godio, et al. "Age-Related Changes in Bile Acid Synthesis and Hepatic Nuclear Receptor Expression." *European Journal of Clinical Investigation* 37, no. 6 (2007): 501–8. https://doi.org/10.1111/j.1365-2362.2007.01808.x.
20. Dubuc, Geneviève, Michel Tremblay, Guillaume Paré, Hélène Jacques, Josée Hamelin, Suzanne Benjannet, Lucie Boulet, et al. "A New Method for Measurement of Total Plasma PCSK9: Clinical Applications." *Journal of Lipid Research* 51, no. 1 (January 2010): 140–49. https://doi.org/10.1194/jlr.M900273-JLR200.
21. Cooney, M. T., A. Dudina, D. De Bacquer, L. Wilhelmsen, S. Sans, A. Menotti, G. De Backer, i in. „HDL Cholesterol Protects against Cardiovascular Disease in Both Genders, at All Ages and at All Levels of Risk". *Atherosclerosis* 206, nr 2 (1 październik 2009): 611–16. https://doi.org/10.1016/j.atherosclerosis.2009.02.041.

22. Ferrara Assiamira, Barrett-Connor Elizabeth, and Shan Jun. "Total, LDL, and HDL Cholesterol Decrease With Age in Older Men and Women." *Circulation* 96, no. 1 (July 1, 1997): 37–43. https://doi.org/10.1161/01.CIR.96.1.37.
23. Yi, Sang-Wook, Jee-Jeon Yi, and Heechoul Ohrr. "Total Cholesterol and All-Cause Mortality by Sex and Age: A Prospective Cohort Study among 12.8 Million Adults." *Scientific Reports* 9 (February 7, 2019). https://doi.org/10.1038/s41598-018-38461-y.
24. Park, Ji Hye, Myung Ha Lee, Jee-Seon Shim, Dong Phil Choi, Bo Mi Song, Seung Won Lee, Hansol Choi, and Hyeon Chang Kim. "Effects of Age, Sex, and Menopausal Status on Blood Cholesterol Profile in the Korean Population." *Korean Circulation Journal* 45, no. 2 (March 2015): 141–48. https://doi.org/10.4070/kcj.2015.45.2.141.
25. Grundy, Scott M., Neil J. Stone, Alison L. Bailey, Craig Beam, Kim K. Birtcher, Roger S. Blumenthal, Lynne T. Braun, et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Circulation* 139, no. 25 (June 18, 2019): e1082–1143. https://doi.org/10.1161/CIR.0000000000000625.
26. An, Jaejin, Yiyi Zhang, Paul Muntner, Andrew E. Moran, Jin-Wen Hsu, and Kristi Reynolds. "Recurrent Atherosclerotic Cardiovascular Event Rates Differ Among Patients Meeting the Very High Risk Definition According to Age, Sex, Race/Ethnicity, and Socioeconomic Status." *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease* 9, no. 23 (November 23, 2020). https://doi.org/10.1161/JAHA.120.017310.
27. Morris, Alanna A., Yi-An Ko, Sarah H. Hutcheson, and Arshed Quyyumi. "Race/Ethnic and Sex Differences in the Association of Atherosclerotic Cardiovascular Disease Risk and Healthy Lifestyle Behaviors." *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease* 7, no. 10 (May 3, 2018). https://doi.org/10.1161/JAHA.117.008250.
28. Damen, Johanna A A G, Lotty Hooft, Ewoud Schuit, Thomas P A Debray, Gary S Collins, Ioanna Tzoulaki, Camille M Lassale, et al. "Prediction Models for Cardiovascular Disease Risk in the General Population: Systematic Review." *The BMJ* 353 (May 16, 2016). https://doi.org/10.1136/bmj.i2416.
29. Luy, Marc, Paola Di Giulio, Vanessa Di Lego, Patrick Lazarevič, and Markus Sauerberg. "Life Expectancy: Frequently Used, but Hardly Understood." *Gerontology* 66, no. 1 (January 2020): 95–104. https://doi.org/10.1159/000500955.
30. Townsend, Nick, Lauren Wilson, Prachi Bhatnagar, Kremlin Wickramasinghe, Mike Rayner, and Melanie Nichols. "Cardiovascular Disease in Europe: Epidemiological Update 2016." *European Heart Journal* 37, no. 42 (November 7, 2016): 3232–45. https://doi.org/10.1093/eurheartj/ehw334.
31. Lapid, Kfir, Ajin Lim, Deborah J. Clegg, Daniel Zeve, and Jonathan M. Graff. "Oestrogen Signalling in White Adipose Progenitor Cells Inhibits Differentiation into Brown Adipose and Smooth Muscle Cells." *Nature Communications* 5 (October 21, 2014): 5196. https://doi.org/10.1038/ncomms6196.
32. Beaudry, Kayleigh M., and Michaela C. Devries. "Sex-Based Differences in Hepatic and Skeletal Muscle Triglyceride Storage and Metabolism 1." *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme* 44, no. 8 (August 2019): 805–13. https://doi.org/10.1139/apnm-2018-0635.
33. Svendsen, O. L., C. Hassager, and C. Christiansen. "Age- and Menopause-Associated Variations in Body Composition and Fat Distribution in Healthy Women as Measured by Dual-Energy X-Ray Absorptiometry." *Metabolism: Clinical and Experimental* 44, no. 3 (March 1995): 369–73. https://doi.org/10.1016/0026-0495(95)90168-x.

34. Trentini, Alessandro, Tiziana Bellini, Gloria Bonaccorsi, Carlotta Cavicchio, Stefania Hanau, Angelina Passaro, and Carlo Cervellati. "Sex Difference: An Important Issue to Consider in Epidemiological and Clinical Studies Dealing with Serum Paraoxonase-1." *Journal of Clinical Biochemistry and Nutrition* 64, no. 3 (May 2019): 250–56. https://doi.org/10.3164/jcbn.18-73.
35. Pascot, A., I. Lemieux, D. Prud'homme, A. Tremblay, A. Nadeau, C. Couillard, J. Bergeron, B. Lamarche, and J. P. Després. "Reduced HDL Particle Size as an Additional Feature of the Atherogenic Dyslipidemia of Abdominal Obesity." *Journal of Lipid Research* 42, no. 12 (December 2001): 2007–14.
36. Blaak, E. "Gender Differences in Fat Metabolism." *Current Opinion in Clinical Nutrition and Metabolic Care* 4, no. 6 (November 2001): 499–502. https://doi.org/10.1097/00075197-200111000-00006.
37. Palmisano, Brian T., Lin Zhu, and John M. Stafford. "Role of Estrogens in the Regulation of Liver Lipid Metabolism." *Advances in Experimental Medicine and Biology* 1043 (2017): 227–56. https://doi.org/10.1007/978-3-319-70178-3_12.
38. Magkos, Faidon, Bruce W. Patterson, B. Selma Mohammed, Samuel Klein, and Bettina Mittendorfer. "Women Produce Fewer but Triglyceride-Richer Very Low-Density Lipoproteins than Men." *The Journal of Clinical Endocrinology and Metabolism* 92, no. 4 (April 2007): 1311–18. https://doi.org/10.1210/jc.2006-2215.
39. Matthan, Nirupa R., Susan M. Jalbert, P. Hugh R. Barrett, Gregory G. Dolnikowski, Ernst J. Schaefer, and Alice H. Lichtenstein. "Gender-Specific Differences in the Kinetics of Nonfasting TRL, IDL, and LDL Apolipoprotein B-100 in Men and Premenopausal Women." *Arteriosclerosis, Thrombosis, and Vascular Biology* 28, no. 10 (October 2008): 1838–43. https://doi.org/10.1161/ATVBAHA.108.163931.
40. Sessa, William C. "Estrogen Reduces LDL Transcytosis: A New Mechanism of Cardioprotection ?" *Arteriosclerosis, Thrombosis, and Vascular Biology* 38, no. 10 (October 2018): 2276–77. https://doi.org/10.1161/ATVBAHA.118.311620.
41. Freedman, David S., James D. Otvos, Elias J. Jeyarajah, Irina Shalaurova, L. Adrienne Cupples, Helen Parise, Ralph B. D'Agostino, Peter W. F. Wilson, and Ernst J. Schaefer. "Sex and Age Differences in Lipoprotein Subclasses Measured by Nuclear Magnetic Resonance Spectroscopy: The Framingham Study." *Clinical Chemistry* 50, no. 7 (July 2004): 1189–1200. https://doi.org/10.1373/clinchem.2004.032763.
42. García-Calzón, Sonia, Alexander Perfilyev, Vanessa D de Mello, Jussi Pihlajamäki, and Charlotte Ling. "Sex Differences in the Methylome and Transcriptome of the Human Liver and Circulating HDL-Cholesterol Levels." *The Journal of Clinical Endocrinology and Metabolism* 103, no. 12 (May 28, 2018): 4395–4408. https://doi.org/10.1210/jc.2018-00423.
43. Badeau, Robert M., Jari Metso, Kristiina Wähälä, Matti J. Tikkanen, and Matti Jauhiainen. "Human Macrophage Cholesterol Efflux Potential Is Enhanced by HDL-Associated 17beta-Estradiol Fatty Acyl Esters." *The Journal of Steroid Biochemistry and Molecular Biology* 116, no. 1–2 (August 2009): 44–49. https://doi.org/10.1016/j.jsbmb.2009.04.008.
44. Badeau, Robert M., Jari Metso, Petri T. Kovanen, Miriam Lee-Rueckert, Matti J. Tikkanen, and Matti Jauhiainen. "The Impact of Gender and Serum Estradiol Levels on HDL-Mediated Reverse Cholesterol Transport." *European Journal of Clinical Investigation* 43, no. 4 (April 2013): 317–23. https://doi.org/10.1111/eci.12044.
45. Tang, W. H. Wilson, Yuping Wu, Shirley Mann, Michael Pepoy, Kevin Shrestha, Allen G. Borowski, and Stanley L. Hazen. "Diminished Antioxidant Activity of High-Density Lipoprotein-Associated Proteins in Systolic Heart Failure." *Circulation. Heart Failure* 4, no. 1 (January 2011): 59–64. https://doi.org/10.1161/CIRCHEARTFAILURE.110.958348.

46. Kunutsor, Setor K., Stephan J. L. Bakker, Richard W. James, and Robin P. F. Dullaart. "Serum Paraoxonase-1 Activity and Risk of Incident Cardiovascular Disease: The PREVEND Study and Meta-Analysis of Prospective Population Studies." *Atherosclerosis* 245 (February 2016): 143–54. https://doi.org/10.1016/j.atherosclerosis.2015.12.021.
47. Cervellati, Carlo, Gloria Bonaccorsi, Alessandro Trentini, Giuseppe Valacchi, Juana M. Sanz, Monica Squerzanti, Manuela Spagnolo, et al. "Paraoxonase, Arylesterase and Lactonase Activities of Paraoxonase-1 (PON1) in Obese and Severely Obese Women." *Scandinavian Journal of Clinical and Laboratory Investigation* 78, no. 1–2 (April 2018): 18–24. https://doi.org/10.1080/00365513.2017.1405274.
48. Besler, Christian, Thomas F Lüscher, and Ulf Landmesser. "Molecular Mechanisms of Vascular Effects of High-Density Lipoprotein: Alterations in Cardiovascular Disease." *EMBO Molecular Medicine* 4, no. 4 (April 2012): 251–68. https://doi.org/10.1002/emmm.201200224.
49. Gong, Ming, Melinda Wilson, Thomas Kelly, Wen Su, James Dressman, Jeanie Kincer, Sergey V. Matveev, et al. "HDL-Associated Estradiol Stimulates Endothelial NO Synthase and Vasodilation in an SR-BI–Dependent Manner." *Journal of Clinical Investigation* 111, no. 10 (May 15, 2003): 1579–87. https://doi.org/10.1172/JCI200316777.
50. Palmisano, Brian T., Lin Zhu, Robert H. Eckel, and John M. Stafford. "Sex Differences in Lipid and Lipoprotein Metabolism." *Molecular Metabolism* 15 (May 16, 2018): 45–55. https://doi.org/10.1016/j.molmet.2018.05.008.
51. Romero-Aleshire, Melissa J., Maggie K. Diamond-Stanic, Alyssa H. Hasty, Patricia B. Hoyer, and Heddwen L. Brooks. "Loss of Ovarian Function in the VCD Mouse-Model of Menopause Leads to Insulin Resistance and a Rapid Progression into the Metabolic Syndrome." *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 297, no. 3 (September 2009): R587–92. https://doi.org/10.1152/ajpregu.90762.2008.
52. Zhu, Lin, William C. Brown, Qing Cai, Andrée Krust, Pierre Chambon, Owen P. McGuinness, and John M. Stafford. "Estrogen Treatment After Ovariectomy Protects Against Fatty Liver and May Improve Pathway-Selective Insulin Resistance." *Diabetes* 62, no. 2 (February 2013): 424–34. https://doi.org/10.2337/db11-1718.
53. Della Torre, Sara, Nico Mitro, Roberta Fontana, Monica Gomaraschi, Elda Favari, Camilla Recordati, Federica Lolli, et al. "An Essential Role for Liver ERα in Coupling Hepatic Metabolism to the Reproductive Cycle." *Cell Reports* 15, no. 2 (March 31, 2016): 360–71. https://doi.org/10.1016/j.celrep.2016.03.019.
54. Kim, Jun Ho, Matthew S. Meyers, Saja S. Khuder, Simon L. Abdallah, Harrison T. Muturi, Lucia Russo, Chandra R. Tate, et al. "Tissue-Selective Estrogen Complexes with Bazedoxifene Prevent Metabolic Dysfunction in Female Mice." *Molecular Metabolism* 3, no. 2 (January 9, 2014): 177–90. https://doi.org/10.1016/j.molmet.2013.12.009.
55. Maranhão, Raul Cavalcante, Priscila Oliveira Carvalho, Celia Cassaro Strunz, and Fulvio Pileggi. "Lipoprotein (a): Structure, Pathophysiology and Clinical Implications." *Arquivos Brasileiros de Cardiologia* 103, no. 1 (July 2014): 76–84. https://doi.org/10.5935/abc.20140101.
56. Chung, Tae-Ha, Yu-Jin Kwon, and Yong-Jae Lee. "High Triglyceride to HDL Cholesterol Ratio Is Associated with Low Testosterone and Sex Hormone-Binding Globulin Levels in Middle-Aged and Elderly Men." *The Aging Male: The Official Journal of the International Society for the Study of the Aging Male* 23, no. 2 (June 2020): 93–97. https://doi.org/10.1080/13685538.2018.1501015.
57. Galassi, Andrea, Kristi Reynolds, and Jiang He. "Metabolic Syndrome and Risk of Cardiovascular Disease: A Meta-Analysis." *The American Journal of Medicine* 119, no. 10 (October 2006): 812–19. https://doi.org/10.1016/j.amjmed.2006.02.031.

58. Kapoor, D., E. Goodwin, K. S. Channer, and T. H. Jones. “Testosterone Replacement Therapy Improves Insulin Resistance, Glycaemic Control, Visceral Adiposity and Hypercholesterolaemia in Hypogonadal Men with Type 2 Diabetes.” *European Journal of Endocrinology* 154, no. 6 (June 2006): 899–906. https://doi.org/10.1530/eje.1.02166.
59. Marques-Vidal, P., P. Sie, J. P. Cambou, H. Chap, and B. Perret. “Relationships of Plasminogen Activator Inhibitor Activity and Lipoprotein(a) with Insulin, Testosterone, 17 Beta-Estradiol, and Testosterone Binding Globulin in Myocardial Infarction Patients and Healthy Controls.” *The Journal of Clinical Endocrinology and Metabolism* 80, no. 6 (June 1995): 1794–98. https://doi.org/10.1210/jcem.80.6.7775625.
60. Soisson, Véronique, Sylvie Brailly-Tabard, Catherine Helmer, Olivier Rouaud, Marie-Laure Ancelin, Chahinez Zerhouni, Anne Guiochon-Mantel, and Pierre-Yves Scarabin. “A J-Shaped Association between Plasma Testosterone and Risk of Ischemic Arterial Event in Elderly Men: The French 3C Cohort Study.” *Maturitas* 75, no. 3 (July 2013): 282–88. https://doi.org/10.1016/j.maturitas.2013.04.012.
61. Fagman, Johan B., Anna S. Wilhelmson, Benedetta M. Motta, Carlo Pirazzi, Camilla Alexanderson, Karel De Gendt, Guido Verhoeven, et al. “The Androgen Receptor Confers Protection against Diet-Induced Atherosclerosis, Obesity, and Dyslipidemia in Female Mice.” *The FASEB Journal* 29, no. 4 (April 2015): 1540–50. https://doi.org/10.1096/fj.14-259234.