Uniwersytet Medyczny im. Piastów Śląskich
we Wrocławiu

Katedra i Zakład Zdrowia Środowiskowego,
Medycyny Pracy i Epidemiologii

ROZPRAWA DOKTORSKA

Środowiskowe i behawioralne uwarunkowania zdrowia sercowo-naczyniowego a stężenie renalazy we krwi.

lek. Aleksandra Żórawik

Promotor: prof. dr hab. n. med. Paweł Gać

Wrocław, 2024

Podziękowania

Składam najserdeczniejsze wyrazy wdzięczności mojemu Promotorowi i najlepszemu Opiekunowi

Panu Profesorowi Pawłowi Gaciowi

za cierpliwość, wyrozumiałość, bezcenne rady i inspiracje, motywację na każdym etapie przygotowania rozprawy, zawsze życzliwą atmosferę współpracy, a przede wszystkim za ogromny wkład merytoryczny i organizacyjny, bez której to pomocy powstanie niniejszej rozprawy doktorskiej nie byłoby możliwe.

Serdeczne podziękowania dla ***Grona Współautorów publikacji:***

prof. dr hab. n. med. Krystyny Pawlas

prof. dr hab. n. med. Rafała Poręby

prof. dr hab. n. med. Grzegorza Mazura

dr hab. n. med. Heleny Martynowicz

dr n. biol. med. Iwony Markiewicz Górki

dr n. o zdr. Aleksandry Jaremków

lek. Wojciecha Hajdusianka

mgr Agnieszki Kusnerż

Dziękuję za nieocenioną pomoc i wsparcie, zaangażowanie, czas poświęcony przygotowaniu publikacji i wniesione w nie bezcenne wartości merytoryczne, dzielenie się doświadczeniem, a przede wszystkim za życzliwe przyjęcie do zespołu i przyjazną atmosferę współpracy.

Pragnę wyrazić szczególną wdzięczność ***Pani Dagmarze Banach***

za ogromne wsparcie organizacyjne oraz wyjątkowo czujny i troskliwy nadzór nad wszystkimi aspektami w zakresie niezbędnej dokumentacji związanej z pracą w Katedrze, uczestnictwem w Szkole Doktorskiej i przygotowaniem rozprawy.

Dziękuję ***Rodzinie i Przyjaciołom***

za motywację, cierpliwość i okazane wsparcie w podtrzymywaniu wiary w sukces tego przedsięwzięcia.

Spis treści

Wprowadzenie

Choroby układu sercowo-naczyniowego według Światowej Organizacji Zdrowia to „grupa zaburzeń serca i naczyń krwionośnych, w tym choroba wieńcowa, choroba naczyniowo-mózgowa, choroba tętnic obwodowych, reumatyczna choroba serca, wrodzona choroba serca oraz zakrzepica żył głębokich i zatorowość płucna” [1]. Stanowią one obecnie najpoważniejsze wyzwanie dla systemów opieki zdrowotnej. Ich skutki są bowiem wiodącą przyczynę niesprawności, przedwczesnych zgonów na całym świecie, w szczególności w państwach zaliczanych do kategorii krajów wysoko rozwiniętych. Według najnowszych danych WHO, następstwa chorób układu krążenia są odpowiedzialne za nawet do 42.5% wszystkich zgonów, co oznacza, że średnio dziennie umiera z ich powodu ok. 10 tys. osób [2]. Wśród chorób sercowo-naczyniowych wiodącym czynnikiem ryzyka zgonu jest nadciśnienie tętnicze, które w 2019 roku spowodowało niemal ¼ wszystkich zgonów (24%) wskutek następstw, przede wszystkim zawału serca i udaru mózgu [2, 3].

Do najlepiej udokumentowanych czynników ryzyka wystąpienia chorób sercowo-naczyniowych należy nadciśnienie tętnicze, zaburzenia przemiany lipoprotein (hipercholesterolemia i hipertriglicerydemia), cukrzyca typu 2, palenie papierosów oraz nadmierna masa ciała, ale do środowiskowo-behawioralnych determinant zdrowia sercowo-naczyniowego zaliczyć należy brak aktywności fizycznej, nieprawidłową dietę czy nadmierne spożycie alkoholu [4–7]. Postępowanie mające na celu redukcję częstotliwości występowania chorób niezakaźnych, do jakich zaliczane są choroby układu krążenia, obejmuje zatem dążenie do wyeliminowania szkodliwych nawyków, poprawę parametrów środowiskowych, w tym troskę o odpowiednią jakość wody, poprawę jakości powietrza, bezpieczne i higieniczne warunki pracy, a także przeciwdziałanie degradacji środowiska [8].

Należy podkreślić, że superpozycja wielu czynników ryzyka sercowo-naczyniowego, według dotychczasowych doniesień, może pogarszać rokowanie w przebiegu różnych chorób układu krążenia. Według danych statystycznych taka koincydencja jest bardzo powszechna. W 2012 roku 21% osób w wieku powyżej 15 lat paliło papierosy, w 2014 roku 22% populacji osób dorosłych miało nadciśnienie tętnicze, w 2008 roku u blisko 40% dorosłych na świecie rozpoznano zaburzenia metabolizmu lipoprotein, w 2014 roku 13% światowej populacji

stanowiły osoby otyłe, a 39% miało nadwagę, w 2014 roku prawie 9% osób od 18 roku życia chorowało na cukrzycę [5, 6, 9, 10].

Renalaza to białko będące zależną od dinukleotydu flawinoadeninowego oksydazą (ang. flavin adenine dinucleotide, FAD) [11]. Początkowo przypisywano jej funkcję degradacji amin katecholowych krążących we krwi, co miało skutkować zwolnieniem częstości rytmu serca i regulacją wartości ciśnienia tętniczego [11, 12]. Jednak w na podstawie wniosków z późniejszych badań niniejsze założenie to okazało się błędne [13-15]. W toku obserwacji ustalono również, że substraty dla renalazy stanowią izomery formy natywnej 1,4-dihydro fosforanu dinukleotydu nikotynoamidoadeninowego (1,4-dihydroNAD(P)). Działanie enzymu polega na katalizacji reakcji ich utlenienia i powrotu do formy natywnej poprzez formowanie β-NAD(P)+ i H_2O2[12, 16, 17]. Zaobserwowano ponadto przeciwzapalne i antyapoptotyczne działanie renalazy w odpowiedzi na niedokrwienie i jej związek z czynnikami związanymi z dysfunkcją śródbłonka naczyniowego [18].

Założenie i cele pracy

Zasadniczy cel rozprawy stanowiła weryfikacja założenia, że uwarunkowania środowiskowe i behawioralne mają wpływ na poziom stężenia renalazy we krwi.

Ponadto przyjęto występowanie następujących zależności, które warunkowały cele szczegółowe poszczególnych prac wchodzących w skład rozprawy doktorskiej:

- Istnieje zależność pomiędzy stężeniem renalazy w osoczu a 10-letnim ryzykiem zdarzeń sercowo-naczyniowych zakończonych zgonem szacowanym na podstawie skali SCORE.
- Istnieje zależność pomiędzy osoczowym stężeniem renalazy a poziomem zdrowia sercowo-naczyniowego szacowanego na podstawie klasyfikacji AHA Simple 7.
- Istnieje zależność pomiędzy stężeniem renalazy w osoczu a występowaniem środowiskowego narażenia na dym tytoniowy.
- Istnieje zależność pomiędzy osoczowym stężeniem renalazy we krwi a nadciśnieniem tętniczym oraz występowaniem subklinicznych powikłań narządowych w jego przebiegu.

Kluczowe założenie metodologiczne badania stanowiło bezpieczeństwo uczestników i nienarażanie ich na dodatkowe procedury w postępowaniu terapeutycznym w trakcie hospitalizacji związanej z postępowaniem klinicznym. Tym samym projekt stanowił formę badania nieingerującego w proces terapeutyczny, a wszystkie materiały biologiczne i wyniki pozyskanych badań wykonane były ze wskazań klinicznych.

Pierwszy etap badań zakładał podsumowanie aktualnego stanu wiedzy w zakresie środowiskowych i behawioralnych determinant zdrowia sercowo-naczyniowego oraz przegląd aktualnych metod oceny występowania czynników ryzyka chorób układu krążenia. Kolejne cele harmonogramu przygotowania rozprawy doktorskiej zakładały analizę zależności stężenia renalazy z czynnikami ryzyka chorób sercowo-naczyniowych oraz wpływu ekspozycji na dym tytoniowy na poziom badanego enzymu.

Powyższe założenia znalazły odzwierciedlenie w celach poszczególnych prac cyklu:

Cel pracy nr 1: przegląd aktualnych doniesień na temat behawioralnych i środowiskowych determinant zdrowia sercowo-naczyniowego oraz podsumowanie narzędzi wykorzystywanych do ich oceny.

Cel pracy nr 2: ocena związku pomiędzy ekspozycją na dym tytoniowy (również jako ekspozycja środowiskowa) i stężeniem renalazy we krwi oraz weryfikacja znaczenia współistnienia chorób sercowo-naczyniowych (głównie nadciśnienia tętniczego) i wykorzystywanej metodologii badania na niniejszy związek.

Cel pracy nr 3: weryfikacja zależności pomiędzy występowaniem czynników ryzyka chorób sercowo-naczyniowych ocenianych na podstawie klasyfikacji AHA Simple 7 (konsumpcja wyrobów tytoniowych, otyłość, brak aktywności fizycznej, błędy dietetyczne, zwiększone stężenia cholesterolu, glukozy na czczo i podwyższone wartości ciśnienia tętniczego) na osoczowe stężenie renalazy.

Wykaz publikacji włączonych do rozprawy doktorskiej

1. Żórawik A, Hajdusianek W, Gać P, Poręba R. Environmental and behavioural determinants of cardiovascular health. Journal of Health Inequalities. 2022;8(1):14-24. doi:10.5114/jhi.2022.116483.

100 pkt MNiSW

2. Żórawik A, Hajdusianek W, Kusnerż A, Markiewicz-Górka I, Jaremków A, Martynowicz H, Pawlas K, Mazur G, Poręba R, Gać P. Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases. Cardiovascular Toxicology. 2024;24:737-746. doi: 10.1007/s12012-024-09868-z.

   70 pkt MNiSW, IF 3.4

3. Żórawik A, Hajdusianek W, Markiewicz-Górka I, Jaremków A, Pawlas K, Martynowicz H, Mazur G, Poręba R, Gać P. Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration. International Journal of Molecular Sciences. 2023;24(23):16666. doi: 10.3390/ijms242316666.

   140 pkt MNiSW, IF 4.9

Sumaryczna punktacja: 310 pkt MNiSW, IF 8.3.

Omówienie publikacji

Publikacja nr 1 – praca przeglądowa

Environmental and behavioural determinants of cardiovascular health

Pierwsza publikacja cyklu stanowiąca pracę przeglądową koncentruje się na przeglądzie dostępnej literatury celem usystematyzowania dotychczasowych doniesień badawczych

w obszarze tematyki zdrowia sercowo-naczyniowego. Przeprowadzona kwerenda bibliograficzna objęła bazy PubMed, Scopus i GoogleScholar, gdzie wykorzystano słowa kluczowe: zdrowie sercowo-naczyniowe, ocena czynników ryzyka chorób sercowo-naczyniowych, środowisko, uwarunkowania behawioralne.

W związku z doniosłością problemu, jaki stanowią choroby sercowo-naczyniowe, jako główna przyczyna zgonów na świecie, dotychczasowy zasób literatury poruszający temat czynników ryzyka, ich wystąpienia, jest bardzo obszerny. Spośród licznych publikacji, dotyczących skal oceny zdrowia sercowo-naczyniowego, skupiono się na tych omawiających trzy z najbardziej rozpowszechnionych narzędzi: Framingham Heart Study (FHS), Systemic Coronary Risk Evaluation (SCORE) i AHA Life's Simple 7 (AHALS7). Po ukończeniu niniejszej pracy, w 2021 roku Europejskie Towarzystwo Kardiologiczne zaproponowało nowy system oceny ryzyka sercowo-naczyniowego – SCORE 2: nowy system jako punkt końcowy przyjmuje nie tylko zgony z powodu chorób sercowo-naczyniowych, ale także wystąpienie zawału serca i udaru mózgu, ponadto uwzględnia stężenie cholesterolu nie-HDL, a nie cholesterolu całkowitego jak dotychczas. Zmodyfikowane zostały także punkty odcięcia szacowania ryzyka dla poszczególnych kategorii wiekowych. Dodatkową zmianą jest poszerzenie zakresu wieku osób możliwych do oceny za pomocą niniejszego systemu do 90 roku życia.

Olbrzymi nakład pracy i dynamiczna sytuacja w zakresie prowadzonych badań dotyczących zdrowia sercowo-naczyniowego doskonale odzwierciedla wagę tego problemu, z jakim borykają się systemy ochrony zdrowia na całym świecie.

Publikacja nr 2 – praca oryginalna

Relation between exposure to tobacco smoke assessed by serum cotinine concentration and questionnaire method, and serum renalase concentration – the importance of the coexistence of arterial hypertension and other cardiovascular diseases.

W skład grupy badanej włączono 109 pacjentów (wiek 49.7 ± 14.7 lat) hospitalizowanych ze wskazań klinicznych w Klinice Chorób Wewnętrznych, Zawodowych, Nadciśnienia Tętniczego i Onkologii Klinicznej w Uniwersyteckim Szpitalu Klinicznym we Wrocławiu.

Przeprowadzone badania obejmowały następujące procedury: wywiad, kwestionariusz dotyczący obciążenia chorobami sercowo-naczyniowymi, pomiary ciśnienia tętniczego, podstawowe pomiary antropometryczne i badania laboratoryjne określające stężenie kotyniny i renalazy w surowicy krwi. Nadciśnienie tętnicze rozpoznawano, gdy średnia z dwóch pomiarów wynosiła ≥140 mmHg w przypadku skurczowego ciśnienia krwi i/lub 90 mmHg w przypadku rozkurczowego ciśnienia krwi (w przypadku wywiadu stosowania leków hipotensyjnych pacjent kwalifikowany był jako obciążony nadciśnieniem tętniczym bez względu na wynik pomiaru). Podział na odpowiednie podgrupy według ekspozycji na dym tytoniowy przeprowadzony został niezależnie na podstawie deklaracji uczestników dotyczących palenia papierosów (aktywne, bierne i brak ekspozycji) oraz na podstawie oznaczenia stężenia kotyniny we krwi, gdzie jako punkty odcięcia przyjęto na podstawie dostępnych danych literaturowych wartości >15 ng/ml dla palaczy aktywnych, 1-15 ng/ml dla palaczy biernych i <1 ng/ml dla osób w żaden sposób nienarażonych na dym tytoniowy.

W celu określenia stężenia kotyniny i renalazy w surowicy od każdego badanego pobrano około 10 cm^3 krwi z żyły ramiennej, 12 godzin po ostatnim posiłku do probówki zawierającej EDTA. Materiał odwirowywano z prędkością 10 000 obrotów/minutę, a pobraną surowicę zamrażano i przechowywano w temperaturze -70^oC do czasu wykonania testów.

Badania laboratoryjne przeprowadzone zostały w laboratorium naukowym Katedry i Zakładu Zdrowia Środowiskowego, Medycyny Pracy i Epidemiologii Uniwersytetu Medycznego we Wrocławiu. Do oznaczenia stężenia renalazy i kotyniny w materiale biologicznym, jaki stanowiła surowica krwi, wykorzystano komercyjne standaryzowane testy immunoenzymatyczne (ELISA) ściśle według instrukcji producenta testów. W przeprowadzeniu oceny stężenia renalazy w surowicy zastosowano zestaw E3109Hu ELISA (Bioassay Technology Laboratory, Szanghaj, Chiny), oznaczenia kotyniny dokonano natomiast przy użyciu zestawu E2043Hu-96T ELISA (Bioassay Technology Laboratory, Szanghaj, Chiny). W obu przypadkach wynik wyrażono w nanogramach na mililitr (ng/ml).

Stężenie kotyniny w surowicy w całej badanej grupie wynosiło 16,4 ± 10,4 / 13,1 (7,5) ng/ml, a stężenie renalazy w surowicy wynosiło 189,7 ± 214,8 / 64,0 (318,6) ng/ml.

W analizie porównawczej stężeń renalazy w surowicy w podgrupach opartych na kryteriach narażenia na dym tytoniowy i nadciśnienia tętniczego wykazała istotne statystycznie różnice:

pacjenci deklarujący czynne palenie tytoniu oraz pacjenci deklarujący narażenie na środowiskowy dym tytoniowy bez czynnej konsumpcji wyrobów tytoniowych mieli istotnie niższe stężenia renalazy w surowicy niż pacjenci deklarujący niepalenie tytoniu i brak narażenia na środowiskowy dym tytoniowy.

Jednocześnie należy zauważyć, że w przypadku podziału na podgrupy na podstawie stężenia kotyniny, a nie osobistej deklaracji uczestników, czynni palacze mieli istotnie niższe stężenia renalazy w surowicy niż, zarówno osoby niepalące narażone na środowiskowy dym tytoniowy, jak i osoby niepalące bez narażenia na środowiskowy dym tytoniowy.

Nie zaobserwowano istotnych statystycznie różnic w zakresie stężenia renalazy w surowicy krwi pomiędzy pacjentami chorującymi na nadciśnienie tętnicze a pacjentami nieobciążonymi chorobą. Analiza w podgrupach ze względu na narażenie na dym tytoniowy dała podobne rezultaty, jak w całej badanej grupie.

Na podstawie wyników analizy statystycznej zaobserwowano, że stężenie renalazy w surowicy było ujemnie skorelowane z BMI, rozkurczowym ciśnieniem krwi, chorobą wieńcową i stężeniem kotyniny w surowicy krwi.

Publikacja nr 3 – praca oryginalna

Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration

Badaniem objęto 96 uczestników w wieku 48,51 ± 14,73 lat, z czego 34 osoby obciążone było występowaniem nadciśnienia tętniczego (35,4%). U wszystkich badanych wykonano następujące procedury: wywiad (obejmujący przede wszystkim dane dotyczące czynników zawartych w kwestionariuszach oceny zdrowia sercowo-naczyniowego, tj. palenie tytoniu, aktywność fizyczną, dietę), pomiary ciśnienia krwi, podstawowe pomiary antropometryczne i badania laboratoryjne (lipidogram, stężenie glukozy na czczo, stężenie renalazy w surowicy krwi).

Średnie stężenie renalazy we krwi wynosiło 212,89 ± 281,91 ng/ml.

Wśród uczestników badania stwierdzono następującą liczbę czynników ryzyka sercowo-naczyniowego (CVRF): brak CVRF stwierdzono u 13 pacjentów (13,54%), jeden CVRF u 24 pacjentów (25%), dwa CVRF u 22 pacjentów (22,9%), trzy CVRF u 17 pacjentów (17,7%), cztery CVRF u 11 pacjentów (11,45%), pięć CVRF u ośmiu pacjentów (8,33%) i sześć CVRF u jednego pacjenta (1%). Nie było uczestników z siedmioma CVRF.

W badaniu analizowano różnice w stężeniu renalazy we krwi pomiędzy grupami różniącymi się pod względem każdego z analizowanych indywidualnie czynników ryzyka sercowo-naczyniowego. Wyniki statystyczne wykazały, że stężenie renalazy we krwi (ng/ml) było wyższe w grupach osób niepalących (255.98 ± 217.02 vs 102.77 ± 185.47, $p<0.05$), bez otyłości (260.99 ± 234.61 vs 107.06 ± 129.48,$p<0.05$), z odpowiednią aktywnością fizyczną (248.67 ± 230.40 vs 137.87 ± 172.97, $p<0.05$) i bez nadciśnienia tętniczego (244.02 ± 233.08 vs 156.13 ± 176.59, $p<0.05$).

Przeprowadzono analizę porównawczą w podgrupach zdefiniowanych na podstawie liczby czynników ryzyka sercowo-naczyniowego i stwierdzono ujemną korelację między tym parametrem a stężeniem renalazy we krwi ($r = -0,41$). Ponadto na podstawie wyników analizy statystycznej zaobserwowano, że otyłość, palenie tytoniu i brak aktywności fizycznej są niezależnie związane z wzrostem prawdopodobieństwa niższego stężenia renalazy we krwi.

Wyniki badań wskazują, że stężenie renalazy we krwi może być pomocnym wskaźnikiem predykcyjnym liczby czynników ryzyka sercowo-naczyniowego, szczególnie dla stężenia <38,98 ng/ml (predyktor CVRF ≥ 5), które charakteryzowało się najwyższą dokładnością predykcji. Na podstawie rezultatów opracowanych danych wysnuć można wniosek, że każdorazowo uzyskanie wyniku stężenia renalazy < 38,98 ng/ml skłonić powinno do ściślejszego nadzoru nad identyfikacją i eliminacją czynników ryzyka chorób sercowo-naczyniowych.

Wnioski

1. Pomimo poczynionych znacznych postępów w ciągu ostatnich dziesięcioleci w zakresie zrozumienia patogenezy i czynników ryzyka chorób układu krążenia, pozostają one obecnie jednym z najważniejszych problemów systemów ochrony zdrowia na całym świecie. Dlatego też globalne wysiłki powinny koncentrować się na promocji zdrowego stylu życia, a szczególną uwagę należy zwrócić na modyfikowalne czynniki ryzyka.
2. Wprowadzenie środków dążących do redukcji czynników ryzyka chorób sercowo-naczyniowych znacząco przyczyni się do zwiększenia zarówno oczekiwanej długości życia, jak i jego jakości, a także bezpośrednio przełoży się na poprawę kondycji budżetu opieki zdrowotnej, ponieważ koszty związane z chorobami układu krążenia, choć nie są wysokie w fazie prewencyjnej, ulegają znacznej progresji w przewlekłej fazie choroby.
3. Istnieje możliwy do zaobserwowania związek między narażeniem na dym tytoniowy a niższym poziomem renalazy w surowicy, zarówno w przypadku aktywnego palenia, jak i narażenia środowiskowego na dym tytoniowy.

4. Wyższe BMI, wyższe rozkurczowe ciśnienie krwi i choroba wieńcowa mogą stanowić czynniki ryzyka niższego poziomu renalazy w surowicy niezależnie od narażenia na dym tytoniowy.
5. Ocena narażenia na dym tytoniowy z wykorzystaniem narzędzi opartych na kwestionariuszach może charakteryzować się wysoką czułością, ale tylko umiarkowaną swoistością, szczególnie w zakresie oceny środowiskowego narażenia na dym tytoniowy.
6. Wzrost liczby czynników ryzyka sercowo-naczyniowego może przekładać się na niższe stężenie renalazy we krwi.
7. Czynnikami ryzyka sercowo-naczyniowego, które wydają się najistotniej powiązane z niższym stężeniem renalazy we krwi to otyłość, palenie tytoniu i brak aktywności fizycznej.
8. Odpowiednia standaryzacja punktu odcięcia stężenie renalazy we krwi może stanowić predyktor występowania zwiększonej liczby czynników ryzyka sercowo-naczyniowego (w niniejszym badaniu stężenie renalazy we krwi niższe niż 38,98 ng/ml było najdokładniejszym predyktorem wystąpienia co najmniej pięciu czynników ryzyka chorób układu krążenia).

Streszczenie

Choroby układu sercowo-naczyniowego to obecnie główna przyczyna zgonów (w tym przedwczesnych) na całym świecie, w szczególności w krajach zaliczanych do kategorii państw o wysokim poziomie rozwoju gospodarczego. Stanowią one zatem poważne wyzwanie dla wszystkich systemów opieki zdrowotnej. Wśród chorób sercowo-naczyniowych wiodącym czynnikiem ryzyka zgonu jest nadciśnienie tętnicze, które w 2019 roku spowodowało niemal ¼ wszystkich zgonów (24%) wskutek następstw, przede wszystkim zawału serca i udaru mózgu.

Zgodnie z obecnym stanem wiedzy, występowanie chorób niezakaźnych, do jakich zaliczają się choroby układu krążenia, jest wynikiem wpływu czynników behawioralnych, środowiskowych, fizjologicznych i genetycznych. W kontekście zdrowia sercowo-naczyniowego wspomnieć należy o takich czynnikach jak palenie tytoniu, brak aktywności fizycznej, niezdrowa dieta, szkodliwe spożycie alkoholu, nadciśnienie tętnicze, nadwaga i otyłość, hiperglikemia i hiperlipidemia, spośród których najsilniej udokumentowany związek z rozwojem chorób układu krążenia dotyczy nikotynizmu, nadciśnienia tętniczego, hipercholesterolemii, hipertriglicerydemii, cukrzycy typu 2 oraz nadwagi i otyłości. Ze względu na znaczną ilość modyfikowalnych czynników ryzyka chorób sercowo-naczyniowych, styl życia ma kluczowe znaczenie dla zmniejszenia częstości ich występowania.

Renalaza to flawoproteina po raz pierwszy opisana w 2005 roku jako próba poszerzenia wiedzy na temat funkcji endokrynnej nerek. Początkowo przypisywano jej funkcje obniżania częstości rytmu serca i regulację ciśnienia krwi poprzez metabolizowanie krążących katecholamin, jednak dalsze badania podważyły tę teorię. Wyniki późniejszych analiz zakwalifikowały renalazę jako działającą jako oksydaza/anomeraza α-NAD(P)H i utleniającą α-NAD(P)H do β-NAD(P)+ i H_2O_2 , a w toku dalszych badań doprecyzowano te odkrycia, wykazując, że renalaza utlenia 2- i 6-dihydroNAD(P), wytwarzając β-NAD(P)+ i H_2O_2. Istnieją również doniesienia na temat związku renalazy z czynnikami związanymi z dysfunkcją śródbłonka, a także z działaniem przeciwzapalnym i antyapoptotycznym w odpowiedzi na niedokrwienie.

Zasadniczy cel badań stanowiła weryfikacja założenia, że uwarunkowania środowiskowe i behawioralne mają wpływ na poziom stężenia renalazy w osoczu krwi i ocena ewentualnej przydatności tego parametru do zastosowania klinicznego w postępowaniu diagnostyczno-leczniczym chorób układy krążenia. Niniejsza rozprawa doktorska to cykl trzech publikacji, obejmujący jedną pracę przeglądową i dwie prace oryginalne. W pracy przeglądowej dokonano analizy i syntezy dostępnych dotychczas doniesień naukowych dotyczących behawioralnych i środowiskowych determinant zdrowia sercowo-naczyniowego a także stosowanych systemów do oceny ryzyka wystąpienia chorób układu krążenia. Na podstawie przeglądu systematycznego literatury dokonano podsumowania zagadnienia chorób sercowo-naczyniowych jako problemu epidemiologicznego, dotychczas zidentyfikowanych behawioralnych i środowiskowych czynników ryzyka chorób układu krążenia oraz metod ich oceny wraz z zastosowaniem klinicznym.

Pierwsza praca oryginalna to próba oceny wpływu czynnej i biernej ekspozycji na dym tytoniowy jako czynnika środowiskowo-behawioralnego na stężenie renalazy jako enzymu mogącego odgrywać rolę w patogenezie chorób sercowo-naczyniowych. Na podstawie uzyskanych wyników badań wykazano, że zarówno czynne jak i bierne narażenie na dym tytoniowy wpływa na obniżenie stężenia renalazy w surowicy krwi. Ponadto odnotowano, że wyższe BMI, rozkurczowe ciśnienie krwi, stężenie kotyniny w surowicy krwi oraz choroba wieńcowa stanowią niezależne czynniki ryzyka niższego stężenia renalazy w surowicy.

W drugiej pracy oryginalnej dokonano analizy zależności pomiędzy liczbą występujących czynników ryzyka chorób układu krążenia a stężeniem renalazy wraz z próbą oceny przydatności tego parametru jako predyktora CVRF. Wykazano, że stężenie renalazy ujemnie

koreluje z liczbą CVRF. Otyłość, niedobór aktywności fizycznej i konsumpcja wyrobów tytoniowych były niezależnymi czynnikami wpływającymi na obniżenia stężenia tego enzymu. Można ponadto przypuszczać, że po odpowiedniej standaryzacji punktu odcięcia wartości stężenia renalazy dla badanej populacji, niniejszy parametr stanowić może pomocniczy parametr predykcyjny w szacowaniu liczby CVRF, ułatwiając dalsze postępowanie diagnostyczno-lecznicze i zapobiegając rozwojowi powikłań chorób układu sercowo-naczyniowego.

Podsumowując, na podstawie uzyskanych wyników badań wnioskować można, że ocena stężenia renalazy we krwi stanowić może proste i nieinwazyjne narzędzie wspomagające identyfikację sercowo-naczyniowych czynników ryzyka oraz profilaktykę, diagnostykę i leczenie chorób układu krążenia.

Summary

Cardiovascular diseases are now the leading cause of death (including premature death) worldwide, particularly in countries that fall into the category of countries with high levels of economic development. They therefore represent a major challenge for all health care systems. Among cardiovascular diseases, the leading risk factor for death is hypertension, which in 2019 accounted for almost ¼ of all deaths (24%) due to sequelae, primarily heart attack and stroke.

According to current knowledge, the occurrence of non-communicable diseases, which include cardiovascular diseases, is the result of the influence of behavioural, environmental, physiological and genetic factors. In the context of cardiovascular health, mention should be made of such factors as smoking, physical inactivity, unhealthy diet, harmful alcohol consumption, hypertension, overweight and obesity, hyperglycemia and hyperlipidemia, of which the strongest documented association with the development of cardiovascular disease relates to tobacco consumption, hypertension, hypercholesterolemia, hypertriglyceridemia, type 2 diabetes, and overweight and obesity. Due to the significant number of modifiable risk factors for cardiovascular disease, lifestyle is key to reducing its incidence.

Renalase is a flavoprotein first described in 2005 in an attempt to expand our understanding of renal endocrine function. It was initially attributed with functions of lowering heart rate and regulating blood pressure by metabolizing circulating catecholamines, but further studies have challenged this theory. The results of later analyses classified renalase as acting as an α-NAD(P)H oxidase/anomerase and oxidizing α-NAD(P)H to β-NAD(P)+ and H2O2, and further studies have refined these findings, showing that renalase oxidizes 2- and 6-dihydroNAD(P), producing β-NAD(P)+ and H2O2. There are also reports on the association of renalase with

factors related to endothelial dysfunction, as well as with anti-inflammatory and anti-apoptotic effects in response to ischemia.

The primary purpose of the study was to verify the assumption that environmental and behavioural conditions affect plasma renalase levels and to assess the possible usefulness of this parameter for clinical application in the diagnostic and therapeutic management of cardiovascular diseases.

This dissertation is a series of three publications, including one review paper and two original papers. The review paper analysed and synthesized the scientific reports available to date on the behavioural and environmental determinants of cardiovascular health and also the systems used to assess cardiovascular disease risk. On the basis of a systematic review of the literature, the issue of cardiovascular disease as an epidemiological problem, the behavioural and environmental risk factors for cardiovascular disease identified to date, and the methods used to assess them, along with clinical application, were summarized.

The first original work is an attempt to evaluate the effect of active and passive exposure to tobacco smoke as an environmental-behavioural factor on the concentration of renalase as an enzyme that may play a role in the pathogenesis of cardiovascular disease. Based on the results of the study, it was shown that both active and passive exposure to cigarette smoke affects the reduction of serum renalase concentration. In addition, it was noted that higher BMI, diastolic blood pressure, serum cotinine levels and coronary artery disease were independent risk factors for lower serum renalase levels.

The second original paper analyzed the relationship between the number of cardiovascular risk factors present and renalase concentration, along with an attempt to assess the usefulness of this parameter as a predictor of CVRF. It was shown that renalase concentration negatively correlates with the number of CVRF. Obesity, physical activity deficiency and tobacco consumption were independent factors in lowering the concentration of this enzyme. In addition, it can be assumed that after appropriate standardization of the cut-off point of renalase concentration values for the study population, this parameter can be an auxiliary predictive parameter in estimating the CVRF number, facilitating further diagnostic and therapeutic management and preventing the development of cardiovascular disease complications.

In conclusion, based on the results of this study, it can be concluded that the assessment of blood renalase levels can be a simple and non-invasive tool to assist in the identification of cardiovascular risk factors and the prevention, diagnosis and treatment of cardiovascular diseases.

Piśmiennictwo

[1] Cardiovascular diseases (CVDs), https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed 16 July 2024).

[2] Action on salt and hypertension: reducing cardiovascular disease burden in the WHO European Region, https://www.who.int/europe/publications/i/item/9789289060813 (accessed 26 July 2024).

[3] Arterial Hypertension | European Society of Hypertension, https://www.eshonline.org/guidelines/arterial-hypertension/ (accessed 26 July 2024).

[4] Yusuf PS, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 937–952.

[5] Gać P, Poręba M, Jurdziak M, et al. Cardiovascular risk factors and the concentration of asymmetric dimethylarginine. *Adv Clin Exp Med* 2020; 29: 63–70.

[6] Gać P, Urbanik D, Macek P, et al. Coexistence of cardiovascular risk factors and obstructive sleep apnoea in polysomnography. *Respir Physiol Neurobiol*; 295. DOI: 10.1016/J.RESP.2021.103782.

[7] Bisciglia A, Pasceri V, Irini D, et al. Risk Factors for Ischemic Heart Disease. *Rev Recent Clin Trials* 2019; 14: 86–94.

[8] Who. *World Health Statistics 2023 Monitoring health for the SDGs Sustainable Development Goals HEALTH FOR ALL*, https://www.who.int/publications/book-orders. (2023).

[9] WHO Regional Office for Europe. The European Health Report 2009: health and health systems.

[10] Diabetes, https://www.who.int/news-room/fact-sheets/detail/diabetes (accessed 27 August 2023).

[11] Xu J, Li G, Wang P, et al. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. *Journal of Clinical Investigation* 2005; 115: 1275–1280.

[12] Desir G V. Regulation of blood pressure and cardiovascular function by renalase. *Kidney Int* 2009; 76: 366–370.

[13] Beaupre BA, Hoag MR, Moran GR. Renalase does not catalyze the oxidation of catecholamines. *Arch Biochem Biophys* 2015; 579: 62–66.

[14] Desir G. Novel insights into the physiology of renalase and its role in hypertension and heart disease. *Pediatric Nephrology* 2012; 27: 719–725.

[15] Desir G V. Role of renalase in the regulation of blood pressure and the renal dopamine system. *Curr Opin Nephrol Hypertens* 2011; 20: 31–36.

[16] Beaupre BA, Hoag MR, Roman J, et al. Metabolic function for human renalase: Oxidation of isomeric forms of β-NAD(P)H that are inhibitory to primary metabolism. *Biochemistry* 2015; 54: 795–806.

[17] Guo X, Wang L, Velazquez H, et al. Renalase: its role as a cytokine, and an update on its association with type 1 diabetes and ischemic stroke. *Curr Opin Nephrol Hypertens* 2014; 23: 513–518.

[18] Safdar B, Guo X, Johnson C, et al. Elevated renalase levels in patients with acute coronary microvascular dysfunction - A possible biomarker for ischemia. *Int J Cardiol* 2019; 279: 155–161.

Praca nr 1

REVIEW PAPER

J Health Inequal 2022; 8 (1): 17–24

Submitted: 06.08.2021; accepted: 17.01.2022

DOI: https://doi.org/10.5114/jhi.2022.116483

JOURNAL of Health Inequalities

Environmental and behavioural determinants of cardiovascular health

Aleksandra Żórawik[1], Wojciech Hajdusianek[1], Paweł Gać[1], Rafał Poręba[2]

[1]I Department of Population Health, Division of Environmental Health and Occupational Medicine, Wroclaw Medical University, Poland

[2]Department of Internal and Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, Poland

ABSTRACT

Cardiovascular diseases (CVD) are currently the major cause of death in developed countries, and their percentage share in its rate is systematically and significantly increasing. Over twenty years – between 1990 and 2010 – the number of deaths from CVD increased by a third, and now it is estimated to represent about half of all deaths worldwide, with coronary heart disease and stroke being the two most common causes of loss of years of life. That is why CVD are a significant epidemiological problem. Therefore, determining the risk factors and ways of prevention is (and should remain) a task of high priority for the entire health care sector around the world, especially in the developed countries. The aim of this review is to summarize major environmental and behavioural determinants of cardiovascular health. The keywords "health, cardiovascular, determinants, environmental, behavioural" were used. Most of the articles broadened the knowledge about positive and negative impacts of behaviours on cardiovascular health. Physical activity, appropriate diet, cessation of smoking, and a correct body mass index, and thus the correct parameters such as lipid profile, blood pressure and fasting glucose levels, have a significant impact on improving health and life expectancy. In conclusion, CVD are currently among the most important international issues. During the past decades, remarkable progress has been made in understanding of their pathogenesis and risk factors. Therefore, the global efforts should be focused on healthy life-style promotion and particular attention should be paid to modifiable risk factors.

KEY WORDS: cardiovascular health, environment, behaviour, cardiovascular risk assessment.

ADDRESS FOR CORRESPONDENCE: Prof. Paweł Gać, I Department of Population Health, Division of Environmental Health and Occupational Medicine, Wroclaw Medical University, Mikulicza-Radeckiego 7, 50-368 Wroclaw, Poland, e-mail: pawelgac@interia.pl

HEALTH – DEFINITIONS AND DETERMINANTS

Although it is universally acknowledged that health is the one of the most important subjects for people, defining it was never an easy matter. There have been approximately 300 attempts to state its definition [1], and throughout the ages and centuries, philosophers and poets have tackled the disputed issue. Historically, the word "health" derived from the name of a goddess of wellbeing in ancient Greece. Philosophically, Menander, an ancient Greek poet, wrote that there are "two things in life – the health and the mind" as early as 300 B.C., and Hippocrates stated that *salus aegroti suprema lex* or simply a physician should act in the best interest of the patient, which up to modern days is a major rule for all medical doctors across the whole world [2].

One of the first efforts to define health focused only on the lack of disease though neglected human well-being, and that issue was not considered until 1964 when the constitution of the World Health Organization was signed in New York, where it was stated that "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [3]. Although the definition was widely accepted in many countries, following F. Leonardi, it appears to be unsuitable for modern

challenges in the public health sector, particularly in the aspect of aging society [4].

However, due to the high prevalence of chronic diseases and the fact that an average adult usually presents at least 4 different symptoms during 14 days [5], "complete well-being" is felt to be unattainable and somewhat utopian.

The wide scope of that definition is also being criticised since complete physical, mental and social well-being would mean living in a world free of poverty, discrimination, violence, wars and hunger, which, though being extremely crucial matters, are not by themselves a medical issue (F. Leonardi). Moreover, the combination of treating every social abnormality as a medical concern and progressive medicalisation of many different aspects of life would lead to increasing state expenditure in the medical field as a result of increasing social pressure in this matter [4].

Leonardi proposed the following conditions to establish an accurate definition of health [4]:

- it does not focus only on lack of disease;
- it regards health as a collection of abilities;
- it regards health as a continuous, dynamic process rather than an obtainable state;
- it is potentially attainable by everyone in real life in all circumstances;
- it includes not only good but also bad moods, since difficult, arousing emotions are just a part of human everyday life not influencing health itself. This inclusion is crucial to the idea of not perceiving health as an ideal, almost impossible to achieve. For example, in the elderly chronically ill group, such a definition could be comprehended as an ability to cope with one's limits;
- health must be independent from moral and ethical discourse;
- health must be based on personal priorities, values and needs;
- health must be measured by clearly stated criteria.

Leonardi proposes the definitions as follows: Health is an ability to cope with both good and bad moods, is an ability to react to different environmental events giving rise to desired emotional and cognitive stimuli and at the same time avoiding undesired ones. Despite its simplicity, this definition meets all 9 guidelines, and contrary to the WHO's definition it does not conceive health as unattainable with its all-utopian side effects. Obviously, the definition does not exclude traditional medical criteria, which are curing diseases and alleviation of ailments; they are important elements which influence one's ability to handle good and bad moods. This transformation changes the current idealistic vision of health in a ground-breaking way.

All factors conditioning the state of the organism, both physical and mental, should be considered as health determinants. These aspects together or separately can have either a positive or negative influence on both single persons and whole communities [6]. Different definitions identify different factors, and though they differ in the details, they are generally convergent.

"Health is a result of factors like genetics, environmental, life-style, and available health-service. A promotion of healthy life-style can positively influence health conditions and reduce the need for health medical services" [7]. These definitions, which also differ from the WHO's one, became a starting point for a discussion published in the "New Perspectives on the Health of Canadians" report in 1974, which was the first conception of Marc Lalonde, who was a Canadian health minister, the health field concept [8].

Lalonde was the first to pay attention to the fact that societies' efforts were focused only on improvement of the health system whereas the remaining fields have the greatest influence on shaping people's condition. However, the report did not include a detailed quantification of the influence of groups of factors on people's health. Those studies were conducted by Badura 21 years later in 1995 [7] with the results as follows: lifestyle 54%, biology 25%, environment 9%, health care system 12% [8, 9]. The fractions vary depending on source but remain consistent in the fact that the smallest fraction is associated with the health-care system. In Poland, regarding the National Health Programme (1996-2005), the proportions are: 50-60% lifestyle, 20% biology, 20% environment, 10% health care system.

"The European health report 2009: Health and health systems", which was published by the WHO 35 years after "New Perspectives on the Health of Canadians", distinguishes the following groups of health factors: environmental, socioeconomic, behavioural, lifestyle [10]. The report highlights that due to different presentation of those factors in European countries they have a different level of influence on health there. A general trend can be observed: lower educated people, with lower income and lower employment status, tend to spend more years in a bad condition and have more health-related problems than the opposite group [10, 11]. Consequently, lifestyle and health related behaviours have a common ground that is socioeconomic conditions and social inequalities have direct relations with health inequalities. Therefore, theoretically they can be modified and then eliminated.

As a result of international efforts to improve public health, the first international conference of health promotion was organised 1986 in Ottawa city by the WHO, Welfare Canada and Canadian Public Health Association [12]. Consequently, the Ottawa Charter for Health Promotion was established and defined health promotion as a "process of enabling people to increase control over, and to improve, their health" [13]. The charter aims to create an effective health promotion strategy and focuses on the following directions [14]:

- build healthy public policy;
- create supportive environments;

- strengthen community action;
- develop personal skills;
- reorient health services;
- moving into the future.

CARDIOVASCULAR DISEASES AS AN EPIDEMIOLOGICAL ISSUE

Cardiovascular diseases (CVD) are the main cause of deaths in developed countries and their share in deaths is gradually increasing. Particularly between 1990 and 2010 the number of these deaths rose by one third [15] and currently they comprise about a half of all deaths across the whole world from which coronary artery disease (CAD) and stroke are the main causes of loss of years of life (disability-adjusted life years – DALY) [16]. That is a reason why CVD are an important problem and conducting scientific studies in their area and prevention of unhealthy behaviours should have a high priority for the entire health care system especially in developed countries.

In 2011, the WHO passed a new declaration to achieve a 25% reduction in mortality from noncontagious diseases by 2025 through reducing risk factors that may be subject to reduction [16].

Since the 1930s, when major studies on death causes revealed a decrease in contagious diseases, knowledge of the significant role of CVD has been developed [17]. In the 1950s high levels of cholesterol and blood pressure were identified as major CVD risk factors (Framingham). Then in subsequent studies the risk factors were divided into two groups: modifiable and non-modifiable. These groups were composed of age, sex, family history, comorbidities, tobacco, alcohol, lack of physical activity, obesity, hypertension, and dyslipidaemia [18]. The modifiable factors are related to environmental and behavioural determinants of health and therefore can be significantly decreased.

ENVIRONMENTAL DETERMINANTS OF CARDIOVASCULAR HEALTH

CVD risk factors are measurable and are associated with increased probability of future CVD [19].

1.7 million deaths (18%) are associated with harmful environmental factors annually. They include lack of clean drinking water, poor sanitation conditions, air pollution, organic pollutions, mercury and pesticides, traumas, and occupational exposure [10].

Environmental determinants related to CVD include occupation related: chronic psychological stress due to activation of the hypothalamic-pituitary-adrenal axis (HPA axis) and sympathetic nervous system, which leads to increased blood pressure [20-22]. Acute stress may also trigger acute coronary syndromes in the group of chronic CAD [22] and consequently this stress then may impair rehabilitation and worsen the long-term prognosis [23]. Stress can also contribute to oxidative stress and induce inflammation in walls of blood vessels [24, 25]. It should also be noted that isolation, loneliness, financial difficulties, and problems in private life may contribute to chronic stress and are essential environmental aspects.

According to Evsevyeva's studies on a group of 68 young males employed in chronic stress exposed sectors, the blood pressure measured continuously resulted in an increase in working days contrary to non-working ones [21]. These results can be compared with the multi-centre INTERHEART study, which analysed exposure to emotional stress and myocardial infarction. In the study 6 independent groups of death risk factors were determined, one of which comprised psychosocial factors – exposure to emotional stress. Other factors were hypertension, dyslipidaemia, tobacco, obesity, and diabetes [26].

It was proved that exposure to stress factors, both occupational and everyday life, increases the risk of myocardial infarction more than two-fold [23].

Due to urbanisation and industrialisation increasing air pollution became a major health problem. According to the WHO, 91% of people live in an environment exceeding norms of air pollution and as a result 4.2 million people die annually of stroke, CVD, lung neoplasms and chronic respiratory diseases [27]. Similarly to emotional stress, air pollution leads to oxidative stress and induces vascular tissue inflammation [24, 25].

Equally, increases in pesticide use and concentrations of organic pollutants contribute to human health and may lead to CVD [28, 29].

BEHAVIOURAL DETERMINANTS OF CARDIOVASCULAR HEALTH

The WHO's European Health Report [9, 10] distinguishes seven behavioural and life-style risk-factors which are responsible for 60% of diseases in Europe: high blood pressure, tobacco, alcohol abuse, high level of cholesterol, inappropriate diets, not enough physical activity, and obesity. The main factor in Europe is hypertension and its complications. According to the WHO's strategy for the European's region (1989), lifestyle is a 'way of living based on mutual connection between living conditions and individual patterns of behaviour shaped by sociocultural factors and individual predispositions' [30]. On its basis, it can be presumed that health behaviours are in direct and inseparable relations with lifestyle and the contribution of behavioural aspects in prevention of CVD is increasingly emphasised by both American and European guidelines [19, 31-33].

Identification of harmful behaviours is a vital aspect in prophylaxis of CVD and is a basis for developing algorithms used to determine health risk scores. The behaviours significant in sustaining good health condition are cessation of smoking, maintaining appropriate body weight, physical activity and diet, which lead to normalisation of cholesterol level, glycaemia, and blood pressure [34].

In 2005 approximately 31.4% of people above 15 years old smoked tobacco in Europe, including 44.4% of males

TABLE 1. Chronology of cardiovascular risk assessment development

Year	Algorithm
1991	Framingham Heart Study CHD Prediction: +LVH
1998	Framingham Coronary Heart Disease Risk Prediction
1999	British Joint Societies CHD
2002	PROCAM (Munster)
2003	SCORE
2004	British Joint Societies CVD
2004	WHO/ISH
2007	ASSIGN
2007	QRISK 1
2008	QRISK 2
2008	Framingham General CVD Risk Prediction

and 23.2% of females [35]. In the group of 13-15-year-olds smoking prevalence was estimated at 22.7% for boys and 16.8% for girls [35], which is particularly worrying due to the strong addictive potential of tobacco. Smoking contributes to CVD due to the influence on vessels, where it induces inflammation and proliferation [36] leading to atherosclerosis.

Obesity caused by inappropriate nutrition and sedentary lifestyle consumes around 6% of total healthcare system costs and leads to nearly as many premature deaths as tobacco [10, 37].

In Europe 20% of people do not undertake sufficient physical activity and follow a diet that contains a high number of calories and excessive quantities of fats, carbohydrates, and alcohol. 30-80% of adults and up to 30% of children have BMI greater than 25 kg/m^2 [10]. These factors lead to metabolic abnormalities such as diabetes and dyslipidaemia and lead to increased risk of CVD. About half of diabetics die from CVD [38].

CLASSIFICATIONS OF CARDIOVASCULAR HEALTH

Evaluation of CV health is based on estimating the probability of occurrence of CVD in future by identifying risk factors leading to atherosclerosis. Global CV risk is defined as the probability of either death or occurrence of CVD in a determined interval of time and is a result of synergic contribution of different atherosclerotic risk factors [34]. Therefore a few scales have been developed to assess CV risk, and from which Framingham Heart Study (FHS) classification and SCORE have external validation, that is they have been supervised and assessed for predictive ability in a different group than the one used in creation of the algorithm. The scales differ in the target populations and number of factors considered:

- age;
- sex;
- blood pressure;
- lipidaemia;
- tobacco;
- diabetes;
- family history;
- obesity;
- metabolic syndromes;
- lack of physical activity;
- left ventricular hypertrophy;
- atrial fibrillation;
- heart rate;
- apolipoprotein B;
- CRP concentration;
- hyperuricemia;
- creatinine level;
- albuminuria;
- socioeconomic status;
- intima-media thickness [33].

Despite the high number of factors, most algorithms are based on evaluation of 6 main ones: age, sex, cholesterol level, diabetes, hypertension, tobacco [39].

Estimating CV risk is a basis for preventive cardiology, which plays an important role in the response to the increasing CVD mortality rate. Table 1 presents a chronology of CV risk assessment development.

FRAMINGHAM HEART STUDY CLASSIFICATION

FHS is a scale used to estimation of occurrence of a cardiovascular event that is either followed or not by death (such as coronal artery diseases, ischaemic and haemorrhagic stroke, TIA, peripheral arterial diseases, heart failure, acute coronary syndromes, stable angina) in following Americans 30-74 years old for 10 years. It is one of the oldest (1948) studies of its type, and probably a cornerstone of preventive cardiology. Its history is related to the death of Franklin D. Roosevelt, the 32nd president of the United States, caused by a haemorrhagic stroke caused by hypertension up to 300/190 mmHg [15]. His successor, President Harry Truman, signed the National Heart Act and founded the National Heart Institute. Its headquarters was located in Boston [40].

The Framingham Heart Study (FHS) is the longest American cohort study in the field of CVD [40] and up to 2018 had three generations of participants (15 000 people), with continuous monitoring of the number of cases and mortality from CVD.

In 1961 major risk factors for CAD were identified and became the basis for development of CVD estimating algorithms. The risk factors were high blood pressure, high cholesterol level, and left ventricular hypertrophy in ECG examination. In its present shape FHS is used to evaluate patients aged 30-79, without a history of CVD events and based on the following parameters (2018) (Prevention Guidelines Tool CV Risk Calculator) [40-42]:

- age;
- sex;

- tobacco;
- total and HDL cholesterol;
- diabetes;
- systolic pressure and hypotensive prescriptions.

FHS can be used only as primary prevention due to the fact it is used only to asses' patients without history of CVD events.

There is abundant scientific evidence that the most important risk factor for CVD is blood pressure [41]. Furthermore, during FHS studies it was revealed that blood pressure alone could identify patients with high risk of stroke and approximately 57% of it occurred in the population where systolic pressure was greater than 160 mmHg (19% of total participants and 36.2% of all CVD events) [43]. In hypertensive heart disease statistics were similar as well. However, in CAD and in peripheral arterial diseases the correlation is slightly smaller and high blood pressure precedes a lower rate of CAD and even fewer cases of intermittent claudication [41]. That is why algorithms that include superposition of some of the factors appears to be particularly useful.

SCORE

Systemic COronary Risk Evaluation (SCORE) is a scale developed by the European Society of Cardiology (ESC) and published in 2003. It is used to estimate individual risk of death in European countries due to CVD in the following 10 years in the patient group without a history of CV events and similarly to the previously discussed scale it is also a part of primary prevention [44]. The algorithm was based on a cohort study conducted during 1970-1988 and included 205 178 patients (with 7934 deaths from CVD) in 12 European countries [33]. Two tables have been designed used to estimate global CV risk and countries were divided into either low or high risk. Low risk countries were Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, and the UK. High risk countries were Albania, Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Macedonia, Moldova, the Russian Federation, the Syrian Arab Republic, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan [45]. In Poland since 2007 Pol-SCORE is used and the current version was published in 2015.

Pol-SCORE takes into consideration the following factors:

- age;
- sex;
- tobacco;
- systolic blood pressure;
- cholesterol level concentration.

The relative risk score is expressed as a percentage and puts the patient in one of three categories:

- low CV risk (less than 1%);
- medium CV risk (1-4%);
- high CV risk (5% and above).

Based on this qualification, a decision is made on the implementation and type of preventive treatment which may regard life-style modification, hypotensive and statin prescription. A different approach is for patients with high CV risk – that is called a strategy for high-risk patients [33].

Different circumstances may also influence the final risk, such as:

- sedentary lifestyle;
- family history;
- socioeconomic status;
- diabetes (most diabetic patients are regarded as high or very high CV risk);
- low level of HDL;
- chronic kidney disease (GFR < 60 ml/min/1.73 m^2).

Patients with a history of diabetes 2, diabetes 1 with complications, or CVD events are regarded as a very high-risk group [33].

The main differences of SCORE in comparison to other algorithms is:

- it estimates death risk from not only CAD, but all CV diseases caused by atherosclerosis. It estimates the risk of death itself rather than CV events not necessarily followed by death.

AHA LIFE'S SIMPLE 7

AHA Life's Simple 7 (AHALS7) includes 7 modifiable risk factors defined by the American Heart Association [46] and was designed to improve Americans' CV health by about 20% with a simultaneous decrease in CV event induced mortality by 20% by the year 2020 [47]. It is a part of prevention and these factors, sometimes described as "prescription for health", are control of hypertension, control of cholesterol level and glycaemia, regular physical activity, diet, body weight control, and cessation of tobacco. Altogether there are three biometric and four behavioural factors. These recommendations do not require great financial outlays, are not complicated, and implementation of them may significantly improve public health [48].

Each of these factors may take one of three values: ideal, intermediate, and unfavourable, as presented in Table 2 [47].

Despite the efforts made, the number of people with ideal CV health is still very low. Common problems are poor diet and lack of physical activity, which together lead to overweight and obesity [49].

Both the AHA and the WHO pay attention to socioeconomically inequalities contributing to health status due to unfavourable health behaviours, poor education, and limited access to health care [49].

It is estimated that approximately 20-30% of US annual healthcare costs are spent on diseases associated with

TABLE 2. AHA Life's Simple 7 scoring

Factor	Level of health for each metric		
	Poor	Intermediate	Ideal
Tobacco	Continuous	Ceased in previous 12 months	Never or ceased earlier than 12 months ago
BMI [kg/m^2]	≥ 30	25-29.9	18.5-25
Physical activity minutes per week	None	1-149 of moderate 1-74 of intensive < 60 min daily	≥ 150 of moderate ≥ 75 of intensive ≥ 60 min daily
Number of components included from the healthy diet pattern*	0-1	2-3	4-5
Level of total cholesterol	≥ 240 mg/dl	200-239 mg/dl	< 200 mg/dl
Blood pressure [mmHg]	SBP ≥ 140 DBP ≥ 90	SBP 120-139 DBP 80-89	SBP < 120 DBP < 80
Fasting glycaemia [mg/dl]	≥ 126	100-125	< 100

**Healthy diet pattern is the Dietary Approaches to Stop Hypertension (DASH): ≥ 5 fruit and vegetable servings daily, ≥ 2 fish servings weekly, ≥ 3 grain product servings daily. No more than 1000 g of sugar-sweetened beverages weekly, no more than 1500 mg of salt daily*

modifiable CVD risk factors, most of which are included in AHALS7 [48]. Further studies on an ethnically diverse population proved that people with at least 5 ideal factor values have 78% lower probability of death from CVD than people with no parameters at an ideal value [50].

Similarly, Milstein *et al.* [51] tested three strategies which could decrease mortality and healthcare costs: 1) extended health insurance, 2) increase in preventive and chronic care, 3) promotion of healthier lifestyle and environmental conditions. In the results, when all these three strategies are employed, approximately 90% of patients can be saved and the costs of health care can be reduced by about 30% in 10 years, and in 25 years by 140 and 62%. Furthermore, patients at high risk will benefit from both intensive behavioural and medical interventions which although initially increasing costs, will prevent progression of chronic diseases to a stage at which costs will be much greater. Conversely, in low-risk patients the preventive measures themselves will benefit in the long term and will decrease the needs for sophisticated high-end and highly priced care.

The presented model illustrates the assumption of "guidelines of healthy life" – the elimination of CVD risk factors is easy to implement and an effective way of achieving real benefits for both the individual and society.

CONCLUSIONS

CVD are currently one of the most important international problem. During the past decades, remarkable progress has been made in understanding their pathogenesis and risk factors. Therefore, global efforts should be focused on healthy lifestyle promotion and particular attention should be paid to modifiable risk factors. Introducing such measures will significantly contribute to increases in both life expectancy and quality and will directly support the health care budget. CV related costs, though not expensive in the preventive modifiable stage, rise swiftly when left to progress to chronic and severe disease.

DISCLOSURE

The authors report no conflicts of interest.

References

1. Kozłowska E, Marzec A, Kalinowski P, Bojakowska U. Health concept and its protections in the light of subject literature. J Educ Health Sport 2016; 6(9): 575-585.
2. Zaborowski R. Koncepcje zdrowia w filozofii starożytnej Grecji (Od Siedmiu Mędrców do Arystotelesa) [Concepts of Health in the Philosophy of Ancient Greece (From the Seven Wise Men to Aristotle)]. In: Higiena psychiczna dla studentów medycyny [Mental hygiene for medical students]. Kobierzycki T (ed.). Medical Academy, Warsaw 1993; 157-177.
3. International Health Conference. Constitution of the World Health Organization. 1946. Bull World Health Organ 2002; 80(12): 983-984.
4. Leonardi F. The definition of health: towards new perspectives. Int J Health Serv 2018; 48(4): 735-748.
5. Wood PHN. Health and disease and its importance for models relevant to health research. In: Scientific Approaches to Health and Health Care. Nizetic BZ, Pauli HG, Swensson PG (eds.). World Health Organization, Copenhagen 1986; 57-70.
6. Wierzbicka A. Determinanty zdrowia – analiza taksonomiczna determinant stanu zdrowia starszej subpopulacji krajów europejskich [Determinants of health – taxonomic analysis of health of elder subpopulation in european countries]. Acta Universitatis Lodziensis. Folia Oeconomica 2013; 297: 195-210.
7. Wysocki MJ, Miller M. Paradygmat Lalonde'a, Światowa Organizacja Zdrowia i Nowe Zdrowie Publiczne [Lalonde's paradigm, World Health Organization and New Public Health]. Epidem Rev 2003; 57(3): 505-512.

8. Lalonde M. A New Perspectives on the Health of Canadians a working document, Marc Lalonde Minister of National Health and Welfare, Canada, Ottawa 1974. Available from: https://www.canada.ca/.../new-perspective-health-canadians-lalonde-report.html (accessed: 20 May 2021).
9. Badura B. What is and what determines health. In: Scientific Foundations for Public Health Policy in Europe. Laaser U, de Leeuw E, Stock Ch (eds.). Juventa Verlag. Munchen 1995.
10. The European Health Report 2009: health and health systems. WHO Regional Office for Europe, Copenhagen 2009. Available from: https://www.euro.who.int/en/health-topics/Health (accessed: 4 May 2021).
11. World Health Organization. The world health report 2008. Primary health care – now more than ever. Available from: https://www.who.int/whr/2008/08_overview_en.pdf (accessed: 21 March 2021).
12. Sagar D, Zulfiqar AB, Niranjan K. Empowering people for sustainable development: the Ottawa Charter and beyond. J Glob Health 2017; 7(1): 010308.
13. World Health Organization. Ottawa Charter for Health Promotion, 1986. Available from: https://www.euro.who.int/en/publications/policy... (accessed: 20 May 2021).
14. World Health Organization. Health promotion action means. Available from: https://www.who.int/teams/health-promotion/enhanced-wellbeing/first-global-conference/actions (accessed: 20 March 2021).
15. Mahmooda SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular diseases: a historical perspective. Lancet 2014; 383(9921): 999-1008.
16. Plakht Y, Shiyovich A. Less is more: the dynamic epidemiology of cardiovascular diseases. Pol Arch Intern Med 2016; 126(11): 839-841.
17. O'Donnell CJ, Elosua R. Factores de riesgo cardiovascular. Cardiovascular risk factors. Insights from Framingham Heart Study. Rev Esp Cardiol 2008; 61(3): 299-310.
18. Surma S, Szyndler A, Narkiewicz K. Awareness of hypertension and other risk factors for cardiovascular disease in the adult population. Heart Vasc Dis 2018; 15: 14-22.
19. Smith SC, Jackson R, Pearson TA, et al. Principles for national and regional guidelines on cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum. Circulation 2004; 109(25): 3112-3121.
20. Erdine S, Ari O, Zanchetti A, et al. ESH-ESC guidelines for the management of hypertension. Herz 2006; 31(4): 331-338.
21. Evsevyeva ME, Ivanova LV, Sergeeva OV, Orechova NV. Early diagnosis of stress-induced hypertension in young employees of state law enforcement agencies. Klin Med (Mosk) 2017; 95(1): 45-50.
22. Wirtz PH, von Känel R. Psychological stress, inflammation, and coronary heart disease. Curr Cardiol Rep 2017; 19(11): 111.
23. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol 2012; 9(6): 360-370.
24. Münzel T, Sørensen M, Gori T, et al. Environmental stressors and cardio-metabolic disease: part II – mechanistic insights. Eur Heart J 2017; 38(8): 557-564.
25. Zhang C, Ding R, Xiao C, et al. Association between air pollution and cardiovascular mortality in Hefei, China: a time-series analysis. Environ Pollut 2017; 229: 790-797.
26. Koziński Ł, Krzymińska-Stasiuk E, Głogowska A, Raczak G. Analiza poziomu wiedzy o podstawowych czynnikach ryzyka chorób układu sercowo-naczyniowego z uwzględnieniem zależności społeczno-demograficznych – badanie ankietowe. Folia Cardiologica Excerpta 2012; 7(3): 170-176.
27. World Health Organization. Ambient air pollution. Available from: https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/ambient-air-pollution (accessed: 4 May 2021).
28. Qi Z, Zhang Y, Chen ZF, et al. Chemical identity and cardiovascular toxicity of hydrophobic organic components in PM 2.5. Ecotoxicol Environ Saf 2020; 201: 110827.
29. Mostafalou S, Abdollahi M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicol Appl Pharmacol 2013; 268(2): 157-177.
30. Kickbusch I. Styl życia a zdrowie [Lifestyle and health]. Promocja Zdrowia. Nauki Społeczne i Medycyna 1994; 1(2): 163-176.
31. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics 2010 update: a report from the American Heart Association. Circulation 2010; 121(7): e46-e215.
32. Hobbs FD, Jukema JW, Da Silva PM, et al. Barriers to cardiovascular disease risk scoring and primary prevention in Europe. QJM 2010; 103(10): 727-739.
33. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J 2007; 28(19): 2375-2414.
34. Ślusarska B. Zachowania zdrowotne w prewencji ryzyka sercowo-naczyniowego [Health behaviors in the prevention of cardiovascular risk]. Folia Cardiologica Excerpta 2012; 7(1): 51-59.
35. The Tallinn Charter: Health Systems for Health and Wealth. Copenhagen, WHO Regional Office for Europe, 2008. Available from: https://apps.who.int/iris/handle/10665/349648?-show=full (accessed: 4 May 2021).
36. Noale M, Limongi F, Maggim S. Epidemiology of cardiovascular diseases in the elderly. Adv Exp Med Biol 2020; 1216: 29-38.
37. Jokinen E. Obesity and cardiovascular disease. Minerva Pediatr 2015; 67(1): 25-32.
38. Glovaci D, Fan W, Wong ND. Epidemiology of diabetes mellitus and cardiovascular disease. Curr Cardiol Rep 2019; 21 (4): 21.
39. Novo S, Carita P, Lo Voi A, et al. Impact of preclinical carotid atherosclerosis on global cardiovascular risk stratification and events in a 10-year follow-up: comparison between the algorithms of the Framingham Heart Study, the European SCORE and the Italian 'Progetto Cuore'. J Cardiovasc Med 2019; 20(2): 91-96.
40. Andersson C, Johnson AD, Benjamin EJ, Levy D, Vasan RS. 70-year legacy of the Framingham Heart Study. Nat Rev Cardiol 2019; 16(11): 687-698.

41. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol 1976; 38(1): 46-51.
42. Syllos DH, Calsavara VF, Bensenor IM, Lotufo PA. Validating the Framingham Hypertension Risk Score: a 4-year follow-up from the Brazilian Longitudinal Study of the Adult Health (ELSA-Brasil). J Clin Hypertens 2020; 22: 850-856.
43. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117(6): 743-753.
44. Van Camp G. Cardiovascular disease prevention. Acta Clin Belg 2014; 69(6): 407-411.
45. European Society of Cardiology. Available from: https://www.escardio.org/static-file/Escardio/Subspecialty/EACPR/Documents/score-charts.pdf (accessed: 2 March 2021).
46. 46. My Life Check. Life's simple 7. Available from: https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7 (accessed: 21 March 2021).
47. Life's simple 7. Available from: https://www.heart.org/en/professional/workplace-health/lifes-simple-7 (accessed: 21 March 2021).
48. Life's simple 7. Available from: https://playbook.heart.org/lifes-simple-7/ (accessed: 21 March 2021).
49. Spring B, Ockene JK, Gidding SS, et al. Better population health through behaviour change in adults a call to action. Circulation 2013; 128(19): 2169-2176.
50. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. Circulation 2012; 125(8): 987-995.
51. Milstein B, Homer J, Briss P, Burton D, Pechacek T. Why behavioral and environmental interventions are needed to improve health at lower cost. Health Aff (Millwood) 2011; 30(5): 823-832.

AUTHORS' CONTRIBUTIONS

PG nad RP prepared the concept of the paper. AŻ collected data. AŻ and PG interpreted data. AŻ wrote the article. All authors have given their final approval to the final version of the paper.

Praca nr 2

Cardiovascular Toxicology (2024) 24:737–746
https://doi.org/10.1007/s12012-024-09868-z

RESEARCH

Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration—the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases

Aleksandra Żórawik[1] · Wojciech Hajdusianek[1] · Agnieszka Kusnerż[1] · Iwona Markiewicz-Górka[1] · Aleksandra Jaremków[1] · Helena Martynowicz[2] · Krystyna Pawlas[1] · Grzegorz Mazur[2] · Rafał Poręba[2] · Paweł Gać[1]

Received: 22 December 2022 / Accepted: 26 April 2024 / Published online: 15 May 2024

Abstract

Exposure to tobacco smoke (ETS) is one of the main risk factors for cardiovascular disease (CVD). Renalase is a protein that may play a role in the pathogenesis of CVD. The aim of the study was to assess the relationship between ETS and serum renalase concentration. A group of 109 patients was recruited for this study (49.7 ± 14.7 years). In accordance with the questionnaire, patients were divided into the following subgroups: subgroup A– declaring themselves active smokers ($n = 36$), subgroup B– declaring themselves non-smokers and exposed to environmental tobacco smoke ($n = 35$), subgroup C– declaring themselves non-smokers and not exposed to environmental tobacco smoke ($n = 38$). The same patients were divided based on cotinine concentration into the following subgroups: subgroup D– active smokers ($n = 42$), subgroup E– non-smokers exposed to environmental tobacco smoke ($n = 66$), and subgroup F– non-smokers not exposed to environmental tobacco smoke ($n = 1$). Serum cotinine concentration and serum renalase concentration were measured using ELISA tests. Serum renalase concentration was statistically significantly higher in subgroup C than in subgroups A and B and in subgroup E and F than in D. There was a negative correlation between serum cotinine concentration and serum renalase concentration ($r = -0.41$, $p < 0.05$). Regression analysis showed that higher BMI, higher diastolic blood pressure, coronary artery disease and higher serum cotinine concentration are independent risk factors of lower serum renalase concentration. The questionnaire method of assessing exposure to tobacco smoke was characterized by high sensitivity, but only moderate specificity, especially in terms of assessing environmental exposure to tobacco smoke. In summary, the study showed an independent relationship between exposure to tobacco smoke and lower serum renalase concentration.

Keywords Tobacco smoke · Serum cotinine concentration · Serum renalase concentration · Arterial hypertension

Introduction

Cardiovascular diseases are the leading cause of death and disability in the populations of developed countries. Hypertension is both a major risk factor for cardiovascular disease and an epidemiologically significant cardiovascular disease [1, 2]. Hypertension causes 9.4 million deaths each year and the number of people suffering from hypertension is increasing [1, 3, 4]. This is the result of global aging of societies and increasing exposure to modifiable risk factors, such as alcohol abuse, increased salt and calorie intake in the diet [1]. Coronary heart disease and stroke are the main consequences of hypertensive disease [5]. There is a relationship between socioeconomic status and

Handling Editor: Daniel Conklin.

✉ Paweł Gać
pawelgac@interia.pl

[1] Division of Environmental Health and Occupational Medicine, Department of Population Health, Wroclaw Medical University, Mikulicza-Radeckiego 7, PL 50-368 Wroclaw, Poland

[2] Department of Internal Medicine, Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, Borowska 213, PL 50-556 Wroclaw, Poland

cardiovascular diseases, including hypertension. These diseases are an unfavorable consequence of civilization development. However, the current studies indicate that the morbidity and mortality rates for hypertension in low-income countries are also increasing [1, 6–8].

Exposure to tobacco smoke is a serious health problem [9]. It includes not only active use of tobacco, which relationship with the development of negative changes in the cardiovascular system has been proven by numerous scientific studies, but also environmental exposure to tobacco smoke [10–16]. The research conducted so far indicates that environmental exposure to tobacco smoke may also have many serious negative consequences [12, 13, 17–21]. Second-hand smoke (SHS) and third-hand smoke (THS) are collectively referred to as environmental tobacco smoke (ETS) [20, 22]. WHO defines second-hand smoke as "the combination of smoke emitted from the burning end of a cigarette or other tobacco products and smoke exhaled by the smoker" [23]. Third-hand smoke is defined as "complex phenomenon resulting from residual tobacco smoke pollutants that adhere to the clothing and hair of smokers and to surfaces, furnishings, and dust in indoor environments" [22]. Current trends are noticeably reducing tobacco consumption in the last decade, but there are still over 1.3 billion people smoking cigarettes and over 8 million of them die every year due to tobacco smoke [16]. Exposure to tobacco smoke can be assessed based on the declarations of the examined persons. It is also possible to determine the concentration of nicotine metabolites in biological material, e.g., the cotinine concentration in blood, plasma, serum, urine or saliva [24].

Renalase is a relatively recently discovered flavoprotein that has been proposed to be an enzyme/hormone [25]. Although renalase was initially detected in the kidney, it can be found in a smaller amount in other organs and tissues such as the heart, small intestine, female and male gonads and skeletal muscles [26, 27]. This novel flavin adenine dinucleotide-dependent (FAD-dependent) amine oxidase has been documented to catabolize circulating catecholamines, causing a reduction in heart rate and blood pressure [26, 28, 29]. Later studies questioned the importance of catabolism of catecholamines by renalase [30, 31]. An earlier conclusion for renalase activity in catecholamine metabolism was made based on in vitro formation of hydrogen peroxide because of incubation of this enzyme with catecholamines. Based on subsequent analyzes, it was concluded that the formation of hydrogen peroxide was too slow to be attributed to the enzymatic activity of renalase [31]. However, there is still a scientific discussion in progress whether a renalase has a function in the metabolism of catecholamines. Currently, more and more scientific evidence seems to point the systemic importance of renalase as a compound with antioxidant potential [26, 28, 32, 33].

Renalase may therefore be a new pathogenetic link in the development of cardiovascular diseases. The search for relationships between risk factors for cardiovascular diseases, metabolic pathways of the genesis of these diseases and their clinical manifestations seems interesting.

The main aim of the study was to assess the relationship between exposure to tobacco smoke (ETS), i.e., active smoking and environmental exposure to tobacco smoke, and the serum renalase concentration. Additional goals included determining the significance of the occurrence of cardiovascular diseases, mainly arterial hypertension, for the analysed relationship; and the importance of the methodology for assessing exposure to tobacco smoke for the analysed relationship.

Material and Methods

The study group was composed of patients of the Internal Medicine and Hypertension Clinic of the University Hospital in Wrocław (Poland). The following participants' inclusion criteria were used: adult patients hospitalized in clinic, consenting to participate in the study. The following were used as exclusion criteria: cancer, systemic diseases, chronic kidney disease, active inflammatory process, the ambiguity of smoking declaration, a history of one of the following conditions: cardiac or angio-surgery, stroke, myocardial infarction, and acute vascular incidents.

The required study group size was estimated using the sample size calculator. The following calculation criteria were assumed: estimated fraction size 50%, significance level 0.05, general population size 2,800,000, acceptable error 10%. Based on the above criteria, the required group size was calculated to be 97.

Finally, 109 patients participated in the study. A similar number of men (51.5%) and women (48.5%) participated in the study, with a mean age 49.7 ± 14.7 years and BMI 28.5 ± 5.3 kg/m^2 (47.7% were overweight or obese). 37.6% of participants had arterial hypertension, 8.3% had type 2 diabetes, and 6.4% had coronary artery disease (without myocardial infarction). Table 1 describes the clinical characteristics of the study group.

Subsequently, the study group were divided into subgroups based on different criteria. The first criterion was exposure to tobacco smoke based on participants' declaration. The following subgroups were established: patients declaring active smoking (subgroup A), patients declaring non-smoking and exposure to environmental tobacco smoke (subgroup B) and patients declaring non-smoking and no exposure to environmental tobacco smoke (subgroup C). Environmental exposure to tobacco smoke was defined as staying at least 30 min a day in rooms where tobacco products are smoked or being in the immediate

Table 1 Characteristics of the study group ($n = 109$)

Age (years)[a]	49.7 ± 14.7/50.0 (24.0)
Gender[b]	
Men	51.5
Women	48.5
BMI (kg/m^2)[a]	28.5 ± 5.3/28.8 (6.1)
Overweight[b]	20.2
Obesity[b]	27.5
Arterial hypertension[b]	37.6
Systolic blood pressure (mmHg)[a]	138.6 ± 20.5/135.0 (30.0)
Diastolic blood pressure (mmHg)[a]	89.2 ± 12.5/90.0 (15.0)
Mean blood pressure (mmHg)[a]	105.7 ± 14.4 / 105.0 (20.0)
Hypotensive drugs[b]	
ACE inhibitors	15.6
β-blockers	19.2
Diuretics	18.3
Calcium channel blockers	11.0
Angiotensin receptor blockers	9.2
Comorbidities[b]	
Type 2 diabetes	8.3
Coronary artery disease	6.4
Cotinine (ng/ml)[a]	16.4 ± 10.4/13.1 (7.5)
Renalase (ng/ml)[a]	189.7 ± 214.8/64.0 (318.6)

[a]arithmetic mean ± standard deviation/median (interquartile range)

[b]percentages

ACE angiotensin-converting enzyme, *BMI* body mass index

vicinity of people smoking tobacco products for at least 15 min a day or living with a person/people smoking cigarettes in the place of residence.

The second criterion was exposure to tobacco smoke assessed based on serum cotinine concentration. Based on this criterion, the study group was divided into the following subgroups: active smokers (subgroup D, serum cotinine concentration > 15 ng/ml), non-smokers exposed to ETS (subgroup E, serum cotinine concentration: 1–15 ng/ml) and non-smokers not exposed to environmental tobacco smoke (subgroup F, serum cotinine concentration < 1 ng/ml). The ranges of serum creatinine concentrations corresponding to types of exposure to tobacco smoke were adopted based on literature data [34–37].

The third criterion was a dichotomic division based on the presence of hypertension. Participants included to a group with arterial hypertension, were diagnosed according to the European Society of Cardiology guidelines. Arterial hypertension was diagnosed, when a mean of two measurements amounted to ≥ 140 mmHg in the case of systolic blood pressure and/or 90 mmHg in the case of diastolic blood pressure. In a situation when a participant declared administration of any hypotensive drugs, arterial hypertension was diagnosed independently of the measured values of arterial blood pressure.

The fourth criterion was self-reported exposure to tobacco smoke, but only in patients with hypertension. The fifth criterion was identical to the fourth one, but exposure to tobacco smoke was defined by serum cotinine concentration. The sixth and seventh criterion was analogical to the fourth and fifth criterion, respectively, but in the group without arterial hypertension. The divisions considering the criteria of type 2 diabetes and coronary artery disease were abandoned due to the low percentage of these diseases in the whole study group.

A tabular summary of the criteria for dividing the study group into subgroups is provided in Table 2.

The study methodology included anamnesis, cardiovascular diseases questionnaire, anthropometric measurements, blood pressure measurements, as well as serum cotinine and renalase concentrations.

To determine the serum cotinine concentration and the serum renalase concentration, approximately 10 cm^3 of blood was collected from each subject from the arm vein. Blood was collected 12 h after the last meal into a tube containing EDTA, then the material was centrifuged at a speed of 10 000 revolutions/minute, and the collected serum was frozen and stored at -70 °C until the tests were performed.

Both serum renalase concentration and serum cotinine concentration in the study subgroups were measured using the enzyme-linked immunosorbent assay (ELISA). The determinations were performed strictly according to the test manufacturer's instructions.

Serum renalase determinations were performed using the E3109Hu kit ELISA (Bioassay Technology Laboratory, Shanghai, China). The renalase concentration was expressed as nanogram per milliliter (ng/ml). The reference range of the assay used was 1–400 ng/ml. According to the manufacturer, the sensitivity of the ELISA test used was 0.52 ng/ml. The coefficient of intra- and inter-assay variation was < 8% and < 10%.

Cotinine determinations were performed using the E2043Hu-96 T kit ELISA (Bioassay Technology Laboratory, Shanghai, China). The cotinine concentration was expressed as nanogram per milliliter (ng/ml). The reference range of the assay used was 0.5–80 ng/ml. According to the manufacturer, the sensitivity of the ELISA test used was 0.019 ng/ml. The coefficient of intra- and inter-assay variation was < 8% and < 10%.

Statistica 13 software for Windows was used for all statistical analyses. The arithmetic means, medians, standard deviations and interquartile ranges were calculated for quantitative variables. The normality of the distribution of quantitative variables has been verified. For quantitative variables with a normal distribution, the t-test or ANOVA (one-way parametric) analysis of variance with post-hoc tests were

Table 2 Serum renalase concentration in the study subgroups

Differentiation criterion	Subgroup	Renalase (ng/ml)[a]	$p < 0.05$
Exposure to tobacco smoke (based on the declaration)	A: patients declaring active smoking ($n = 36$)	81.4 ± 164.2/32.0 (19.4)	A vs. C
	B: patients declaring non-smoking and exposure to environmental tobacco smoke ($n = 35$)	147.3 ± 178.2/82.4 (127.2)	B vs. C
	C: patients declaring non-smoking and no exposure to environmental tobacco smoke ($n = 38$)	331.3 ± 215.3/356.8 (379.0)	
Exposure to tobacco smoke (based on serum cotinine concentrations)	D: active smokers ($n = 42$)	94.2 ± 165.7/35.1 (32.4)	D vs. E
	E: non-smokers exposed to environmental tobacco smoke ($n = 66$)	246.7 ± 221.8/134.4 (348.9)	D vs. F
	F: non-smokers not exposed to environmental tobacco smoke ($n = 1$)	441.5 ± 0.0/441.5 (0.0)	
Arterial hypertension (HTA)	HTA(+): patients with arterial hypertension ($n = 41$)	158.4 ± 207.7/56.0 (188.6)	ns
	HTA(−): patients without arterial hypertension ($n = 68$)	208.6 ± 218.4/91.4 (331.7)	
Exposure to tobacco smoke in patients with HTA (based on the declaration)	A/HTA(+): patients with arterial hypertension declaring active smoking ($n = 17$)	100.4 ± 205.7/28.1 (22.1)	A/HTA(+) vs. C/HTA(+) B/HTA(+) vs. C/HTA(+)
	B/HTA(+): patients with arterial hypertension declaring non-smoking and exposure to environmental tobacco smoke ($n = 13$)	93.4 ± 119.5/58.5 (42.8)	
	C/HTA(+): patients with arterial hypertension declaring non-smoking and no exposure to environmental tobacco smoke ($n = 11$)	324.7 ± 214.8/358.2 (368.9)	
Exposure to tobacco smoke in patients with HTA (based on serum cotinine levels)	D/HTA(+): active smokers with arterial hypertension ($n = 21$)	114.1 ± 202.4/31.6 (34.2)	ns
	E/HTA(+): non-smokers exposed to environmental tobacco smoke with arterial hypertension ($n = 20$)	204.8 ± 208.1/82.2 (333.2)	
	F/HTA(+): non-smokers not exposed to environmental tobacco smoke with arterial hypertension ($n = 0$)	–	
Exposure to tobacco smoke in patients without HTA (based on the declaration)	A/HTA(−): patients without arterial hypertension declaring active smoking ($n = 19$)	64.5 ± 119.2/36.0 (18.7)	A/HTA(−) vs. C/HTA(−) B/HTA(−) vs. C/HTA(−)
	B/HTA(−): patients without arterial hypertension declaring non-smoking and exposure to environmental tobacco smoke ($n = 22$)	179.2 ± 200.9/99.0 (157.3)	
	C/HTA(−): patients without arterial hypertension declaring non-smoking and no exposure to environmental tobacco smoke ($n = 27$)	334.1 ± 219.5/355.5 (406.5)	
Exposure to tobacco smoke in patients without HTA (based on serum cotinine levels)	D/HTA(−): active smokers without arterial hypertension ($n = 21$)	74.2 ± 120.3/36.8 (22.0)	D/HTA(−) vs. E/HTA(−) D/HTA(−) vs. F/HTA(−)
	E/HTA(−): non-smokers exposed to environmental tobacco smoke without arterial hypertension ($n = 46$)	265.0 ± 227.3/180.0 (373.0)	
	F/HTA(−): non-smokers not exposed to environmental tobacco smoke without arterial hypertension ($n = 1$)	441.5 ± 0.0/441.5 (0.0)	

[a]arithmetic mean ± standard deviation/median (interquartile range)

HTA arterial hypertension, *ns* non-statistically significant

used for further statistical analysis. For quantitative variables with a non-normal distribution, the Mann–Whitney U test or a non-parametric equivalent of the analysis of variance, the Kruskal–Wallis ANOVA and post-hoc tests were used. The percentage distribution for categorical variables has been specified. Relationships between variables were assessed using correlation analysis, and univariate and multivariate regression analysis. In addition, the assessment of the sensitivity and specificity of the survey method of assessing exposure to tobacco smoke in relation to the determination of serum cotinine concentration as a reference method was made. The result at the level of $p < 0.05$ was considered significant.

Results

Serum cotinine concentration in whole study group was 16.4 ± 10.4 / 13.1 (7.5) ng/ml [data presentation format: arithmetic mean ± standard deviation / median (interquartile range)] and serum renalase concentration was 189.7 ± 214.8 / 64.0 (318.6) ng/ml. Characteristics of the study group are shown in Table 1.

Comparative analysis of serum renalase concentrations in subgroups based on the criteria of exposure to tobacco smoke and hypertension showed statistically significant differences, Table 2. Patients declaring active smoking and patients declaring non-smoking and exposure to environmental tobacco smoke had significantly lower serum renalase concentrations than patients declaring non-smoking and no exposure to environmental tobacco smoke. However, when patients were analyzed not on basis of declaration, but in the context of cotinine concentration, active smokers were found to have significantly lower serum renalase concentrations than both non-smokers exposed to environmental tobacco smoke and non-smokers not exposed to environmental tobacco smoke. Hypertensive and non-hypertensive patients did not differ in serum renalase concentration. In hypertensive and non-hypertensive patients, similar differences in serum renalase concentrations between subgroups differing in exposure to tobacco smoke were found, as in the entire study group.

Serum renalase concentration was negatively corelated with BMI, systolic blood pressure, diastolic blood pressure, mean blood pressure and serum cotinine concentration, Fig. 1.

To analyze the relationship between serum renalase concentration and other factors the univariable and multivariable regression analysis was conducted. In the first step a univariate regression was performed to determine the variables associated with serum renalase concentration. It has been shown that there are relationships between BMI, systolic blood pressure, diastolic blood pressure, mean blood pressure, hypotensive drugs use, coronary artery disease and serum cotinine concentration with serum renalase concentration. Then in the second step, multivariable stepwise

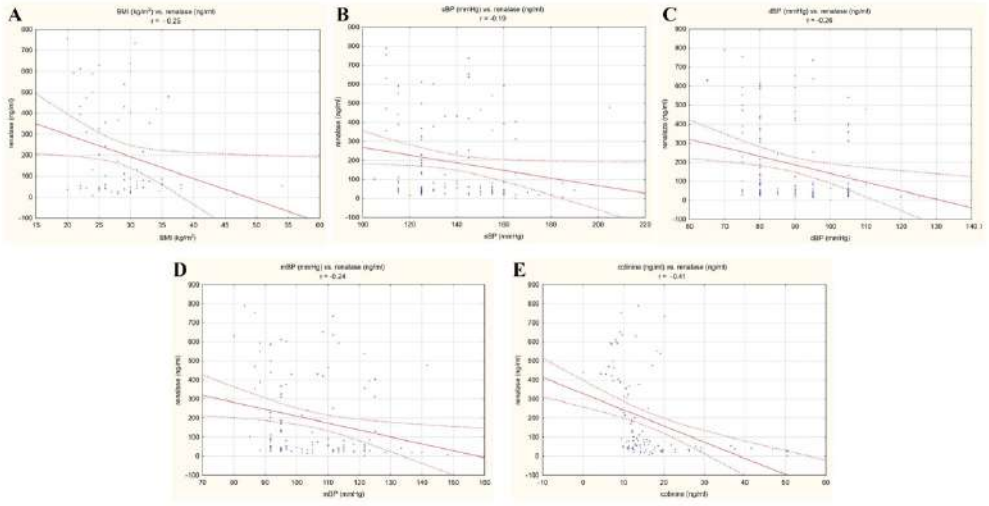

Fig. 1 Correlations in the study group ($n = 109$). **A** BMI (kg/m^2) vs. renalase (ng/ml). **B** systolic blood pressure (mmHg) vs. renalase (ng/ml). **C** diastolic blood pressure (mmHg) vs. renalase (ng/ml). **D** mean blood pressure (mmHg) vs. renalase (ng/ml). **E** cotinine (ng/ml) vs. renalase (ng/ml)

backward regression was performed, and it was shown that higher BMI, higher diastolic blood pressure, coronary artery disease and higher serum cotinine concentration are independent risk factors for lower serum renalase concentrations. The results of the regression analysis are presented in Table 3.

The questionnaire method of assessing exposure to tobacco smoke was characterized by high sensitivity, but only moderate specificity, especially in terms of assessing environmental exposure to tobacco smoke. The sensitivity of the questionnaire assessment of exposure to tobacco smoke in relation to the assessment using serum cotinine concentration was 100% for both active smoking and environmental exposure. The specificity of the survey assessment of exposure to tobacco smoke in relation to the assessment using serum cotinine concentration was 85.7% for active smoking, but only 65.7% for environmental exposure. Several participants declared no exposure to environmental tobacco smoke but were found to be exposed in serum cotinine concentration assessment. The results of the sensitivity and specificity analysis of the test are presented in Table 4.

Discussion

Renalase is a relatively recent discovery and still insufficiently investigated. The keyword "renalase" has only 255 Pubmed scores and 302 Scopus scores. In our study, we have documented that lower serum renalase concentration may be a consequence of cardiovascular risk factors as well as cardiovascular disease.

We obtained important results in relation to tobacco smoke exposure. In our study, we found that both active smoking and exposure to environmental tobacco smoke is related to lower serum renalase concentration. In the literature, we found only a few studies about the relationship between nicotine and renalase. In systemic review describing regulatory promoter and transcription factors of renalase gene, it was found that renalase promoter activity was augmented by nicotine [38]. This mentioned article is the only Pubmed and Scopus search result for the following search terms: 'nicotine', 'renalase', 'tobacco', 'smoking' in different combinations. Furthermore, one of research investigated the role of renalase in pancreatic cancer, high renalase (which promoter activity was increased by nicotine) was found to promote growth of pancreatic ductal adenocarcinoma (PDAC). High renalase concentration was associated with increase of PDAC mortality. Renalase concentration was inversely associated with metastatic melanoma [39].

Our study showed that blood pressure was statistically significantly related with serum renalase concentration. Systolic, diastolic, and mean arterial pressure were found to be negatively associated with serum renalase concentration. It has been documented that diastolic blood pressure is an independent risk factor for lower serum renalase concentration. The relationship between blood pressure and renalase has been documented in other studies to date. In research carried by Xianshu Li et al., aiming to determine renalase relation to pregnancy and preeclampsia, in a group of 384 Chinese participants, blood renalase concentration was negatively corelated with systolic and diastolic blood pressure. Study results were indicated that low blood renalase concentration could be a factor associated with increased risk of preeclampsia (PE) during pregnancy, and its gene polymorphism determined its blood concentration level and development of PE [40]. Similarly, in Polish study blood

Table 3 Results of multivariable stepwise backward regression analysis in the study group ($n = 109$). Estimation for serum renalase concentration as the dependent variable

	Model for: renalase (ng/ml)						
	Univariate regression			Multivariable stepwise regression			
	Rc	SEM of Rc	*p*	Rc	SEM of Rc	*p*	*p* of the model
Age (years)	−1.130	1.406	0.423				0.012
BMI (kg/m^2)	−10.441	4.933	0.038	−8.774	2.716	0.031	
Gender male[a]	53.126	41.044	0.198				
Arterial hypertension[a]	−50.286	42.401	0.238				
Systolic blood pressure (mmHg)	−2.007	0.993	0.046				
Diastolic blood pressure (mmHg)	−4.513	1.601	0.006	−3.243	0.893	0.014	
Mean blood pressure (mmHg)	−3.624	1.397	0.010				
Hypotensive drugs[a]	64.158	30.483	0.039				
Type 2 diabetes[a]	−89.275	74.620	0.234				
Coronary artery disease[a]	−157.454	78.951	0.040	−117.718	49.002	0.019	
Cotinine (ng/ml)	−8.501	1.814	0.011	−9.089	2.667	0.016	

[a]dichotomous variable, in which 1-yes, 0-no

Table 4 Analysis of sensitivity and specificity of the declared exposure to ETS in relation to the reference method for the determination of serum cotinine concentration

A. Active smoking			
	Active smoking (based on serum cotinine concentration): NO	Active smoking (based on serum cotinine concentration): YES	Total
Active smoking (based on the declaration): NO	67	6	73
Active smoking (based on the declaration): YES	0	36	36
Total	67	42	109
Sensitivity			1.000
Specificity			0.857
Accuracy			0.945
Positive likelihood ratio			7.000
Negative likelihood ratio			0.000
Positive predictive value			0.918
Negative predictive value			1.000
J Youden index			0.857
B. Exposure to environmental tobacco smoke (ETS)			
	Exposure to ETS (based on serum cotinine concentration): NO	Exposure to ETS (based on serum cotinine concentration): YES	Total
Exposure to ETS (based on the declaration): NO	1	37	38
Exposure to ETS (based on the declaration): YES	0	71	71
Total	1	108	109
Sensitivity			1.000
Specificity			0.657
Accuracy			0.661
Positive likelihood ratio			2.919
Negative likelihood ratio			0.000
Positive predictive value			0.026
Negative predictive value			1.000
J Youden index			0.657

renalase concentration was lesser in patients with arterial hypertension [41].

We showed an independent relationship between coronary artery disease and lower serum renalase concentration. Few reports are available on the relationship between coronary artery disease and subsequent heart failure, and blood renalase concentration. Heart failure was found to be associated with blood renalase concentration decrease. In the study on rats, reduced renal blood perfusion (caused by heart failure) was found to be a possible cause of impaired renalase synthesis [42].

We found also that renalase concentration was independently inversely associated with BMI, but so far little has been published about this additional relationship. Similar results were obtained in a study conducted on 87 participants in which a negative correlation was observed between blood renalase concentration and BMI [41]. Similarly, Rybi-Szuminska et al. described a statistically significant negative correlation between urine renalase/creatinine ratio and BMI in a healthy pediatric population [43].

In addition, in our study, we examined whether the information declared by patients in the questionnaire about smoking corresponds to real exposure assessed by determining the concentration of cotinine in the serum. The questionnaire method of assessing exposure to tobacco smoke was characterized by high sensitivity, but only moderate specificity, especially in terms of assessing environmental exposure to tobacco smoke. This may be caused by lack of awareness about ETS exposure or neglecting it as non-important exposition. Similar problem was described by Benedetti et al. [44]. These authors emphasized that with the survey method of exposure assessment, respondents tend to give misleading

answers about smoking, due to the currently growing awareness of the harmfulness of smoking, and thus the reluctance to admit to unhealthy habits, especially to medical personnel [44].

Our study has several important limitations that require discussion. The study group is relatively small. The minimum required size of the study group was estimated using a sample size calculator. A better solution would be to use multiple means test power analysis (one-way ANOVA). To confirm the results obtained and provide a more generalizable result, it would be necessary to perform the study again on a larger group of patients. Due to obtaining more accurate results and strengthening the level of evidence, it would be necessary to repeat the study with a larger number of participants, especially in the subgroup of those not actually exposed to ETS. Data from the survey method of assessing exposure to tobacco smoke should be interpreted with caution. Patients may tend to give answers that do not reflect the actual situation, as tobacco smoking may be perceived as an addiction they do not want to admit, especially to medical personnel. Moreover, it should be remembered that the term "exposure to tobacco smoke assessed by serum cotinine concentration" is a simplification. Cotinine measurements do not indicate sole tobacco smoke exposure, but exposure to any products containing nicotine. The study did not verify possible exposure to nicotine other than exposure to tobacco smoke. Other limitations of the study include the small number of patients with coronary artery disease and diabetes included in the study, the lack of data on the number of cigarette-years characterizing active smokers, the lack of determination of lipid profile and glycemia in the study group of patients, as well as information on the organ effects of hypertension assessed by imaging methods. In our opinion, the above limitations do not significantly reduce the value of the obtained results, but they may be a starting point for further research.

Conclusion

There is an independent relationship between exposure to tobacco smoke and lower serum renalase levels, both for active smoking and for environmental exposure to tobacco smoke.

Higher BMI, higher diastolic blood pressure and coronary artery disease are risk factors for lower serum renalase levels independent of exposure to tobacco smoke.

The questionnaire method of assessing exposure to tobacco smoke was characterized by high sensitivity, but only moderate specificity, especially in terms of assessing environmental exposure to tobacco smoke.

Author contributions AŻ - collecting data, gather resources, drafting the manuscript; WH - gather resources, drafting the manuscript; AK - collecting data; IMG - collecting data; AJ - collecting data; HM - collecting data, supervision; KP - supervision; GM - supervision; RP - conception and design, interpretation of data, supervision; PG - conception and design, statistical analysis, interpretation of data, drafting the manuscript, supervision.

Funding This study was funded by Wroclaw Medical University (SUB. A100.19.009).

Data Availability The data presented in this study are available upon request from the corresponding author. The data are not publicly available.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Poulter, N. R., Prabhakaran, D., & Caulfield, M. (2015). Hypertension. *The Lancet, 386*(9995), 801–812.
2. Lim, S. S., Vos, T., Flaxman, A. D., et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. *The Lancet, 380*, 2224–2260.
3. Kearney, P. M., Whelton, M., Reynolds, K., et al. (2005). Global burden of hypertension: analysis of worldwide data. *The Lancet, 365*(9455), 217–223.
4. Rapsomaniki, E., Timmis, A., George, J., et al. (2014). Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *The Lancet, 383*, 1899–1911.
5. Peters, S. A., Huxley, R. R., & Woodward, M. (2013). Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke, 44*(9), 2394–2401.

6. Ibrahim, M. M., & Damasceno, A. (2012). Hypertension in developing countries. *The Lancet, 380*, 611–619.
7. Chow, C. K., Teo, K. K., Rangarajan, S., et al. (2013). Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA - Journal of the American Medical Association, 310*, 959–968.
8. Colhoun, H. M., Hemingway, H., & Poulter, N. R. (1998). Socioeconomic status and blood pressure: An overview analysis. *Journal of Human Hypertension, 12*(2), 91–110.
9. World Health Organization. WHO report on the global tobacco epidemic, 2015: raising taxes on tobacco.
10. Graham, I., Atar, D., Borch-Johnsen, K., et al. (2007). European guidelines on cardiovascular disease prevention in clinical practice: executive summary - fourth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal, 28*, 2375–2414.
11. Mainali, P., Pant, S., Rodriguez, A. P., et al. (2015). Tobacco and Cardiovascular Health. *Cardiovascular Toxicology, 15*, 107–116.
12. Gać, P., Jaźwiec, P., Mazur, G., et al. (2017). Exposure to cigarette smoke and the carotid arteries calcification index in patients with essential hypertension. *Cardiovascular Toxicology, 17*, 335–343.
13. Gać, P., Poręba, M., Mazur, G., et al. (2015). The aortic mechanical properties in patients with the essential hypertension environmentally exposed to cigaret smoke. *Inhalation Toxicology, 27*, 717–723.
14. Gać, P., Poręba, R., Poręba, M., et al. (2014). Effect of environmental exposure to cigarette smoke on blood pressure in 24-hour ambulatory blood pressure monitoring in patients with essential hypertension. *Polskie Archiwum Medycyny Wewnetrznej, 124*(9), 436–442.
15. Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. PMID: 21452462.
16. WHO. Tobacco, https://www.who.int/news-room/fact-sheets/detail/tobacco (accessed 4 August 2022).
17. Gać, P., Martuszewski, A., Paluszkiewicz, P., et al. (2021). Aortic valve calcification score in patients with arterial hypertension environmentally exposed to tobacco smoke. *Cardiovascular Toxicology, 21*, 869–879.
18. Gać, P., Jaźwiec, P., Mazur, G., et al. (2017). Exposure to cigarette smoke and the morphology of atherosclerotic plaques in the extracranial arteries assessed by computed tomography angiography in patients with essential hypertension. *Cardiovascular Toxicology, 17*, 67–78.
19. Gać, P., Poręba, M., Pawlas, K., et al. (2017). Influence of environmental tobacco smoke on morphology and functions of cardiovascular system assessed using diagnostic imaging. *Inhalation Toxicology, 29*, 518–529.
20. Gać, P., Czerwińska, K., Poręba, M., et al. (2021). Environmental tobacco smoke exposure estimated using the shses scale and epicardial adipose tissue thickness in hypertensive patients. *Cardiovascular Toxicology, 21*, 79–87.
21. Gać, P., Jaźwiec, P., Poręba, M., et al. (2017). The risk of coronary artery disease estimated non-invasively in patients with essential hypertension environmentally exposed to cigarette smoke. *Environmental Toxicology and Pharmacology, 56*, 114–120.
22. Protano, C., & Vitali, M. (2011). The new danger of thirdhand smoke: Why passive smoking does not stop at secondhand smoke. *Environmental Health Perspectives, 119*, 422.
23. World Health Organization. Tobacco Free Initiative (World Health Organization). Protection from exposure to second-hand tobacco smoke: policy recommendations. World Health Organization, 2007.
24. Hajdusianek, W., Żórawik, A., Waliszewska-Prosół, M., et al. (2021). Tobacco and nervous system development and function—new findings 2015–2020. *Brain Sciences, 11*(6), 797.
25. Xu, J., Li, G., Wang, P., et al. (2005). Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. *The Journal of Clinical Investigation, 115*(5), 1275–1280.
26. Xu, J., & Desir, G. V. (2007). Renalase, a new renal hormone: Its role in health and disease. *Current Opinion in Nephrology and Hypertension, 16*, 373–378.
27. Desir, G. V. (2009). Regulation of blood pressure and cardiovascular function by renalase. *Kidney International, 76*, 366–370.
28. Desir, G. V. (2011). Role of renalase in the regulation of blood pressure and the renal dopamine system. *Current Opinion in Nephrology and Hypertension, 20*, 31–36.
29. Desir, G. V., Tang, L., Wang, P., et al. (2012). Renalase lowers ambulatory blood pressure by metabolizing circulating adrenaline. *Journal of the American Heart Association, 1*, e002634.
30. Czerwińska, K., Poręba, R., & Gać, P. (2022). Renalase—A new understanding of its enzymatic and non-enzymatic activity and its implications for future research. *Clinical and Experimental Pharmacology and Physiology, 49*, 3–9.
31. Boomsma, F., & Tipton, K. F. (2007). Renalase, a catecholamine-metabolising enzyme? *Journal of Neural Transmission, 114*, 775–776.
32. Beaupre, B. A., Hoag, M. R., & Moran, G. R. (2015). Renalase does not catalyze the oxidation of catecholamines. *Archives of Biochemistry and Biophysics, 579*, 62–66.
33. Beaupre, B. A., Carmichael, B. R., Hoag, M. R., et al. (2013). Renalase is an α-NAD(P)H oxidase/anomerase. *Journal of the American Chemical Society, 135*, 13980–13987.
34. Heller, W. D., Scherer, G., Sennewald, E., et al. (1998). Misclassification of smoking in a follow-up population study in southern Germany. *Journal of Clinical Epidemiology, 51*(3), 211–218.
35. Venn, A., & Britton, J. (2007). Exposure to secondhand smoke and biomarkers of cardiovascular disease risk in never-smoking adults. *Circulation, 115*(8), 990–995.
36. Whincup, P. H., Gilg, J. A., Emberson, J. R., et al. (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ, 329*(7459), 200–205.
37. Xie, J., Hu, D., Wang, X., Luo, Y., et al. (2009). Smoking state determined by cotinine and arterial stiffness. *Circulation Journal, 73*(8), 1537–1542.
38. Sonawane, P. J., Gupta, V., Sasi, B. K., et al. (2014). Transcriptional regulation of the novel monoamine oxidase renalase: crucial roles of transcription factors Sp1, STAT3, and ZBP89. *Biochemistry, 53*, 6878–6892.
39. Guo, X., Hollander, L., Macpherson, D., et al. (2016). Inhibition of renalase expression and signaling has antitumor activity in pancreatic cancer. *Science and Reports, 6*, 229–296.
40. Li, X., Huang, Q., & Xu, J. (2021). Renalase gene polymorphisms and plasma levels are associated with preeclampsia: a hospital-based study in the Chinese cohort. *Women and Health, 61*(10), 957–967.
41. Martynowicz, H., Wieckiewicz, M., Poreba, R., et al. (2019). The relationship between sleep bruxism intensity and renalase concentration—An enzyme involved in hypertension development. *Journal of Clinical Medicine, 9*(1), 16.
42. Gu, R., Lu, W., Xie, J., et al. (2011). Renalase deficiency in heart failure model of rats-a potential mechanism underlying circulating norepinephrine accumulation. *PLoS ONE, 6*(1), e14633.

43. Rybi-Szumińska, A., Michaluk-Skutnik, J., Osipiuk-Remża, B., et al. (2014). Normal values for urine renalase excretion in children. *Pediatric Nephrology, 29*, 2191–2195.
44. Benedetti, G., Campus, G., Strohmenger, L., et al. (2013). Tobacco and dental caries: a systematic review. *Acta Odontologica Scandinavica, 71*, 363–371.

Praca nr 3

International Journal of *Molecular Sciences*

MDPI

Article

Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration

Aleksandra Żórawik [1], Wojciech Hajdusianek [1], Iwona Markiewicz-Górka [1], Aleksandra Jaremków [1], Krystyna Pawlas [1], Helena Martynowicz [2], Grzegorz Mazur [2], Rafał Poręba [2] and Paweł Gać [1,*]

[1] Department of Population Health, Division of Environmental Health and Occupational Medicine, Wroclaw Medical University, Mikulicza-Radeckiego 7, PL 50-368 Wroclaw, Poland
[2] Department of Internal Medicine, Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, Borowska 213, PL 50-556 Wroclaw, Poland
* Correspondence: pawelgac@interia.pl or pawel.gac@umw.edu.pl

Abstract: Cardiovascular diseases (CVDs) are one of the biggest health challenges facing health systems around the world. There are certain risk factors (CVRFs) that contribute to CVD. Risk factors associated with lifestyle such as tobacco consumption are particularly essential. Renalase is a recently discovered flavoprotein that may be involved in the progression of cardiometabolic diseases. The aim of the study was to investigate the relation between CVRFs and blood renalase concentration (BRC). The study group consisted of 96 people (51% women) who were hospitalized in the internal medicine department. CVRFs were measured using the AHA Life 7 scale. The E3109Hu ELISA kit was used to assess BRC. We found higher BRC in groups with a lower number of CVRFs ($p < 0.05$). We found a negative correlation between BRC and the number of CVRFs ($r = -0.41$). With the regression analysis, obesity, smoking, and a lack of physical activity (LoPE) were independently associated with lower blood renalase concentration. ROC analysis indicated the highest accuracy of BRC < 38.98 ng/mL in patients with ≥5 CVRFs. In conclusion, patients with a higher number of CVRFs had lower BRCs. The CVRFs particularly associated with a lower BRC were obesity, smoking, and LoPE.

Keywords: renalase; cardiovascular health; CVRF

Citation: Żórawik, A.; Hajdusianek, W.; Markiewicz-Górka, I.; Jaremków, A.; Pawlas, K.; Martynowicz, H.; Mazur, G.; Poręba, R.; Gać, P. Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration. *Int. J. Mol. Sci.* **2023**, *24*, 16666. https://doi.org/10.3390/ijms242316666

Academic Editors: Serena Martini and Davide Tagliazucchi

Received: 13 October 2023
Revised: 20 November 2023
Accepted: 21 November 2023
Published: 23 November 2023

1. Introduction

Cardiovascular disease (CVD) is one of the biggest health challenges facing health systems around the world. According to the World Health Statistics 2023, non-communicable diseases (NCDs) continued to cause the highest disease burden worldwide: the impact of NCDs grew from causing 61% of global deaths (31 million) in 2000 to 74% (41 million) in 2019. In total, the four major NCDs caused the deaths of about 33.3 million people in 2019 (this represents an increase of 28% in 2000). Of the four major non-communicable diseases (cardiovascular disease, cancer, chronic respiratory disease, diabetes), cardiovascular disease accounts for the largest share of global mortality (17.9 million) [1–3]. However, the increase in the absolute number of deaths caused by NCDs was mainly due to population growth and aging and at the individual level, the overall risk of death from NCDs is declining, showing progress over the last twenty years [2,4].

The World Health Organization defines cardiovascular diseases as "a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease and deep vein thrombosis and pulmonary embolism" [3].

According to current knowledge, the onset of non-communicable diseases is the resultant influence of behavioral, environmental, physiological, and genetic factors. Some of these risk factors are modifiable, which include harmful alcohol consumption, smoking, physical inactivity, and an unhealthy diet. Metabolic risk factors include elevated blood

pressure, overweight and obesity, hyperglycemia (high blood glucose levels), and hyperlipidemia (high blood fat levels). What is more, prevention of non-communicable diseases can be supported by improved environmental factors—including proper water hygiene, improving air quality, safe use of chemicals, ensuring safe and hygienic working conditions, protection against radiation, or stopping/slowing down climate change and environmental degradation [2].

In the context of cardiovascular health and CVD prevention, lifestyle is key to reducing the incidence of these diseases [5]. The most strongly documented cardiovascular disease risk factors (CVRFs) include tobacco use, arterial hypertension (AH), hypercholesterolemia, hypertriglyceridemia, type 2 diabetes mellitus (DM), and excessive body weight [6–9]. Therefore, cardiovascular diseases can be prevented by avoiding modifiable behavioral risk factors such as smoking, an unhealthy diet, alcohol abuse, excessive body weight, and physical activity deficiency [3,10].

At the same time, the presence of all the mentioned risk factors is common, often as a coincidence of many of them. In the context of the most serious CVRFs (smoking cigarettes, AH, hypercholesterolemia and hypertriglyceridemia, DM, overweight and obesity), the statistics are as follows [7,8,11]: in 2012, 21% of the world's population aged 15 and over smoked cigarettes (in Poland 26% [12]); in 2014, 22% of the adult population had hypertension (in Poland 33% [12]); in 2008, nearly 40% of adults worldwide were diagnosed with lipoprotein metabolic disorders (in Poland 64% of women and 70% presented abnormally high total cholesterol levels—according to the results of the WOBASZ II study [13,14]); in 2014, 13% of the world's population was obese and 39% was overweight (in Poland, one in four people were obese [15]); in 2014, almost 9% of adults aged 18 years and older had diabetes [16] (in Poland 7% in 2021) [12,17]. Previous studies indicate that the coexistence of CVRFs may worsen the prognosis of various cardiovascular diseases, including congestive heart failure [18].

Renalase is a relatively recently discovered flavoprotein that remains a subject of scientific interest [19]. Renalase was first described in 2005 as an effort to increase knowledge of renal endocrine function [20–22]. Initially, the function of renalase—this novel flavin adenine dinucleotide-dependent (FAD-dependent) amine oxidase—was described as responsible for slowing down the heart and the regulation of blood pressure due to its ability to catabolize circulating catecholamines [20,21,23]. However, further research has challenged this theory [19,24–26]. The results of later studies described renalase as acting as α-NAD(P)H oxidase/anomerase and oxidizing α-NAD(P)H to β-NAD(P)+ and H_2O_2 [27]. Further analysis has updated these findings, demonstrating that renalase oxidizes two specific substrates, namely 2- and 6-dihydroNAD(P), resulting in the inhibition of primary metabolism dehydrogenase, producing β-NAD(P)+ and H_2O_2 [28,29]. Renalase was also linked to factors associated with dysfunction of the endothelium. Recently, renalase was also found to have anti-inflammatory and anti-apoptotic effects as a response to ischemia [30].

In previous studies on the relationship between the risk factors of cardiovascular disease and blood renalase concentration, most data were collected in relation to arterial hypertension [31]. Studies on the relationship between, on the one hand, obesity, lack of physical activity, smoking, diet, and dyslipidemia, and on the other hand, the blood renalase concentration are few, ambiguous, and mainly concern animal models.

The aim of the study was to investigate the relationship between the coexistence of cardiovascular risk factors and blood renalase concentration.

2. Results

2.1. Basic Demographic and Clinical Parameters

The studied population was composed of 96 participants: 49 (51%) females and 47 (49%) males. The mean age of participants was 48.51 ± 14.73 years and, in particular, 50.64 ± 14.12 years in males and 46.47 ± 15.15 years in females. Among the participants, 33 (34.4%) were obese, 17 (36.2%) males and 13 (26.5%) females. The mean body mass

index in the study group was 27.82 ± 4.78 kg/m^2, with 27.92 ± 3.77 kg/m^2 for males and 27.71 ± 5.61 kg/m^2 for females.

Arterial hypertension occurred in 34 patients (35.4%). The mean systolic blood pressure was 136.77 ± 19.65 mmHg and the mean diastolic blood pressure was 87.24 ± 11.17 mmHg. The number of participants with hypercholesterolemia was 42 (43.7%) and the mean total cholesterol was 217.48 ± 39.17 mg/dL. Diabetes mellitus occurred in eight patients (8.3%) The mean fasting glucose concentration was 116.75 ± 41.18 mg/dL. In the study group, 27 (28.1%) of the participants were smokers. The mean cardiovascular risk factor was 2.19 ± 1.42. We found no significant differences between males and females in our study in the parameters described above.

The number of cardiovascular risk factors in the study group was as follows: no CVRFs were found in 13 patients (13.54%), one CVRF in 24 patients (25%), two CVRFs in 22 patients (22.9%), three CVRFs in 17 patients (17.7%), four CVRFs in 11 patients (11.45%), five CVRFs in eight patients (8.33%), and six CVRFs in one patient (1%). There were no participants with seven CVRFs.

The mean blood renalase concentration was 212.89 ± 281.91 ng/mL. The minimum blood renalase concentration was 26.70 ng/mL and the maximum concentration was 790.48 ng/mL.

2.2. Comparative Analysis: Cardiovascular Risk Factors and Blood Renalase Concentration

In our study, we analysed blood renalase concentration differences between the groups that differed on each individually analysed cardiovascular risk factor. Among the statistical results, we found that blood renalase concentration was higher in the non-smoking, without obesity, with appropriate physical activity, and without arterial hypertension groups. Normal fasting glucose was also related to the blood renalase concentration. The group with normal fasting glucose was less likely to have blood renalase concentration < the first quartile, see Table 1.

Table 1. Blood renalase concentration in groups distinguished based on individually analysed cardiovascular disease risk factors.

		Renalase [b] [ng/mL]	Renalase < 1st Quartile [a]	Renalase ≥ Median [a]	Renalase ≥ 3rd Quartile [a]
Active smoking	yes	102.77 ± 185.47	18/66.7	3/11.1	3/11.1
	no	255.98 ± 217.02	6/8.7	45/65.2	21/30.4
	p	<0.05	<0.05	<0.05	<0.05
Obesity	yes	107.06 ± 129.48	12/40.0	8/26.7	3/10.0
	no	260.99 ± 234.61	12/18.2	40/60.6	21/31.8
	p	<0.05	<0.05	<0.05	<0.05
Lack of physical activity	yes	137.87 ± 172.97	11/35.5	10/32.3	4/12.9
	no	248.67 ± 230.40	13/20.0	38/58.5	20/30.8
	p	<0.05	ns	<0.05	ns
Unhealthy diet	yes	184.12 ± 215.29	13/35.1	15/40.5	8/21.6
	no	230.93 ± 221.06	11/18.6	33/55.9	16/27.1
	p	ns	ns	ns	ns
Hypercholesterolemia	yes	193.12 ± 198.85	10/23.8	21/50.0	9/21.4
	no	228.27 ± 234.01	14/25.9	27/50.0	15/27.8
	p	ns	ns	ns	ns
Arterial hypertension	yes	156.13 ± 176.59	13/38.2	13/38.2	6/17.6
	no	244.02 ± 233.08	11/17.7	35/56.4	18/29.0
	p	<0.05	<0.05	ns	ns
Fasting hyperglycemia	yes	111.67 ± 133.61	4/50.0	2/25.0	1/12.5
	no	222.09 ± 223.31	20/22.7	46/52.3	23/26.1
	p	ns	<0.05	ns	ns

[a] The values represent absolute values/percentages; [b] values represent means ± standard deviation; ns—non-significant.

2.3. Comparative Analysis: Number of Cardiovascular Risk Factors and Blood Renalase Concentration

We studied the blood renalase concentration in the groups when defined by the number of cardiovascular risk factors. We found a higher blood renalase concentration in the groups with a lower number of CVRFs, see Table 2.

Table 2. Blood renalase concentration in groups distinguished based on the number of identified risk factors for cardiovascular diseases.

		Renalase [b] [ng/mL]	Renalase < 1st Quartile [a]	Renalase ≥ Median [a]	Renalase ≥ 3rd Quartile [a]
CVRF number	0–1	284.33 ± 232.20	2/5.4	26/70.3	13/35.1
	2–3	207.97 ± 218.40	11/28.2	19/48.7	9/23.1
	≥4	90.33 ± 127.50	11/55.0	3/15.0	2/10.0
	p	0–1 vs. ≥4: <0.05 2–3 vs. ≥4: <0.05	0–1 vs. ≥4: <0.05	0–1 vs. ≥4: <0.05 2–3 vs. ≥4: <0.05	ns
CVRF number = 0	yes	305.47 ± 213.61	0/0.0	9/81.8	4/36.4
	no	200.91 ± 217.94	24/28.2	39/45.9	20/23.5
	p	ns	<0.05	<0.05	ns
CVRF number > Me (>2)	yes	92.59 ± 111.30	17/45.9	9/24.3	3/8.1
	no	288.34 ± 236.18	7/11.9	39/66.1	21/35.6
	p	<0.05	<0.05	<0.05	<0.05

[a] The values represent absolute values/percentages; [b] values represent means ± standard deviation; CVRF—cardiovascular risk factor; ns—non-significant.

2.4. Correlation Analysis

We found a negative correlation between the number of cardiovascular risk factors and the blood renalase concentration with r = −0.41, see Figure 1.

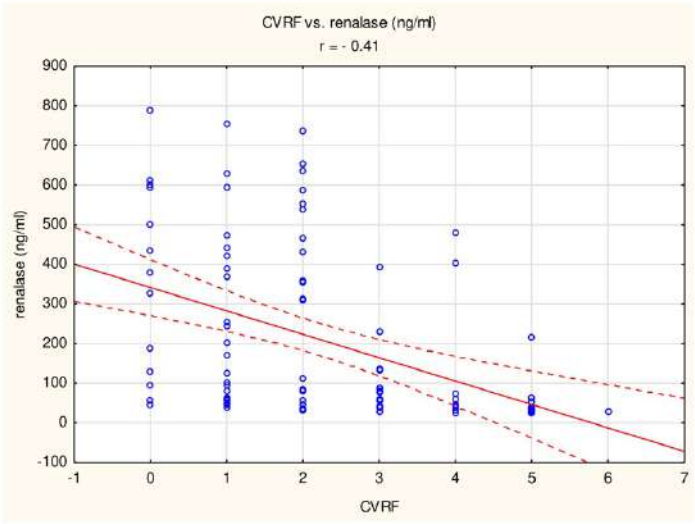

Figure 1. Correlation between the number of cardiovascular risk factors (CVRFs) and the blood renalase concentration. Blue dots indicate individual cases, red line indicates the correlation line, red dashed lines indicate the confidence interval (±95%) of the correlation line.

2.5. Regression Analysis

The results of the multivariate regression analysis are summarized in Table 3. We used a progressive stepwise analysis method.

Table 3. Results of estimation for model obtained in progressive stepwise multivariable analysis of regression.

Model for: Renalase [ng/mL]				
	Regression Coefficient	**SEM of Rc**	***p***	***p* of the Model**
Intercept	333.195	34.938	<0.001	<0.001
Obesity	−121.748	44.582	<0.001	
Active smoking	−118.151	46.217	<0.05	
Lack of physical activity	−87.029	43.570	<0.05	

SEM of Rc—standard error of the mean of regression coefficient.

Considering cardiovascular risk factors, the following statistically significant relationship model was obtained: renalase [ng/mL] = 333.195 − 121.748 obesity − 118.115 active smoking − 87.029 lack of physical activity. The presence of obesity, being a current smoker, and a lack of physical activity are independently linked with a higher probability of lower blood renalase concentration.

2.6. Prediction Analysis

We analysed blood renalase concentration as a predictor of the number of cardiovascular risk factors. The sensitivity and specificity of the analysis are presented in Table 4.

Table 4. The sensitivity and specificity of blood renalase concentration as a predictor of the number of CVRFs.

	CVRF ≥ 1	**CVRF ≥ 2**	**CVRF ≥ 3**	**CVRF ≥ 4**	**CVRF ≥ 5**
Blood renalase concentration as predictor of number of CVRFs [ng/mL]	<93.33	<89.41	<89.41	<75.59	<38.98
Sensitivity	0.846	0.703	0.661	0.658	0.874 *
Specificity	0.578	0.644	0.784	0.800 **	0.556
Accuracy	0.615	0.667	0.708	0.688	0.844 ***
Positive predictive values	0.239	0.553	0.830	0.926	0.950
Negative predictive values	0.960	0.776	0.592	0.381	0.313
Likelihood ratios positive	2.007	1.974	3.057	3.289	1.966
Likelihood ratios negative	0.266	0.462	0.432	0.428	0.228

* Highest prediction sensitivity; ** highest prediction specificity; *** highest prediction accuracy; CVRF—cardiovascular risk factor.

The conducted receiver operating characteristic (ROC) analysis indicated blood renalase concentration values constituting predictor conditions for the number of CVRFs, being less than 93.33 ng/mL for CVRF ≥ 1, less than 89.41 ng/mL for CVRF ≥ 2, less than 89.41 ng/mL for CVRF ≥ 3, less than 75.59 ng/mL for CVRF ≥ 4, and less than 38.98 ng/mL for CVRF ≥ 5. The highest calculated prediction sensitivity of 0.874 was demonstrated for a blood renalase concentration < 38.98 ng/mL—the predictor of CVRFs ≥ 5. The highest specificity was 0.800 for a blood renalase concentration < 75.59 ng/mL—the predictor of CVRF ≥ 4. Overall, the highest prediction accuracy was 0.844 for a blood renalase concentration < 38.98 ng/mL—the predictor of CVRF ≥ 5. A summary of the ROC analysis is presented in Figure 2.

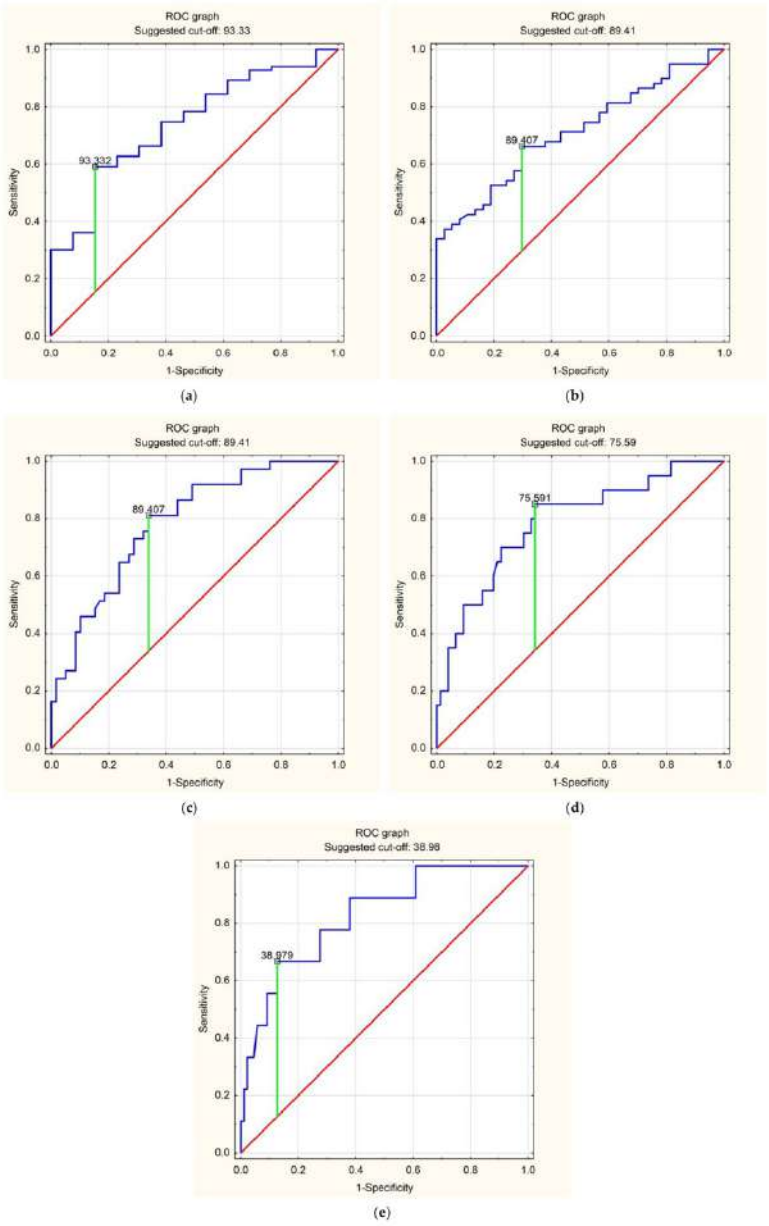

Figure 2. ROC curves predicting the number of CVRFs using blood renalase concentration. The red line denotes the baseline of the analysis, the blue line denotes the prediction line in the analysis, the green line locates the optimal cut-off point in the analysis. (**a**) CVRF $\geq$ 1 predicted by blood renalase concentration; (**b**) CVRF $\geq$ 2 predicted by blood renalase concentration; (**c**) CVRF $\geq$ 3 predicted by blood renalase concentration; (**d**) CVRF $\geq$ 4 predicted by blood renalase concentration; (**e**) CVRF $\geq$ 5 predicted by blood renalase concentration.

3. Discussion

3.1. Most Important Findings

In our study, we observed a negative relationship between the number of cardiovascular disease risk factors and the blood renalase concentration. The occurrence of obesity, being a current smoker, and physical inactivity are independent risk factors for a lower blood renalase concentration. Lower blood renalase concentration in patients with hypertension compared to patients with normal blood pressure values is secondary to the above-mentioned relationships. Similarly, only in univariate analysis was it observed that in the group with fasting hyperglycemia the blood renalase concentration significantly more often was lower than the first quartile. The lack of significance of the above-mentioned relationship in the multivariate analysis again indicates the secondary nature of this relationship.

3.2. Obesity

The few studies to date on the association of renalase with obesity have described renalase as an adipokine produced by both white and brown adipose tissue. Based on animal studies, Ramanjaneya et al. tentatively linked renalase functionality to the regulation of thermogenesis, metabolism, and brown adipose tissue development, which could provide a basis for future treatment of obesity-related cardiometabolic complications [32].

In addition, Tokinoya et al. in a study on mice, linked the reduction of excess body weight to increased renalase gene expression in the kidneys and skeletal muscle [33].

The Fang et al. study on the effect of the gut microbiota on the development of obesity described the association of renalase gene knockout in mice on a normal diet with the presence of a high abundance of Firmicutes bacteria, suggesting that renalase gene knockout promotes the development of obesity or diabetes through changes in the proportions of Firmicutes and Bacteroidetes. The results of their study strongly suggest that deletion of the gene for renalase affects the composition of the microbiota and the abundance of certain bacteria in mice, and although it is pointed out that further studies are needed to describe the mechanisms in human models, it can be assumed that mouse models provide a good tool to study the pathogenesis and treatment of metabolic diseases, as they show genetic similarity to humans [34].

In a human study, Martynowicz et al. described that blood renalase concentration was reversely correlated with BMI in a group of 87 subjects [35]. Similarly, Rybi-Szumińska et al. described a statistically significant negative correlation between urinary renalase excretion levels and body mass index Z-score ($r = -0.22$, $p < 0.05$) in a healthy pediatric population [36].

Our research confirms the relationship between obesity and lower blood renalase concentration. At the same time, it indicates, which has not been indicated in previous studies, that this relationship is independent of other cardiovascular risk factors.

3.3. Smoking

Few scientific publications to date explicitly address the relationship between cigarette smoking and blood renalase concentration. Most of the studies to date focus on smoking as a factor in the development of cardiovascular disease (e.g., coronary artery disease) and the association of the latter with renalase concentration (e.g., research by Safdar et al. and Wang et al. [30,37]), rather than the direct effect of tobacco consumption on renalase concentration. One review reports on the mechanisms of regulatory promoter and transcription factors in relation to the renalase gene in which it was found that renalase promoter activity was augmented by nicotine. According to the data in this publication, individuals exposed to tobacco smoke present higher renalase concentrations than individuals without significant exposure to this harmful agent [38].

Our study is the first to show a clear negative relationship between smoking and blood renalase concentration, a relationship independent of the co-occurrence of other cardiovascular risk factors.

3.4. Physical Activity

The results of animal studies conducted to date on the effect of exercise on blood renalase concentration are partly discrepant. According to Tokinoya et al., moderate-intensity exercise performed for 60 min causes an increase in both blood renalase concentration and its expression in the skeletal muscle [39]. In another study, Tokinoya et al. reported that in addition to an increase in renalase gene expression in the muscle due to physical activity, there is an opposite effect in other tissues (kidneys, heart, and liver). According to the authors, this increase may be related to exercise-induced oxidative stress [39].

Czarkowska-Paczek et al. obtained more inhomogeneous results. No significant changes were observed either in the expression of the gene for renalase or in the concentration of renalase itself (both in the blood and in red muscle cells), both after acute and prolonged exercise. Moreover, in white muscle, gene expression and concentration of its product decreased after acute exercise in untrained rats. At the same time, renalase concentration remained unchanged in the white muscle fibres of trained rats, despite a decrease in gene expression. Based on the above, the authors concluded that exercise only affected renalase expression in white muscle fibres, which are not mainly recruited during exercise, concluding by stating that exercise differentially regulates renalase gene expression [40].

The results of our study constitute another voice in the above discussion. They indicate that there is an independent proportional relationship between physical activity and blood renalase concentration. Moreover, and importantly, they confirm the above relationship in studies conducted in the population, and not only in animal models.

3.5. Diet

The effect of certain elements of the diet on renalase concentration has already been described. In a study on rats conducted by Wang et al., it was shown that dietary salt intake caused a significant decrease in renalase expression in the kidneys. Furthermore, it was observed that the group with a high-salt diet presented increased systolic blood pressure and proteinuria with respect to the normal-salt diet group [41].

In human studies, by selecting 720 participants from the HyperPATH consortium program and genotyping with the use of a multiethnic genotyping array of their renalase (*RNLS*) gene, the research group of Heydarpour et al. determined that certain genetic variants of the *RNLS* gene associated with salt sensitivity of blood pressure and responded to dietary salt intervention [42]. Many other studies also confirm a decrease in blood renalase concentration caused by the influence of a high-salt diet [43–45].

In our study, there was no relationship between the quality of the diet assessed according to the criteria of the AHA Life 7 scale and the blood renalase concentration.

3.6. Arterial Hypertension

The association between blood renalase concentration, hypertension, and cardiovascular dysfunction was documented in experimental animal models and in several human studies [46]. The study by Zhao et al., which was one of the first studies in humans on the effects of renalase on cardiovascular health, described that two (rs2576178 A > G and rs2296545 C > G) of the several studied single-nucleotide polymorphisms (SNP) of the RNLS gene (the gene responsible for encoding the renalase protein) were associated with the occurrence of hypertension in northern Han Chinese [47]. Another large study conducted on the Chinese population on renalase gene polymorphisms was undertaken by Wang et al. (Baoji Salt-Sensitive Study) [37]. In a cohort study over a 14-year follow-up of 514 participants, they observed that, over the observed time period, the presence of certain renalase single-nucleotide polymorphisms (SNP) influenced the increase in blood pressure in the study population: SNP rs7922058 was associated with a change in systolic blood pressure; rs10887800, rs796945, rs1935582, rs2296545, and rs2576178 were associated with a change in diastolic blood pressure; rs1935582 and rs2576178 were associated with a change in mean arterial pressure. In addition, a group of 2392 individuals (participants

from the Hanzhong Adolescent Hypertension Study cohort) were followed up for the association of renalase concentration and blood pressure. As a result, a linear correlation between serum renalase concentration and blood pressure was observed in this study. In hypertensive patients, serum renalase concentrations were higher than in those with normal blood pressure values (27.2 ± 0.4 vs. 25.1 ± 0.2 μg/mL) [37]. Subsequent studies by other research groups have also focused on the polymorphism in this gene and its impact in different populations on cardiovascular disease incidence—not only hypertension, but also cardiac hypertrophy, ventricular dysfunction, poor exercise capacity, and inducible ischemia in individuals with stable coronary artery disease [48–51]. In addition, due to the frequent co-occurrence of hypertension with type 2 diabetes, studies were also conducted that show the association of the C allele of the rs2296545 SNP occurrence with hypertension in type 2 diabetes [51]. The results obtained varied according to the study population and genotyped single-nucleotide polymorphisms—such as the fact that in the Caucasian group from the Heart and Soul Study, similar results to the northern Han Chinese population mentioned above were not obtained [52]. Thus, the incidence of relationships of renalase gene single-nucleotide polymorphisms with hypertension and other cardiovascular events should be assessed by group according to ethnicity and comorbidities in a large sample size [46].

The results of our study regarding arterial hypertension partially confirm the above views. Patients with arterial hypertension were characterised by lower blood renalase concentration. However, what must be emphasised is that the multivariate analysis did not confirm the existence of a relationship between arterial hypertension and blood renalase concentration, independent of co-occurring cardiovascular risk factors.

3.7. Hypercholesterolemia

Among the data evaluating the relationship between renalase concentration and cholesterol concentration, there are studies evaluating this type of relationship in kidney transplant patients: renalase positively correlated with lipoprotein metabolism disorder. However, the authors point out that such observations may be related to the fact that in renal transplant patients, a sympathetic overdrive might occur: the metabolic effect of elevated sympathetic activity is an increase in plasma total cholesterol concentration, suppression of LDL receptor activity, and a decrease in HDL cholesterol levels [53].

The above explanation may be confirmed by the results of our study, in which there was no relationship between hypercholesterolemia and blood renalase concentration in patients without chronic kidney disease.

3.8. Hyperglycemia

There are reports on the protective function of renalase in the context of the development of hyperglycemic complications, which include diabetic nephropathy. The protective potential of increased renalase concentration in diabetic individuals, in the context of the development of renal complications, was demonstrated in a mouse study by Yin et al. [54].

With the current understanding of renalase function as a cytokine, reports on the association of single-nucleotide polymorphisms of the renalase gene with the development of type 1 diabetes appear to be relevant. In studies by Barrett et al. and Walace et al., new loci were located and confirmed, among others (a total of 48 and 18 new ones) in the renalase gene in the region of rs10509540, located on chromosome 10q23.31, whose polymorphisms may influence the development of autoimmune destruction of pancreatic beta-cells [29,55,56].

The results of our study regarding fasting hyperglycemia only partially confirm the above views. Patients with fasting hyperglycemia were characterised by a more frequent occurrence of blood renalase concentration lower than the first quartile. However, what must be emphasized is that the multivariate analysis did not confirm the existence of a relationship between fasting hyperglycemia and blood renalase concentration, independent of co-occurring cardiovascular risk factors.

3.9. Study Strengths and Limitations

The strength of the research conducted is that it is a study exploring the, as yet, insufficiently investigated area of the relationship between the coexistence of cardiovascular risk factors and blood renalase concentration; however, the limitations of this study cannot be overlooked. First of all, the size of the sample group is relatively small, so further research is needed, taking into account larger group sizes to confirm our conclusions and the possibility of generalising and extrapolating them for a larger population. An additional limitation of the small group is that there was only one participant in the subgroup with only one CVRF and there was no participant with seven CVRFs. Due to obtaining more accurate results and strengthening the level of evidence, it would be necessary to repeat the study with a larger number of participants in all subgroups, especially in the subgroups with one and seven CVRFs.

In addition, the identification of some risk factors was based on patient testimonials and, therefore, not objectively verifiable. Therefore, it cannot be ruled out that some answers missed the facts because patients wanted to perform 'better' in the surveys. This is because in the AHA Life 7 scale, which was used to assess the level of lifestyle 'healthiness' of the patients studied, some parameters are based on patient history and are not verifiable by objective measurements or laboratory tests. It can therefore be assumed that the results for the level of activity, tobacco dependence, and type of parameters may be subject to error.

It should also be emphasised that the study conducted was designed to look for a relationship between the criteria in the AHA Life 7 scale and blood renalase concentration and to select those with the greatest relationship. Accordingly, several statistical tests were conducted, each involving the possibility of statistical error. In order to verify the validity of the selected variables and strengthen the level of evidence, it is advisable to repeat the tests to verify the adequacy of the parameters already selected (i.e., the presence of obesity, being a current smoker, and lack of physical activity is linked with a higher probability of lower blood renalase concentration).

4. Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the Wroclaw Medical University (protocol code KB-39/2020).

Group size was determined using a sample size calculator. The selection conditions were as follows: population size 2.8 million (population size of the macroregion from which patients are referred to our study center), fraction size 0.5, maximum error 10%, confidence level 95%.

The studied population was composed of 96 participants. Group description is summarised in Table 5.

All patients included in the study were hospitalised in the Department of Internal Medicine, Occupational Diseases, Hypertension, and Clinical Oncology to verify suspicions, extend diagnostics, optimise therapy, or diagnose complications of hypertension, atherosclerosis, diabetes and/or sleep disorders; and voluntarily consented to participate in the study. Patients with cancer, systemic disease, chronic kidney disease, active inflammatory process, who had a problem with clearly declaring their smoking status, or patients who had undergone cardiac- or angio-surgery or myocardial infarction, stroke or acute vascular incidents were excluded from the study.

To measure cardiovascular health, we used a scale invented by American Heart Association (AHA): AHA Life 7, according to the survey methodology proposed by the AHA. The presence and co-occurrence of the following CVD risk factors were assessed: (1) obesity, (2) active smoking, (3) lack of physical activity, (4) unhealthy diet, (5) hypercholesterolemia, (6) fasting hyperglycemia, (7) arterial hypertension. The occurrence of CVRF was a score of 0 on the AHA Life 7 scale in each category [57].

Table 5. Basic clinical parameters in the whole study group.

	Whole Study Group (n = 96)	Men (M) (n = 47)	Women (W) (n = 49)	P M vs. W
Age [b] [years]	48.51 ± 14.73	50.64 ± 14.12	46.47 ± 15.15	ns
Male gender [a]	47/49.0	-	-	-
Female gender [a]	49/51.0	-	-	-
BMI [b] [kg/m^2]	27.82 ± 4.78	27.92 ± 3.77	27.71 ± 5.61	ns
Obesity [a]	33/34.4	17/36.2	13/26.5	ns
Systolic blood pressure [b] [mmHg]	136.77 ± 19.65	139.26 ± 21.57	134.39 ± 17.52	ns
Diastolic blood pressure [b] [mmHg]	87.24 ± 11.17	88.09 ± 11.96	86.43 ± 10.41	ns
Arterial hypertension [a]	34/35.4	20/42.5	14/28.6	ns
Total cholesterol [b] [mg/dL]	217.48 ± 39.17	225.49 ± 38.61	210.57 ± 37.94	ns
Hypercholesterolemia [a]	42/43.7	24/51.1	18/36.7	ns
Glucose [b] [mg/dL]	116.75 ± 41.18	114.03 ± 38.71	118.52 ± 40.92	ns
Diabetes mellitus [a]	8/8.3	4/8.5	4/8.2	ns
Smoking [a]	27/28.1	15/31.9	12/24.5	ns
CVRF number [b]	2.19 ± 1.42	2.43 ± 1.44	1.96 ± 1.37	ns
Renalase [b] [ng/mL]	212.89 ± 218.91	191.94 ± 193.34	232.95 ± 241.21	ns

[a] The values represent absolute values/percentages; [b] values represent means ± standard deviation; BMI—body mass index; CVRF—cardiovascular risk factor; ns—non-significant.

The blood pressure measurements were taken by qualified medical personnel using clinically approved upper arm blood pressure monitors during hospitalisation. All the laboratory parameters were measured during hospitalisation. In laboratory measurements, fasting glucose, total cholesterol, and renalase concentrations were determined. Blood was collected by ulnar venipuncture and kept at a stable temperature. E3109Hu ELISA kit (enzyme-linked immunosorbent assay) (Bioassay Technology Laboratory, Shanghai, China) was used to determine blood renalase concentration, in accordance with the manufacturer's instructions. As specified by the producer, the parameters of the test used were as follows. The reference range: 1–400 ng/mL, the sensitivity of the ELISA: 0.52 ng/mL, the coefficient of intra- and inter-assay variation: <8% and <10%, respectively.

The variables related to the blood renalase concentration (quantitative variable: blood renalase concentration, and categorical variables: renalase concentration < 1st quartile, renalase concentration ≥ median, renalase concentration ≥ 3rd quartile) were compared with each CVRF and with the number CVRF.

We used Statistica 13 TIBCO Software Inc. provided by StatSoft Poland to conduct all analyses. Categorical variables are presented as absolute values and percentages. We used Chi-square test to conduct categorical analysis. The arithmetic means and standard deviations were calculated for quantitative variables. The normality of the distribution of quantitative variables was verified. For quantitative variables with a normal distribution, the *t*-test or ANOVA (one-way parametric) analysis of variance with post-hoc tests was used for further statistical analysis. For quantitative variables with a non-normal distribution, the Mann–Whitney U test or a non-parametric equivalent of the analysis of variance, the Kruskal–Wallis ANOVA, and post-hoc tests were used. Relationships between variables were assessed using correlation analysis and multivariate regression analysis. In addition, the assessment of the sensitivity and specificity was made. A result at the level of $p < 0.05$ was considered significant.

5. Conclusions

In conclusion, we found that patients with a higher number of cardiovascular risk factors had lower blood renalase concentrations. The cardiovascular risk factors that we found most strongly associated with lower blood renalase concentration were obesity, smoking, and lack of physical activity. A blood renalase concentration lower than 38.98 ng/mL was the most accurate predictor of having at least five cardiovascular risk factors.

Author Contributions: Conceptualisation, R.P. and P.G.; Funding acquisition, K.P. and P.G.; Investigation, A.Ż., W.H., I.M.-G., A.J. and H.M.; Project administration, P.G.; Resources, A.Ż. and W.H.; Software, P.G.; Supervision, H.M., G.M., R.P. and P.G.; Visualisation, P.G.; Writing—original draft, A.Ż. and W.H.; Writing—review and editing, P.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Wroclaw Medical University (SUB.A100.19.009, SUBZ.E264.23.039).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of Wroclaw Medical University (protocol code KB-39/2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Global Health Estimates. Available online: https://www.who.int/data/global-health-estimates (accessed on 24 August 2023).
2. WHO. World Health Statistics 2023 Monitoring Health for the SDGs Sustainable Development Goals Health for All. 2023. Available online: https://www.who.int/publications/book-orders (accessed on 24 August 2023).
3. Cardiovascular Diseases (CVDs). Available online: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed on 24 August 2023).
4. Global Burden of Disease (GBD). Available online: https://www.healthdata.org/research-analysis/gbd (accessed on 24 August 2023).
5. Gać, P.; Czerwińska, K.; Macek, P.; Jaremków, A.; Mazur, G.; Pawlas, K.; Poręba, R. The importance of selenium and zinc deficiency in cardiovascular disorders. *Environ. Toxicol. Pharmacol.* **2021**, *82*, 35–53. [CrossRef] [PubMed]
6. Yusuf, S.; Hawken, S.; Ounpuu, S.; Dans, T.; Avezum, A.; Lanas, F.; McQueen, M.; Budaj, A.; Pais, P.; Varigos, J.; et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* **2004**, *364*, 937–952. [CrossRef] [PubMed]
7. Gać, P.; Poręba, M.; Jurdziak, M.; Trzmielewska, E.; Gocławska, K.; Derkacz, A.; Mazur, G.; Szuba, A.; Poręba, R. Cardiovascular risk factors and the concentration of asymmetric dimethylarginine. *Adv. Clin. Exp. Med.* **2020**, *29*, 63–70. [CrossRef] [PubMed]
8. Gać, P.; Urbanik, D.; Macek, P.; Martynowicz, H.; Mazur, G.; Poręba, R. Coexistence of cardiovascular risk factors and obstructive sleep apnoea in polysomnography. *Respir. Physiol. Neurobiol.* **2022**, *295*, 103782. [CrossRef]
9. Bisciglia, A.; Pasceri, V.; Irini, D.; Varveri, A.; Speciale, G. Risk Factors for Ischemic Heart Disease. *Rev. Recent. Clin. Trials* **2019**, *14*, 86–94. [CrossRef] [PubMed]
10. Cardiovascular Diseases. Available online: https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1 (accessed on 24 August 2023).
11. Global Health Observatory. Available online: https://www.who.int/data/gho (accessed on 27 August 2023).
12. Zdrojewski, T.; Rutkowski, M.; Bandosz, P.; Gaciong, Z.; Jędrzejczyk, T.; Solnica, B.; Pencina, M.; Drygas, W.; Wojtyniak, B.; Grodzicki, T.; et al. Prevalence and control of cardiovascular risk factors in Poland. Assumptions and objectives of the NATPOL 2011 Survey. *Kardiol. Pol.* **2013**, *71*, 381–392. [CrossRef] [PubMed]
13. Szymański, F.M.; Barylski, M.; Cybulska, B.; Wożakowska-Kapłon, B.; Krasiński, Z.; Mamcarz, A.; Widecka, K.; Płatek, A.E.; Dudek, D.; Mickiewicz, A.; et al. Recommendation for the management of dyslipidemia in Poland—Third Declaration of Sopot. Interdisciplinary Expert Position Statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy. *Cardiol. J.* **2018**, *25*, 655–665. [CrossRef] [PubMed]
14. Pająk, A.; Szafraniec, K.; Polak, M.; Polakowska, M.; Kozela, M.; Piotrowski, W.; Kwaśniewska, M.; Podolecka, E.; Kozakiewicz, K.; Tykarski, A.; et al. Changes in the prevalence, treatment, and control of hypercholesterolemia and other dyslipidemias over 10 years in Poland: The WOBASZ study. *Pol. Arch. Med. Wewn.* **2016**, *126*, 642–652.
15. Brzeziński, M.; Metelska, P.; Sutkowska, B. 23 Eurohealth Systems and Policies Obesity in Poland-Public Health Activities. *Eurohealth Syst. Policies* **2019**, *25*, 23–26.
16. Diabetes. Available online: https://www.who.int/news-room/fact-sheets/detail/diabetes (accessed on 27 August 2023).
17. Diabetes Prevalence (% of Population Ages 20 to 79)—Poland | Data. Available online: https://data.worldbank.org/indicator/SH.STA.DIAB.ZS?locations=PL (accessed on 27 August 2023).
18. Yin, Q.; Zhao, Y.; Li, J.; Xue, Q.; Wu, X.; Gao, L.; He, P.; Zhu, M.; Wang, S. The coexistence of multiple cardiovascular diseases is an independent predictor of the 30-day mortality of hospitalized patients with congestive heart failure: A study in Beijing. *Clin. Cardiol.* **2011**, *34*, 442–446. [CrossRef]
19. Czerwińska, K.; Poręba, R.; Gać, P. Renalase-A new understanding of its enzymatic and non-enzymatic activity and its implications for future research. *Clin. Exp. Pharmacol. Physiol.* **2022**, *49*, 3–9. [CrossRef]

20. Xu, J.; Desir, G.V. Renalase, a new renal hormone: Its role in health and disease. *Curr. Opin. Nephrol. Hypertens.* **2007**, *16*, 373–378. [CrossRef] [PubMed]
21. Xu, J.; Li, G.; Wang, P.; Velazquez, H.; Yao, X.; Li, Y.; Wu, Y.; Peixoto, A.; Crowley, S.; Desir, G.V. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. *J. Clin. Investig.* **2005**, *115*, 1275–1280. [CrossRef] [PubMed]
22. Desir, G.V. Regulation of blood pressure and cardiovascular function by renalase. *Kidney Int.* **2009**, *76*, 366–370. [CrossRef]
23. Desir, G.V.; Tang, L.; Wang, P.; Li, G.; Sampaio-Maia, B.; Quelhas-Santos, J.; Pestana, M.; Velazquez, H. Renalase lowers ambulatory blood pressure by metabolizing circulating adrenaline. *J. Am. Heart Assoc.* **2012**, *1*, 24–38. [CrossRef] [PubMed]
24. Boomsma, F.; Tipton, K.F. Renalase, a catecholamine-metabolising enzyme? *J. Neural Transm.* **2007**, *114*, 775–776. [CrossRef] [PubMed]
25. Pandini, V.; Ciriello, F.; Tedeschi, G.; Rossoni, G.; Zanetti, G.; Aliverti, A. Synthesis of human renalase1 in Escherichia coli and its purification as a FAD-containing holoprotein. *Protein Expr. Purif.* **2010**, *72*, 244–253. [CrossRef]
26. Vijayakumar, A.; Mahapatra, N.R. Renalase: A novel regulator of cardiometabolic and renal diseases. *Hypertens. Res.* **2022**, *45*, 1582–1598. [CrossRef]
27. Beaupre, B.A.; Carmichael, B.R.; Hoag, M.R.; Shah, D.D.; Moran, G.R. Renalase is an α-NAD(P)H oxidase/anomerase. *J. Am. Chem. Soc.* **2013**, *135*, 13980–13987. [CrossRef]
28. Beaupre, B.A.; Hoag, M.R.; Roman, J.; Försterling, F.H.; Moran, G.R. Metabolic function for human renalase: Oxidation of isomeric forms of β-NAD(P)H that are inhibitory to primary metabolism. *Biochemistry* **2015**, *54*, 795–806. [CrossRef]
29. Guo, X.; Wang, L.; Velazquez, H.; Safirstein, R.; Desir, G.V. Renalase: Its role as a cytokine, and an update on its association with type 1 diabetes and ischemic stroke. *Curr. Opin. Nephrol. Hypertens.* **2014**, *23*, 513–518. [CrossRef]
30. Safdar, B.; Guo, X.; Johnson, C.; D'Onofrio, G.; Dziura, J.; Sinusas, A.J.; Testani, J.; Rao, V.; Desir, G. Elevated renalase levels in patients with acute coronary microvascular dysfunction—A possible biomarker for ischemia. *Int. J. Cardiol.* **2019**, *279*, 155–161. [CrossRef]
31. Li, Y.; Wu, W.; Liu, W.; Zhou, M. Roles and mechanisms of renalase in cardiovascular disease: A promising therapeutic target. *Biomed. Pharmacother.* **2020**, *131*, 110712. [CrossRef]
32. Ramanjaneya, M.; Tan, B.; Patel, V.; Hu, J.; Lehnert, H.; Hillhouse, E.; Chen, J.; Randeva, H. Renalase a key regulator of brown adipose tissue activity. *Endocr. Abstr.* **2014**, *34*, 235–243. [CrossRef]
33. Tokinoya, K.; Ono, S.; Aoki, K.; Yanazawa, K.; Shishikura, Y.; Sugasawa, T.; Takekoshi, K. Gene expression level of renalase in the skeletal muscles is increased with high-intensity exercise training in mice on a high-fat diet. *Physiol. Int.* **2021**, *108*, 274–284. [CrossRef]
34. Fang, H.; Aoki, K.; Tokinoya, K.; Yonamine, M.; Sugasawa, T.; Kawakami, Y.; Takekoshi, K. Effects of High-Fat Diet on the Gut Microbiota of Renalase Gene Knockout Mice. *Obesities* **2022**, *2*, 303–316. [CrossRef]
35. Martynowicz, H.; Wieckiewicz, M.; Poreba, R.; Wojakowska, A.; Smardz, J.; Januszewska, L.; Markiewicz-Gorka, I.; Mazur, G.; Pawlas, K.; Gać, P. The relationship between sleep bruxism intensity and renalase concentration—An enzyme involved in hypertension development. *J. Clin. Med.* **2020**, *9*, 16. [CrossRef]
36. Rybi-Szumińska, A.; Michaluk-Skutnik, J.; Osipiuk-Remża, B.; Kossakowska, A.; Wasilewska, A. Normal values for urine renalase excretion in children. *Pediatr. Nephrol.* **2014**, *29*, 2191–2195. [CrossRef]
37. Wang, Y.; Chen, C.; Hu, G.L.; Chu, C.; Zhang, X.Y.; Du, M.F.; Zou, T.; Zhou, Q.; Liao, Y.Y.; Ma, Q.; et al. Associations of Renalase with Blood Pressure and Hypertension in Chinese Adults. *Front. Cardiovasc. Med.* **2022**, *9*, 321–343. [CrossRef]
38. Sonawane, P.J.; Gupta, V.; Sasi, B.K.; Kalyani, A.; Natarajan, B.; Khan, A.A.; Sahu, B.S.; Mahapatra, N.R. Transcriptional regulation of the novel monoamine oxidase renalase: Crucial roles of transcription factors Sp1, STAT3, and ZBP89. *Biochemistry* **2014**, *53*, 6878–6892. [CrossRef]
39. Tokinoya, K.; Shiromoto, J.; Sugasawa, T.; Yoshida, Y.; Aoki, K.; Nakagawa, Y.; Ohmori, H.; Takekoshi, K. Influence of acute exercise on renalase and its regulatory mechanism. *Life Sci.* **2018**, *210*, 235–242. [CrossRef] [PubMed]
40. Czarkowska-Paczek, B.; Zendzian-Piotrowska, M.; Gala, K.; Sobol, M.; Paczek, L. Exercise differentially regulates renalase expression in skeletal muscle and kidney. *Tohoku J. Exp. Med.* **2013**, *231*, 321–329. [CrossRef] [PubMed]
41. Wang, Y.; Xie, B.Q.; Gao, W.H.; Yan, D.Y.; Zheng, W.L.; Lv, Y.B.; Cao, Y.M.; Hu, J.W.; Yuan, Z.Y.; Mu, J.J. Effects of Renin-Angiotensin System Inhibitors on Renal Expression of Renalase in Sprague-Dawley Rats Fed with High Salt Diet. *Kidney Blood Press. Res.* **2015**, *40*, 605–613. [CrossRef] [PubMed]
42. Heydarpour, M.; Parksook, W.W.; Hopkins, P.N.; Pojoga, L.H.; Williams, G.H.; Williams, J.S. A candidate locus in the renalase gene and susceptibility to blood pressure responses to the dietary salt. *J. Hypertens.* **2023**, *41*, 723–732. [CrossRef] [PubMed]
43. Wang, Y.; Liu, F.Q.; Wang, D.; Mu, J.J.; Ren, K.Y.; Guo, T.S.; Chu, C.; Wang, L.; Geng, L.K.; Yuan, Z.Y. Effect of salt intake and potassium supplementation on serum renalase levels in Chinese adults: A randomized trial. *Medicine* **2014**, *93*, 154–165. [CrossRef] [PubMed]
44. Zheng, W.L.; Wang, J.; Mu, J.J.; Liu, F.Q.; Yuan, Z.Y.; Wang, Y.; Wang, D.; Ren, K.Y.; Guo, T.S.; Xiao, H.Y. Effects of salt intake and potassium supplementation on renalase expression in the kidneys of Dahl salt-sensitive rats. *Exp. Biol. Med.* **2016**, *241*, 382–386. [CrossRef]
45. Desir, G.V. Role of renalase in the regulation of blood pressure and the renal dopamine system. *Curr. Opin. Nephrol. Hypertens.* **2011**, *20*, 31–36. [CrossRef]
46. Malyszko, J.; Bachorzewska-Gajewska, H.; Dobrzycki, S. Renalase, kidney and cardiovascular disease: Are they related or just coincidentally associated? *Adv. Med. Sci.* **2015**, *60*, 41–49. [CrossRef]

47. Zhao, Q.; Fan, Z.; He, J.; Chen, S.; Li, H.; Zhang, P.; Wang, L.; Hu, D.; Huang, J.; Qiang, B.; et al. Renalase gene is a novel susceptibility gene for essential hypertension: A two-stage association study in northern Han Chinese population. *J. Mol. Med.* **2007**, *85*, 877–885. [CrossRef]
48. Kozieradzka, A.; Pepinski, W.; Waszkiewicz, E.; Olszewska, M.; Maciorkowska, D.; Skawronska, M.; Niemcunowicz-Janica, A.; Dobrzycki, S.; Musial, W.J.; Kaminski, K.A. The rs1801133 polymorphism of methylenetetrahydrofolate reductase gene- the association with 5-year survival in patients with ST-elevation myocardial infarction. *Adv. Med. Sci.* **2012**, *57*, 106–111. [CrossRef]
49. Li, X.; Jiang, W.; Li, L.; Huang, R.; Yang, Q.; Yang, Y.; Hong, Y.; Tang, X. Renalase gene polymorphism in patients with hypertension and concomitant coronary heart disease. *Kidney Blood Press. Res.* **2014**, *39*, 9–16. [CrossRef]
50. Fava, C.; Montagnana, M.; Danese, E.; Sjögren, M.; Almgren, P.; Engström, G.; Hedblad, B.; Guidi, G.C.; Minuz, P.; Melander, O. The Renalase Asp37Glu polymorphism is not associated with hypertension and cardiovascular events in an urban-based prospective cohort: The Malmö Diet and cancer study. *BMC Med. Genet.* **2012**, *13*, 147–157. [CrossRef] [PubMed]
51. Buraczynska, M.; Zukowski, P.; Buraczynska, K.; Mozul, S.; Ksiazek, A. Renalase gene polymorphisms in patients with type 2 diabetes, hypertension and stroke. *Neuromolecul. Med.* **2011**, *13*, 321–327. [CrossRef] [PubMed]
52. Farzaneh-Far, R.; Desir, G.V.; Na, B.; Schiller, N.B.; Whooley, M.A. A Functional Polymorphism in Renalase (Glu37Asp) Is Associated with Cardiac Hypertrophy, Dysfunction, and Ischemia: Data from the Heart and Soul Study. *PLoS ONE* **2010**, *5*, 32–47. [CrossRef] [PubMed]
53. Stojanovic, D.; Cvetkovic, T.; Stojanovic, M.; Stefanovic, N.; Velickovic-Radovanovic, R.; Zivkovic, N. Renalase Assessment with Regard to Kidney Function, Lipid Disturbances, and Endothelial Dysfunction Parameters in Stable Renal Transplant Recipients. *Prog. Transplant.* **2017**, *27*, 125–130. [CrossRef]
54. Yin, J.; Liu, X.; Zhao, T.; Liang, R.; Wu, R.; Zhang, F.; Kong, Y.; Liu, L.; Xing, T.; Wang, N.; et al. A protective role of renalase in diabetic nephropathy. *Clin. Sci.* **2020**, *134*, 75–85. [CrossRef]
55. Barrett, J.C.; Clayton, D.G.; Concannon, P.; Akolkar, B.; Cooper, J.D.; Erlich, H.A.; Julier, C.; Morahan, G.; Nerup, J.; Nierras, C.; et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat. Genet.* **2009**, *41*, 703–707. [CrossRef]
56. Wallace, C.; Rotival, M.; Cooper, J.D.; Rice, C.M.; Yang, J.H.; McNeill, M.; Smyth, D.J.; Niblett, D.; Cambien, F.; Cardiogenics Consortium. Statistical colocalization of monocyte gene expression and genetic risk variants for type 1 diabetes. *Hum. Mol. Genet.* **2012**, *21*, 2815–2831. [CrossRef]
57. Lloyd-Jones, D.M.; Hong, Y.; Labarthe, D.; Mozaffarian, D.; Appel, L.J.; Van Horn, L.; Greenlund, K.; Daniels, S.; Nichol, G.; Tomaselli, G.F.; et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* **2010**, *121*, 586–613. [CrossRef]

Oświadczenia współautorów

Lek. Aleksandra Żórawik
Katedra i Zakład
Zdrowia Środowiskowego, Medycyny Pracy
i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Paweł Gać, Rafał Poręba. **Environmental and behavioural determinants of cardiovascular health.** Journal of Health Inequalities. 2022 Aug;8(1):14-24. doi:10.5114/jhi.2022.116483.
   Mój udział polegał na opracowaniu koncepcji i metodologii badania, analizie dostępnego piśmiennictwa, współredagowaniu i korektach manuskryptu w ostatecznym przygotowaniu publikacji.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases.** Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na opracowaniu założeń i koncepcji pracy, gromadzeniu i opracowaniu danych, przeglądzie piśmiennictwa związanego z tematem pracy, analizie i interpretacji uzyskanych wyników badań, współredagowaniu i korektach manuskryptu w ostatecznym przygotowaniu publikacji.
3. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał opracowaniu założeń i koncepcji pracy, gromadzeniu i opracowaniu danych, przeglądzie piśmiennictwa związanego z tematem pracy, analizie i interpretacji uzyskanych wyników badań, współredagowaniu i korektach manuskryptu w ostatecznym przygotowaniu publikacji.

Aleksandra Żórawik

Prof. dr hab. n. med. Paweł Gać
Katedra i Zakład Zdrowia Środowiskowego, Medycyny Pracy i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Paweł Gać, Rafał Poręba. **Environmental and behavioural determinants of cardiovascular health.** Journal of Health Inequalities. 2022 Aug;8(1):14-24. doi:10.5114/jhi.2022.116483.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii pracy, współudziale merytorycznym przy analizie i interpretacji danych, korekcie i akceptacji przygotowanego manuskryptu.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases.** Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, nadzorowaniu postępu prac, udziale w analizie statystycznej i wsparciu merytorycznym przy interpretacji danych, korekcie i akceptacji przygotowanego manuskryptu.
3. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, nadzorowaniu postępu prac, udziale w analizie statystycznej i wsparciu merytorycznym przy interpretacji danych, korekcie i akceptacji przygotowanego manuskryptu.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

prof. dr hab. n. med. Paweł Gać
specjalista radiologii i diagnostyki obrazowej
European Diploma in Radiology
EACVI Cardiac Computed Tomography Exam
EACVI Cardiovascular Magnetic Resonance Exam
PWZ 2590859

Prof. dr hab. n. med. Rafał Poręba
Katedra i Klinika Angiologii
i Chorób Wewnętrznych
Uniwersytetu Medycznego we Wrocławiu
Ul. Borowska 213
50-556 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Paweł Gać, Rafał Poręba. **Environmental and behavioural determinants of cardiovascular health.** Journal of Health Inequalities. 2022 Aug;8(1):14-24. doi:10.5114/jhi.2022.116483.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii pracy, współudziale merytorycznym przy analizie i interpretacji danych, korekcie i akceptacji przygotowanego manuskryptu.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases.** Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, udziale w analizie i wsparciu merytorycznym przy interpretacji danych, korekcie i akceptacji przygotowanego manuskryptu.
3. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, udziale w analizie i wsparciu merytorycznym przy interpretacji danych, korekcie i akceptacji przygotowanego manuskryptu.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Prof. dr hab. med. Rafał Poręba
specjalista chorób wewnętrznych
kardiolog, diabetolog, angiolog
4190345

Dr hab. n. med. Helena Martynowicz, prof. UMW
Katedra i Klinika Diabetologii,
Nadciśnienia Tętniczego
i Chorób Wewnętrznych
Uniwersytetu Medycznego we Wrocławiu
Ul. Borowska 213
50-556 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnierz, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases**. Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, korekcie i akceptacji przygotowanego manuskryptu.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration**. Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, korekcie i akceptacji przygotowanego manuskryptu.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Helena Martynowicz

Prof. dr hab. n. med. Grzegorz Mazur
Katedra i Klinika Diabetologii,
Nadciśnienia Tętniczego
i Chorób Wewnętrznych
Uniwersytetu Medycznego we Wrocławiu
Ul. Borowska 213
50-556 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases**. Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, korekcie i akceptacji przygotowanego manuskryptu.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, korekcie i akceptacji przygotowanego manuskryptu.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Prof. dr hab. n. med. Krystyna Pawlas
Katedra i Zakład
Zdrowia Środowiskowego, Medycyny Pracy
i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases**. Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, korekcie i akceptacji przygotowanego manuskryptu.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w opracowaniu koncepcji i metodologii badań, korekcie i akceptacji przygotowanego manuskryptu.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Uniwersytet Medyczny we Wrocławiu
Katedra Zdrowia Środowiskowego,
Medycyny Pracy i Epidemiologii
ZAKŁAD ZDROWIA ŚRODOWISKOWEGO,
MEDYCYNY PRACY I EPIDEMIOLOGII
profesor
prof. dr hab. Krystyna Pawlas

Dr n. biol. med. Iwona Markiewicz-Górka
Katedra i Zakład
Zdrowia Środowiskowego, Medycyny Pracy
i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases**. Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w tworzeniu baz danych.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w tworzeniu baz danych.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Uniwersytet Medyczny we Wrocławiu
Katedra Zdrowia Środowiskowego,
Medycyny Pracy i Epidemiologii
ZAKŁAD ZDROWIA ŚRODOWISKOWEGO,
MEDYCYNY PRACY I EPIDEMIOLOGII
adiunkt
dr Iwona Markiewicz-Górka

Dr n. o zdr. Aleksandra Jaremków
Katedra i Zakład
Zdrowia Środowiskowego, Medycyny Pracy
i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 23.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine *Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance* of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases**. Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wsparciu w tworzeniu baz danych.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na wsparciu w tworzeniu baz danych.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Lek. Wojciech Hajdusianek
Katedra i Zakład
Zdrowia Środowiskowego, Medycyny Pracy
i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Paweł Gać, Rafał Poręba. **Environmental and behavioural determinants of cardiovascular health.** Journal of Health Inequalities. 2022 Aug;8(1):14-24. doi:10.5114/jhi.2022.116483.
   Mój udział polegał na gromadzeniu danych naukowych, przygotowaniu i współredagowaniu merytorycznym publikacji.
2. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases**. Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na gromadzeniu danych naukowych, współudziale w analizie i interpretacji wyników badań, przygotowaniu i współredagowaniu merytorycznym publikacji.
3. Aleksandra Żórawik, Wojciech Hajdusianek, Iwona Markiewicz-Górka, Aleksandra Jaremków, Krystyna Pawlas, Helena Martynowicz, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Coexistence of Cardiovascular Risk Factors and Blood Renalase Concentration.** Int J Mol Sci. 2023 Nov 23;24(23):16666. doi: 10.3390/ijms242316666.
   Mój udział polegał na gromadzeniu danych naukowych, współudziale w analizie i interpretacji wyników badań, przygotowaniu i współredagowaniu merytorycznym publikacji.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

WOJCIECH HAJDUSIANEK
lekarz
3644223

Mgr Agnieszka Kusnerż
Katedra i Zakład
Zdrowia Środowiskowego, Medycyny Pracy
i Epidemiologii
Uniwersytetu Medycznego we Wrocławiu
Ul. Jana Mikulicza-Radeckiego
50-345 Wrocław

Wrocław, 25.09.24

OŚWIADCZENIE O WSPÓŁAUTORSTWIE

Oświadczam, że w pracy:

1. Aleksandra Żórawik, Wojciech Hajdusianek, Agnieszka Kusnerż, Iwona Markiewicz-Górka, Aleksandra Jaremków, Helena Martynowicz, Krystyna Pawlas K, Grzegorz Mazur, Rafał Poręba, Paweł Gać. **Relation Between Exposure to Tobacco Smoke Assessed by Serum Cotinine Concentration and Questionnaire Method, and Serum Renalase Concentration-the Importance of the Coexistence of Arterial Hypertension and Other Cardiovascular Diseases.** Cardiovasc Toxicol. 2024 Aug;24(8):737-746. doi: 10.1007/s12012-024-09868-z.
   Mój udział polegał na wykonywaniu analiz laboratoryjnych oraz wsparciu w tworzeniu bazy danych.

Ponadto wyrażam zgodę na wykorzystanie w/w prac w cyklu artykułów stanowiących podstawę rozprawy doktorskiej lek. Aleksandry Żórawik.

Kusnerz Agnieszka

Zgoda komisji bioetycznej

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu

OPINIA KOMISJI BIOETYCZNEJ Nr KB –717/2022

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 278/XVI R/2020 z dnia 21 grudnia 2020 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 514 z 2020 r.) w składzie:

dr Joanna Birecka (psychiatria)

dr Beata Freier (onkologia)

dr hab. Tomasz Fuchs (ginekologia, położnictwo)

prof. dr hab. Dariusz Janczak (chirurgia naczyniowa, transplantologia)

dr hab. Krzysztof Kaliszewski, prof. UMW (chirurgia endokrynologiczna)

dr prawa Andrzej Malicki (prawo)

dr hab. Marcin Mączyński, prof. UMW (farmacja)

Urszula Olechowska (pielęgniarstwo)

prof. dr hab. Leszek Szenborn (pediatria, choroby zakaźne)

prof. dr hab. Andrzej Szuba (choroby wewnętrzne, angiologia

ks. prof. Andrzej Tomko (duchowny)

prof. dr hab. Mieszko Więckiewicz (stomatologia)

dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)

dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jerzego Rudnickiego (chirurgia, proktologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.:

„Środowiskowe i behawioralne uwarunkowania zdrowia sercowo-naczyniowego a stężenie renalazy we krwi"

zgłoszonym przez **lek. Aleksandrę Żórawik** uczestnika Szkoły Doktorskiej UMW oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Katedrze Zdrowia Populacyjnego Wydziału Nauk o Zdrowiu, Zakład Zdrowia Środowiskowego i Medycyny Pracy UMW, pod nadzorem dr hab. Jarosława Drobnika **pod warunkiem zachowania anonimowości uzyskanych danych.**

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Przewodniczący Komisji Bioetycznej
przy Uniwersytecie Medycznym

prof. dr hab. Jerzy Rudnicki

Wrocław, dnia 06 10 2022