Programma Pre-University College 2020: Geneeskunde in getallen

Maandag 3 februari 13:00–17:00 uur, locatie: LUMC Gebouw 1 C7P-108/111

Ontvangst: Edouard Fu, tel 071 5264037 (secretariaat)

13:00 – 14:00 uur:	Introductie blok en epidemiologie	Edouard Fu, Prof. Friedo Dekker
14:00 – 14:45 uur:	Frequentie en effectmaten	Edouard Fu
14:45 – 15:00 uur:	Pauze	
15:00 – 16:00 uur:	Studie design: observationeel en experimenteel	Prof. Frits Rosendaal
16:00 – 16:45 uur:	Introductie obesitas	Dr. Renée de Mutsert
16:45 – 17:00 uur:	Indelen groepjes en onderwerpen eindopdracht	Edouard Fu

Maandag 10 februari 13:00–17:00 uur, locatie: LUMC Gebouw 1 C7P-108/111

13.00 – 14.00 uur:	Confounding en bias	Prof. Suzanne Cannegieter
14.00 – 14.45 uur:	P-waarden en betrouwbaarheidsintervallen	Prof. Rolf Groenwold
14.45 – 15.00 uur:	Pauze	
15.00 – 16.00 uur:	Overgewicht en cardiologie	Drs. Laurien Zijlstra
16:00 – 17.00 uur:	Recap en vragenuur	Edouard Fu

Maandag 17 februari 13:00–17:00 uur, locatie: LUMC Gebouw 1 C7P-108/111

13:00 – 13:45 uur:	Hoe schrijf ik een protocol?	Edouard Fu
13:45 – 14:45 uur:	Rondleiding laboratorium	Pat van Beelen
14:45 – 15:00 uur:	Pauze	
15:00 – 16:00 uur:	Klinische gevolgen van obesitas	Prof. Hanno Pijl
16:00 – 16:20 uur:	Instructie eindopdracht	Edouard Fu
16:20 – 17:00 uur:	Ethiek in onderzoek	Prof. Olaf Dekkers

Maandag 2 maart 13:00 – 16:00 uur, locatie: LUMC Gebouw 1 C7P-108/111

13:00 – 15:30 uur:	Presentaties	Edouard Fu, Prof. Frits Rosendaal, Prof. Friedo Dekker
15:30 – 16:00 uur:	Afsluiting	Edouard Fu

Coördinatoren: Edouard Fu, promovendus klinische epidemiologie, Prof. Dr. Frits Rosendaal

e-mail: e.l.fu@lumc.nl

Pre-University College Blok II
Serie 2: Geneeskunde in getallen

Medische detectives

Als je als patiënt bij de dokter komt dan wil je wel een behandeling krijgen die echt werkt. Daarnaast zit je misschien met vragen als: waarom heb ik deze ziekte gekregen? En nu ik deze ziekte heb, hoe gaat het dan verder? Het vakgebied dat zich bezig houdt met het beantwoorden van dit soort vragen heet de klinische epidemiologie. Epidemiologen lijken op medische detectives, die medische gegevens verzamelen en analyseren, kijken wat de oorzaken zijn van ziektes en beoordelen of behandelingen goed werken. Die kennis gebruiken dokters vervolgens meteen in de spreekkamer om patiënten zo goed mogelijk verder te behandelen. Veel epidemiologen zijn dan ook arts.

Bij het opzetten van medisch onderzoek liggen echter verschillende valkuilen op de loer. In de serie *Geneeskunde in Getallen* ga je leren hoe jij zo'n onderzoek op de juiste manier opzet om antwoorden te vinden op deze vragen. We gaan daarbij specifiek in op het medische vraagstuk "overgewicht", dé epidemie van de 21^{e} eeuw. Meer dan de helft van de Nederlanders is te zwaar, en overgewicht is een belangrijke risicofactor voor o.a. hart- en vaatziekten, diabetes en nierziekten. Nadat je de benodigde kennis hierover hebt opgedaan in de colleges, neem je een kijkje achter de schermen bij een "echt", grootschalig onderzoek op het gebied van overgewicht. Daarnaast zullen artsen vertellen over verschillende ziektebeelden die als gevolg van overgewicht ontstaan. Aan het einde van deze serie heb jij de epidemiologische en klinische kennis opgedaan om een protocol te schrijven voor een onderzoek op het gebied van overgewicht. Dit protocol presenteer je in de laatste bijeenkomst aan je medestudenten.

Maandag 3 februari 13:00-17:00 uur

In de eerste bijeenkomst zal een introductie gegeven worden op de epidemiologie en overgewicht. Je leert waar epidemiologen zich mee bezig houden en wat voor soort onderzoek zij doen. Ook zal aan bod komen hoe frequentie- en effectmaten gebruikt kunnen worden om verbanden aan te tonen en hoe observationele en experimentele onderzoeken gebruikt kunnen worden om vragen te beantwoorden zoals: "wat zijn de oorzaken van ziekte" (etiologie) en "is er een effectieve behandeling voor ziekte" (therapie). Daarna volgt een introductie over obesitas. Aan het einde van de middag worden de deelvragen voor de presentaties op de laatste bijeenkomst verdeeld. NB: Voor een goed verloop van de eerste bijeenkomst is het van belang om het voorbereidende materiaal goed door te nemen, dat bestaat uit het kijken van een documentaire (35 minuten), het lezen van een artikel en het beantwoorden van de vragen bij dit artikel (1.5 uur).

Leerdoelen

- Je hebt een beeld van het vakgebied epidemiologie en weet wat voor soort vragen epidemiologen beantwoorden.
- Je kent de begrippen prevalentie, incidentie, relatief risico, absoluut risico, risicoverschil, en kunt deze uitleggen. Je kunt aan de hand van een 2x2 tabel het relatief risico berekenen.
- Je begrijpt de verschillen tussen observationeel en experimenteel onderzoek.
- Je weet wat een cohort en case-control onderzoek is.
- Je hebt een overzicht van de wereldwijde obesitasepidemie.

Voorbereidend materiaal (vóór de bijeenkomst doornemen)

1. Kijk de documentaire "Waarom ik?" (35 minuten) https://www.youtube.com/watch?v=sLP3lwMnhxc&feature=emb_title. In de film 'Waarom ik?' tonen Spinozaprijswinnaar prof. Frits Rosendaal en collega's hoe zij als 'medische detectives' onderzoek doen naar de oorzaken van ziekten. De film gaat nader in op de NEO-studie, een nu 10 jaar lopend onderzoek dat de relatie tussen overgewicht en verschillende ziekten onderzoekt. We zien hoe de afdeling van Rosendaal, de Klinische Epidemiologie, werd opgericht om verbanden tussen allerlei factoren en ziekte te onderzoeken, welke struikelblokken de onderzoekers tegenkwamen en wat ze daarvan leerden. Ook enkele deelnemers van de NEO-studie komen aan het woord. Zij vertellen waarom ze meedoen aan de NEO-studie en we zien hoe ze deelnemen aan een uniek onderzoek.

2. Lees het artikel "*Health Effects of Overweight and Obesity in 195 countries over 25 years*" dat aan het einde van het blokboek is toegevoegd. Onderstaande vragen zijn bedoeld om je door het artikel te leiden.
    1. Welke chronische ziekten zijn geassocieerd met een hoog BMI? Heb je wel eens van deze ziekten gehoord? Zoek ze op als je ze niet kent.

2. Wat is de definitie van overgewicht en obesitas aan de hand van BMI waarden? Hoe wordt BMI berekend?
3. Wat betekent prevalentie? Kijk naar Figuur 1B en 1C. Is de prevalentie van overgewicht in kinderen en volwassenen toegenomen of juist afgenomen tussen 1990 en 2015?
4. Kijk naar figuur 1A. Is de obesitasprevalentie groter in mannen of vrouwen? Welke leeftijdsgroep heeft de grootste prevalentie van obesitas? Is er een verschil in obesitas tussen landen met een hoge en lage SDI (betekenis van SDI wordt uitgelegd op pagina 16)?
5. Kijk naar figuur 2. In welke landen is de prevalentie van obesitas het hoogst? Zie je een relatie tussen geografische ligging en de prevalentie van obesitas?
6. Kijk naar Figuur 3. Wat is een DALY? Welke ziekte is de belangrijkste oorzaak van DALY's en sterfte onder mensen met obesitas? Welke ziekte is de tweede belangrijkste oorzaak van DALY's onder mensen met obesitas?

Naslagwerk en verdieping (eventueel na de bijeenkomst voor opfrissen van kennis)

Als je na de bijeenkomst meer zou willen weten, dan vind je hier wat extra materiaal dat je door zou kunnen nemen. Ga naar www.coursera.org en maak een account aan. Meld je aan voor de cursus "Population Health: Study Design" van de Universiteit Leiden. Ga daarna naar "Week 1: Welcome to Study Design". Bekijk de filmpjes "Experimental versus observational studies" (8 minuten), "The cohort study" (7 minuten) en "The case-control study" (8 minuten).

Herhaling van de stof over frequentie- en effectmaten kan gevonden worden in "Week 2: Measures" in de filmpjes "Frequency measures" (9 minuten), "Effect measures" (8 minuten) en "Odds and odds ratios" (6 minuten). Als je nog wilt oefenen met het berekenen van effectmaten kun je de practice quiz "Calculate frequency and effect measures" maken. NB: *cumulative incidence* is het Engelse woord voor cumulatieve incidentie. *Incidence rate* is het Engelse woord voor incidentiecijfer.

Maandag 10 februari 13:00-17:00 uur

In deze bijeenkomst gaan we dieper in op de epidemiologie. In de vorige bijeenkomst heb je geleerd hoe je met observationeel onderzoek en effectmaten associaties kunt aantonen tussen een risicofactor en een uitkomst. Een associatie betekent echter nog niet dat dit een oorzakelijk verband is. Er liggen bij epidemiologisch onderzoek namelijk twee soorten fouten op de loer: systematische (confounding en bias) en random fouten (kans). Deze concepten zullen vandaag worden geïntroduceerd. Daarnaast zal een onderzoeker van de afdeling cardiologie wat vertellen over de relatie tussen overgewicht en het ontwikkelen van hart- en vaatziekten. NB: Voor een goed verloop van de tweede bijeenkomst is het van belang om al wat voorkennis te hebben over confounding en hiermee te oefenen. Bekijk de filmpjes op coursera (20 minuten) en maak de e-learning over confounding (1 uur).

Leerdoelen

- Je begrijpt dat een gevonden associatie niet per se een oorzakelijk verband hoeft te zijn.
- Je kent het begrip confounding, kan dit herkennen en hiervoor corrigeren.
- Je kent de drie criteria van een confounder.
- Je kent een aantal voorbeelden van bias, zoals selectiebias en informatiebias.
- Je begrijpt de invloed van kans op studieresultaten.
- Je kent de relatie tussen overgewicht en het ontwikkelen van hart- en vaatziekten.

Voorbereidend materiaal (vóór de bijeenkomst doornemen)

Ga naar www.coursera.org en maak een account aan. Meld je aan voor de cursus "Population Health: Study Design" van de Universiteit Leiden. Ga daarna naar "Week 3: Confounding and bias". Bekijk de filmpjes "Random and systematic error" (9 minuten) en "Confounding and bias" (8 minuten).

Ga nu naar www.medischonderwijs.nl en maak een account aan. Zodra je bent ingelogd, zoek dan op het woord "confounding" en maak de e-learning "Confounding I" (60 minuten).

Naslagwerk en verdieping (eventueel na de bijeenkomst voor opfrissen van kennis)

Als je na de bijeenkomst meer zou willen weten over hoe je moet corrigeren voor confounding, dan kan je meer informatie vinden in week 3 van de cursus "Population Health: Study design" in de filmpjes "Countering confounding" (9 minuten) en "Standardisation" (7 minuten).

Als je meer wilt weten over random fouten (kans), meld je dan aan voor de cursus "Population Health: Responsible Data Analysis" op www.coursera.org. Ga naar week 2 en kijk de filmpjes "Statistical Inference" (9 minuten) en "Fundamentals of Hypothesis Testing" (7 minuten).

Maandag 17 februari 13:00-17:00 uur

De derde bijeenkomst staat in het teken van de voorbereiding op de eindpresentatie, waarvoor jullie in groepjes een protocol zullen presenteren voor een epidemiologisch onderzoek op het gebied van overgewicht. We beginnen daarom met een uitleg hoe een protocol eruitziet als we de vraag willen beantwoorden of overgewicht leidt tot nierziekten. Daarna gaan jullie langs bij het lab en zien jullie welke medische testen bij deelnemers van de NEO studie worden afgenomen. Na de pauze zullen jullie leren over de klinische gevolgen van obesitas en over ethiek in medisch onderzoek, en krijgen jullie instructies voor de eindopdracht. Voor een goed verloop van de bijeenkomst is het belangrijk onderstaand artikel goed door te nemen, omdat dit gebruikt zal worden bij de eerste lezing.

Leerdoelen

- Je herkent de structuur van een epidemiologisch artikel.
- Je weet hoe een protocol voor een epidemiologische studie eruitziet en welke elementen hierin beschreven moeten worden.
- Je kent de klinische gevolgen van overgewicht op het lichaam.
- Je hebt basale kennis van ethiek in medisch onderzoek.

Voorbereidend materiaal (vóór de bijeenkomst doornemen)

Lees het bijgevoegde artikel in de Annals of Internal Medicine over de relatie tussen BMI en het ontwikkelen van eindstadium nierfalen ("Body mass index and risk for end-stage renal disease"). Dit artikel zal als leidraad dienen voor de lezing "Hoe schrijf ik een protocol?". Beantwoord de volgende vragen:

Introduction

1. Wat is de vraagstelling van dit artikel? Zie je er al een 2x2 tabel doorheen schemeren?
2. Elke alinea van de introductie dient één boodschap te hebben. Benoem voor elke alinea van de introductie wat die boodschap is.

Methods

3. Welke BMI categorieën zijn met elkaar vergeleken, en welke daarvan is als referentiecategorie genomen (relatief risico van 1)?
4. Kun je bedenken welke confounders er zouden kunnen zijn in de relatie tussen BMI en ESRD? Voor welke confounders hebben de auteurs daadwerkelijk gecorrigeerd? Zie ook de kleine lettertjes onder tabel 3.
5. Waarom twijfelen de auteurs of gecorrigeerd moet worden voor hypertension (= hoge bloeddruk) en diabetes? Zijn dit confounders in de relatie tussen BMI en ESRD of juist niet? Denk aan de drie criteria waaraan een confounder moet voldoen.

Results

6. Wat is de functie van Tabel 1? Zie je verschillen tussen mensen met een normale BMI en klasse III obesitas?

7. Kijk naar de figuur. Welke effectmaat hebben de auteurs van dit artikel gebruikt? Hoe interpreteer je deze effectmaat? Welke BMI categorie heeft het grootste risico op het ontwikkelen van ESRD?
8. Ga nu naar Tabel 2. Bereken aan de hand van het aantal ESRD events en het aantal persoonsjaren de incidentiecijfers per 100.000 persoonsjaren voor mensen met normaal gewicht en overgewicht. Je zult op iets andere getallen uitkomen dan in de laatste kolom van Tabel 2 staan, omdat daar incidentiecijfers staan gecorrigeerd voor leeftijd, geslacht en ras. Bereken daarna het relatieve risico op ESRD voor mensen met klasse II obesitas ten opzichte van mensen met een normaal gewicht.

Discussion

9. Kijk naar de opbouw van de discussie en benoem het doel van iedere alinea.

Naslagwerk en verdieping (eventueel na de bijeenkomst voor opfrissen van kennis)

Als je na de bijeenkomst meer zou willen weten over ethiek van medisch-wetenschappelijk onderzoek kun je het bijgevoegde artikel lezen over informed consent en therapeutische misconceptie.

Maandag 2 maart 13:00-16:00 uur

In de laatste bijeenkomst zullen jullie in groepjes van 2-3 een presentatie geven van 15 minuten. Hierin presenteren jullie het protocol dat hoort bij de vraagstelling die jullie hebben uitgekozen.

Een aantal elementen die in de presentatie verwerkt kunnen worden:

- Klinische achtergrondinformatie bij het onderwerp en relevantie van het beantwoorden van deze vraag.
- Presenteren van een duidelijke onderzoeksvraag: In welke populatie ga je dit onderzoeken? Wat is de determinant (risicofactor/behandeling) en wat is de uitkomst?
- Wat is de 2x2 tabel?
- Welk studiedesign ga je gebruiken? Observationeel (cohort studie of case-control studie) of experimenteel? Waarom heb je juist voor dit design gekozen?
- Wat ga je allemaal meten, en hoe lang ga je proefpersonen volgen?
- Confounding
    - Welke eventuele confounders zijn er in de relatie determinant-uitkomst?
    - Voldoen ze aan de drie criteria?
    - Hoe ga je corrigeren voor deze confounders?
- Welke andere vormen van bias kun je tegenkomen (selectiebias en informatiebias) in deze studie? Hoe ga je hiermee om?
- Welke effectmaat ga je berekenen?
- Ethische aspecten van dit onderzoek

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2017 VOL. 377 NO. 1

Health Effects of Overweight and Obesity in 195 Countries over 25 Years

The GBD 2015 Obesity Collaborators*

ABSTRACT

BACKGROUND

Although the rising pandemic of obesity has received major attention in many countries, the effects of this attention on trends and the disease burden of obesity remain uncertain.

METHODS

We analyzed data from 68.5 million persons to assess the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. Using the Global Burden of Disease study data and methods, we also quantified the burden of disease related to high body-mass index (BMI), according to age, sex, cause, and BMI in 195 countries between 1990 and 2015.

RESULTS

In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. High BMI accounted for 4.0 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to high BMI were due to cardiovascular disease. The disease burden related to high BMI has increased since 1990; however, the rate of this increase has been attenuated owing to decreases in underlying rates of death from cardiovascular disease.

CONCLUSIONS

The rapid increase in the prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation, and evaluation of evidence-based interventions to address this problem. (Funded by the Bill and Melinda Gates Foundation.)

*The names, academic degrees, and affiliations of the authors, who are members of the Global Burden of Disease (GBD) 2015 Obesity Collaborators, are listed in the Appendix. The authors assume responsibility for the content and integrity of this article. Address reprint requests to Dr. Murray at the Institute for Health Metrics and Evaluation, University of Washington, 2301 5th Ave., Suite 600, Seattle, WA 98121, or at cjlm@uw.edu.

This article was published on June 12, 2017, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Final Manuscript, which is the author's version after external peer review and before publication in the *Journal,* is available under a CC BY license at PMC5477817.

N Engl J Med 2017;377:13-27.
DOI: 10.1056/NEJMoa1614362

A Quick Take is available at NEJM.org

The prevalence of overweight and obesity is increasing worldwide.[1] Epidemiologic studies have identified high body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) as a risk factor for an expanding set of chronic diseases, including cardiovascular disease,[2,3] diabetes mellitus, chronic kidney disease,[2] many cancers,[4] and an array of musculoskeletal disorders.[5,6] As the global health community works to develop treatments and prevention policies to address obesity, timely information about levels of high BMI and health effects at the population level is needed.

In recent years, increasing efforts have been made to assess the trends in BMI within and across nations.[7,8] Other studies have quantified the potential effects of high BMI on a variety of health outcomes.[2,4] These efforts, while useful, did not consider the relationship of high BMI with broader socioeconomic development; they also excluded many data sources, focused exclusively on adults, inadequately captured the skewed distribution of BMI, did not capture emerging evidence on additional outcomes, and did not assess the effect of epidemiologic and demographic transition on disease burden. The BMI that is associated with the lowest risk of death has also been questioned.[9,10]

To address these gaps in knowledge, we systematically evaluated the trends in the prevalence of overweight and obesity as well as the patterns of deaths and disability-adjusted life-years related to high BMI, according to age and sex, in 195 countries. This analysis supersedes all previous results from the Global Burden of Disease study with respect to high BMI by comprehensively reanalyzing all data from 1990 through 2015 using consistent methods and definitions.

Methods

Prevalence and Disease Burden of Overweight and Obesity

We systematically estimated the prevalence of overweight and obesity among children (<20 years of age) and adults between 1980 and 2015. Using the comparative-risk-assessment approach from the Global Burden of Disease study, we also quantified the burden of disease related to high BMI during the period from 1990 through 2015. The burden of disease was assessed by deaths and disability-adjusted life-years, a composite metric computed as the sum of years lived with disability and years of life lost due to high BMI. In this analysis, we used the distribution of BMI according to age, sex, country, and year; the effect size of the change in BMI on disease end points; the BMI associated with the lowest risk of death from all causes; and disease-specific mortality and morbidity according to age, sex, country, and year.

Global Distribution of BMI

We systematically searched Medline for studies that provide nationally or subnationally representative estimates of BMI, overweight, or obesity among children or adults. We included studies if they used standard cutoff points of BMI to define overweight (BMI, 25 to 29) and obesity (BMI, ≥30) among adults or standards of the International Obesity Task Force to define overweight and obesity among children. The search terms, selection criteria, and flow diagrams of screening are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org. In addition, we searched the Global Health Data Exchange (http://ghdx.healthdata.org) for multicountry survey programs, national surveys, and longitudinal studies that provide self-reported or measured data on height and weight for children or adults.

With respect to data regarding adults, we identified 1276 unique data sources (855 measured and 421 self-report) from 176 countries that provide data on BMI, 1333 sources (802 measured and 531 self-report) from 176 countries that provide data on overweight, and 1514 sources (713 measured and 801 self-report) from 174 countries that provide data on obesity. With respect to data regarding children, we identified 1211 unique data sources (800 measured and 411 self-report) from 173 countries that provide data on BMI, 1236 sources (832 measured and 404 self-report) from 174 countries that provide data on overweight, and 1437 sources (928 measured and 509 self-report) from 175 countries that provide data on obesity. Using mixed-effects linear-regression models, we separately estimated and corrected for self-reporting bias among men and women according to geographic region and age group. We characterized the age and sex patterns for BMI, overweight, and obesity and applied these patterns to split aggregated data into

5-year age groups according to sex (see the Methods section in the Supplementary Appendix).

We used spatiotemporal Gaussian process regression to estimate the mean prevalence of obesity and overweight.[11] To improve our estimates in data-sparse countries, we tested a wide range of covariates with plausible relationships to overweight and obesity. We selected three country-level covariates with best fit and coefficients in the expected direction, as have been used in other studies.[8] These factors included 10-year lag-distributed energy intake (i.e., time-weighted average of daily energy intake) per capita, the absolute latitude of the country, and the proportion of persons living in urban areas. To estimate the mean BMI, we first used mixed-effects linear regression to characterize the relationship between BMI, overweight, and obesity in sources containing information on all three measures. We applied the coefficients of this regression to the prevalence of overweight and of obesity generated through spatiotemporal Gaussian process regression to estimate the mean BMI for each country, according to age, sex, and year. Among the 195 countries and territories that are included in the present study, data regarding overweight, obesity, or BMI were unavailable for only 8: Antigua and Barbuda, Bermuda, Brunei, Northern Mariana Islands, Saint Vincent and the Grenadines, the Bahamas, Turkmenistan, and Venezuela. The estimates in these countries were constructed purely from the covariates used in the estimation of the linear model and the weighted and smoothed residuals from data for neighboring countries.

To identify the appropriate distribution of BMI at the population level, we examined how various distributions (i.e., log-normal, gamma, inverse Gaussian, and beta) approximated the distribution of actual data from national surveys in six countries; the best fit was provided by the beta distribution.[12] We characterized the shape of the beta distribution on the basis of the mean BMI and the prevalence of overweight and obesity in each country according to age, sex, and year. Details of this approach have been described previously.[12]

EFFECT OF HIGH BMI ON HEALTH OUTCOMES

We used Bradford Hill's criteria for causation and the evidence-grading criteria of the World Cancer Research Fund to systematically evaluate epidemiologic evidence supporting the causal relationship between high BMI and various disease end points among adults 25 years of age or older.[13] We found convincing or probable evidence for an association with 20 health outcomes (Table S1 in the Supplementary Appendix). For each outcome, we obtained the relative risk from a dose–response meta-analysis of prospective observational studies (Table S2 in the Supplementary Appendix). Using pooled analyses of prospective cohort studies, we estimated the relative risk associated with a change of five units of BMI in 5-year age groups for ischemic heart disease, ischemic stroke, hemorrhagic stroke, hypertensive heart disease, and diabetes mellitus. For breast cancer, we calculated the relative risk for premenopausal and postmenopausal women according to region (as specified in the Global Burden of Disease study) because of evidence that overweight and obesity have a protective effect against breast cancer in premenopausal women in all countries except for the Asia–Pacific regions,[14,15] whereas a positive association between high BMI and the incidence of postmenopausal breast cancer has been observed worldwide.[15]

THE LOWEST-RISK BMI

We used the most recent pooled analysis of prospective observational studies to determine the BMI associated with the lowest overall risk of death.[9] To address the limitations of previous studies on this topic, which have included residual confounding among smokers and reverse causation due to preexisting chronic diseases,[10] the analysis was restricted to never-smokers without identified chronic diseases who survived 5 years after recruitment. The lowest overall risk of death was observed for a BMI of 20 to 25.

STATISTICAL ANALYSIS

To quantify the burden of disease related to high BMI for each disease end point, we calculated the population attributable fraction according to country, age, sex, and year.[16] We computed the numbers of deaths and disability-adjusted life-years related to high BMI for each country, according to age, sex, year, and cause, by multiplying the population attributable fraction by the total number of deaths or disability-adjusted life-years, as estimated in the Global Burden of Disease study for that country, age, sex, year, and cause. We calculated the total disease burden

related to high BMI as the sum of disease-specific burdens. To understand where in the distribution of BMI most of the burden occurs, we estimated population attributable fractions for three ranges of BMI (20 to 24, 25 to 29, and ≥30) and for five groups of disease end points (cardiovascular disease, diabetes mellitus, chronic kidney disease, cancers, and musculoskeletal disorders).

Using the methods developed by Das Gupta,[17] we broke down the change in the numbers of deaths and the numbers of disability-adjusted life-years that are attributed to high BMI between population growth, population age structure, risk exposure to high BMI, and rates of risk-deleted mortality and disability-adjusted life-years. (Risk-deleted rates are the burden of disease in the absence of the risk factor — for example, rates of death from cardiovascular disease that would have been observed if everyone had been at the lowest-risk BMI.)

We computed 95% uncertainty intervals for all results using Monte Carlo simulations, keeping 1000 draws of each quantity of interest to propagate uncertainty into final estimates. The model included uncertainty from examination surveys, the relative risks for each outcome from the pooled analyses or meta-analyses of cohorts, the lowest-risk BMI, and the number of deaths and disability-adjusted life-years estimated for each country, age, sex, year, and outcome from the Global Burden of Disease 2015 study. According to the methods outlined in that study, we used a sociodemographic index (SDI) — a summary measure of lag-distributed income per capita, average educational attainment among persons over the age of 15 years, and total fertility rate — to position countries on the development continuum. We then generated quintiles of SDI to categorize countries as low, low-middle, middle, high-middle, and high development level (Table S3 in the Supplementary Appendix).[13]

RESULTS

PREVALENCE OF OBESITY (1980–2015)

Global Level

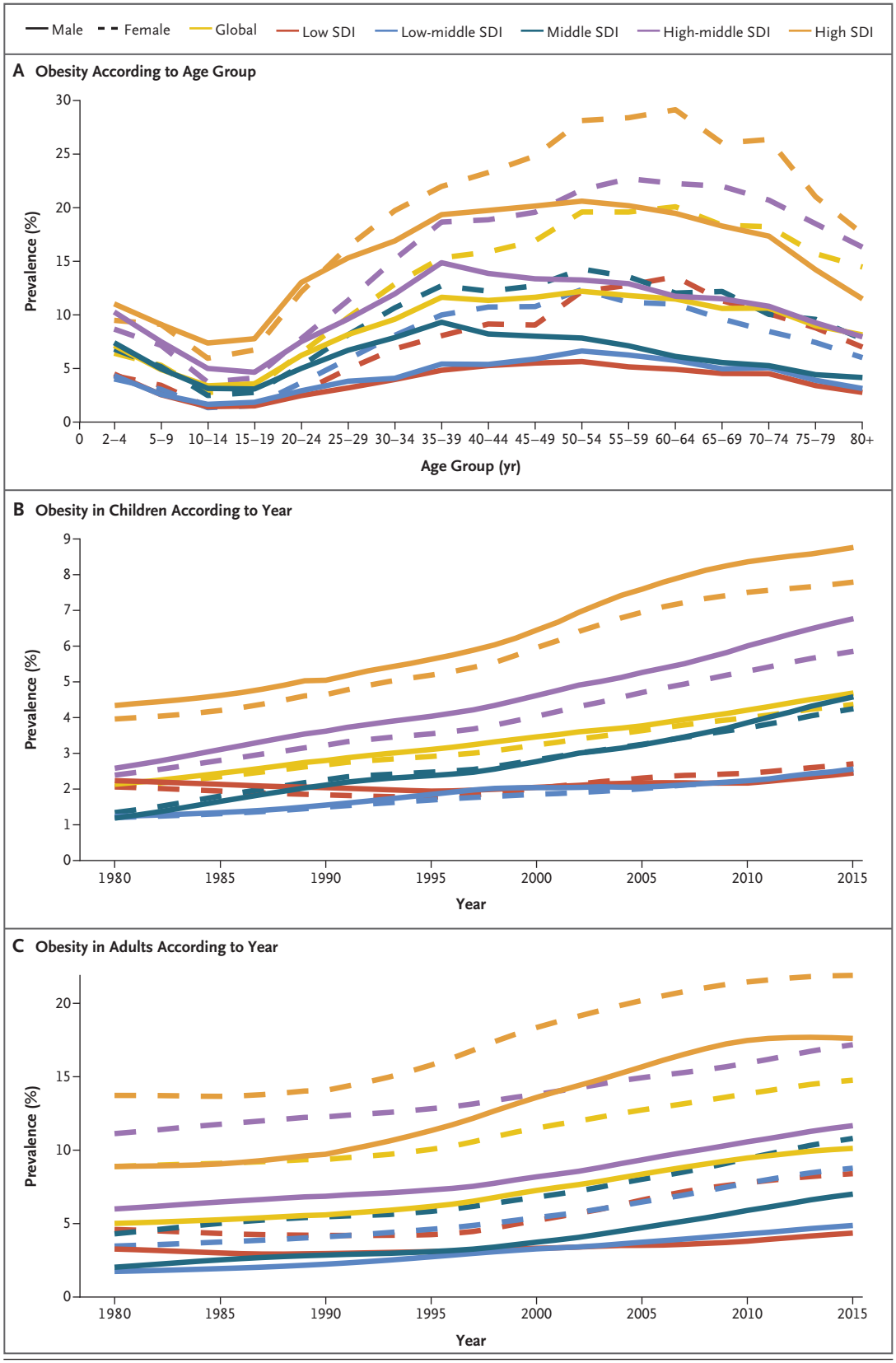
In 2015, we estimated that 107.7 million children (uncertainty interval, 101.1 to 115.1) and 603.7 million adults (uncertainty interval, 592.9 to 615.6) were obese worldwide. The overall prevalence of obesity was 5.0% among children and 12.0% among adults. Among adults, the prevalence of obesity was generally higher among women than among men in all age brackets (Fig. 1). The peak in the prevalence of obesity was observed between the ages of 60 and 64 years among women and between the ages of 50 and 54 years among men. The rates of increase in obesity between 1980 and 2015 did not differ significantly between women and men in any age bracket; for both groups, the rates of increase were highest in early adulthood. Among children, the prevalence of obesity in 2015 decreased with age until the age of 14 years and then increased; no sex differences were observed in obesity prevalence before the age of 20 years. Between 1980 and 2015, the rates of increase in global childhood obesity were equal for boys and girls in all age brackets.

Figure 1 (facing page). Prevalence of Obesity at the Global Level, According to Sociodemographic Index (SDI).

Shown is the age-specific prevalence of obesity at the global level and according to SDI quintile in 2015 (Panel A) and age-standardized prevalence trends at the global level and according to SDI quintile from 1980 through 2015 among children (Panel B) and adults (Panel C).

SDI Level

In 2015, at all SDI levels and for all age groups, the prevalence of obesity was generally higher for women than for men, with the highest prevalence among women between the ages of 60 to 64 years living in countries with a high SDI (Fig. 1). In general, the prevalence of obesity among both women and men increased with the increase in the SDI across all age groups. An exception was the prevalence of obesity among women living in countries with a low SDI, since after the age of 55 years, the prevalence was higher than that observed for women in countries with a low-middle SDI (Fig. 1). During the period from 1980 to 2015, the most rapid relative increase in the prevalence of obesity occurred among men between the ages of 25 and 29 years who were living in countries with a low-middle SDI — from 1.1% (uncertainty interval, 0.9 to 1.5) in 1980 to 3.8% (95% uncertainty interval, 3.1 to 4.8) in 2015. During the same time period, the prevalence of obesity increased by a factor of 1.7 among both men and women in countries with a low-middle SDI.



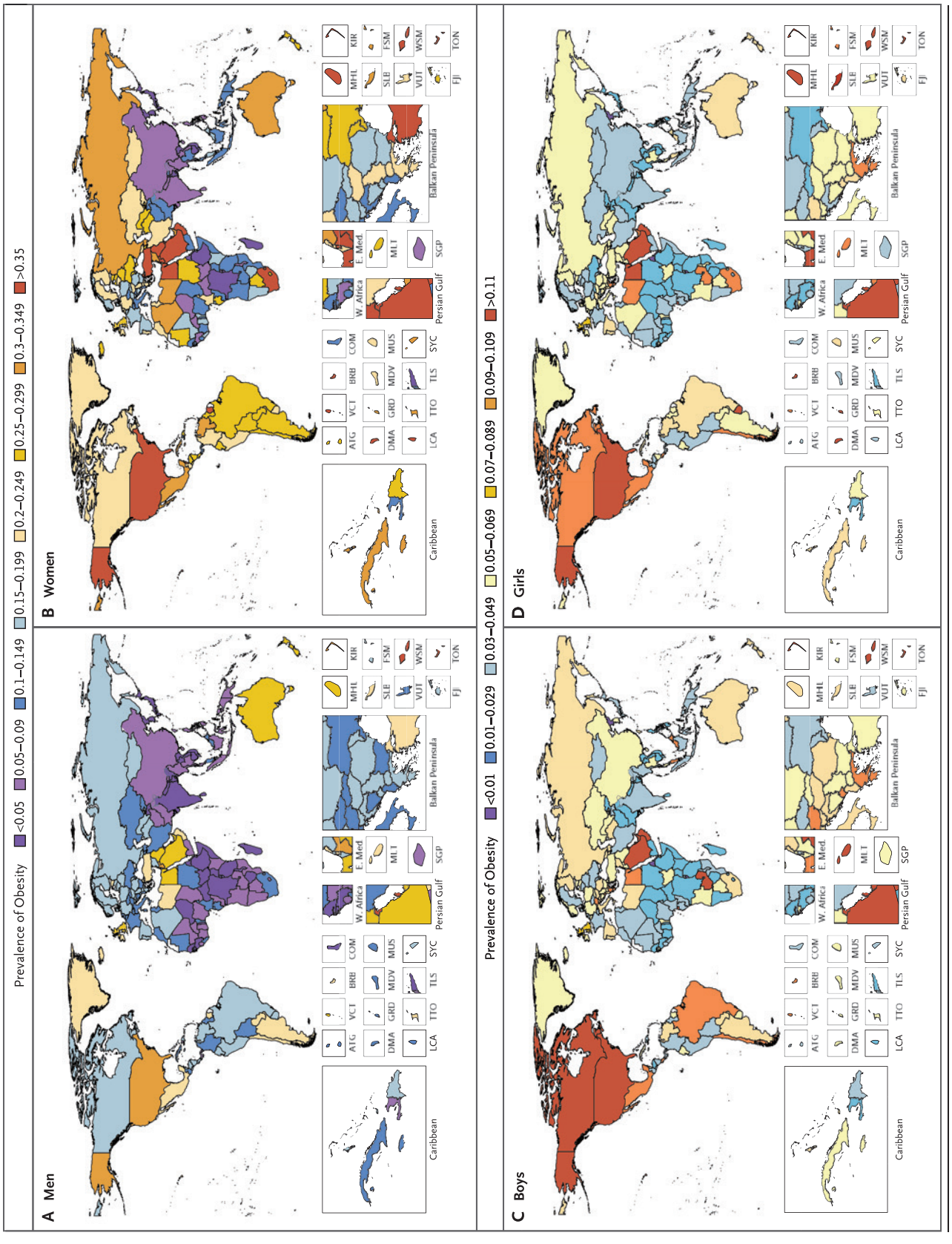


Figure 2 (facing page). Age-Standardized Prevalence of Obesity Worldwide in 2015.

Shown is the age-standardized prevalence of obesity among adults (Panel A [men] and Panel B [women]) and among children (Panel C [boys] and Panel D [girls]) in 2015. Children were defined as being under the age of 20 years. Values for prevalence are provided as decimals. ATG denotes Antigua and Barbuda, BRB Barbados, COM Comoros, DMA Dominica, E. Med. Eastern Mediterranean, FJI Fiji, FSM Federated States of Micronesia, GRD Grenada, KIR Kiribati, LCA Saint Lucia, MDV Maldives, MHL Marshall Islands, MLT Malta, MUS Mauritius, SGP Singapore, SLB Solomon Islands, SYC Seychelles, TLS Timor-Leste, TON Tonga, TTO Trinidad and Tobago, VCT Saint Vincent and the Grenadines, VUT Vanuatu, W. Africa Western Africa, and WSM Samoa.

Among children, the prevalence of obesity was greater in countries with higher SDI levels (Fig. 1). At most SDI levels, the prevalence of obesity was lowest among both boys and girls between ages of 10 and 14 years. In countries with high and high-middle SDI levels, the prevalence was generally greater among boys than among girls, although this difference reversed beginning with late adolescence (Fig. 1). Between 1980 and 2015, there was a significant relative increase of 20.0% (95% uncertainty interval, 5.5 to 35.3) in the prevalence of obesity in countries with a low SDI among both girls and boys. During that period, the highest rates of increase were observed in countries with a middle SDI among both girls and boys.

National Level

The prevalence of obesity among children and adults has doubled in 73 countries since 1980 and has shown a continuous increase in most other countries. Although the prevalence of childhood obesity has been lower than the prevalence of adult obesity, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. The estimated age-standardized prevalence of overweight and obesity among children and adults for all 195 countries and territories is provided in Table S3 in the Supplementary Appendix. A complete data set of all results for each country according to age, sex, and year is available on the Global Health Data Exchange website (http://ghdx.healthdata.org/), and an interactive data visualization of the prevalence of overweight and obesity is provided online (https://vizhub.healthdata.org/obesity/). Here we highlight the findings related to obesity in the most populous countries (Fig. 2).

In 2015, among the 20 most populous countries, the highest level of age-standardized adult obesity was observed in Egypt (35.3%; 95% uncertainty interval, 33.6 to 37.1), and the highest level of age-standardized childhood obesity was observed in the United States (12.7%; 95% uncertainty interval, 12.2 to 13.2). The prevalence was lowest among adults in Vietnam (1.6%; 95% uncertainty interval, 1.4 to 2.0) and among children in Bangladesh (1.2%; 95% uncertainty interval, 0.9 to 1.7). Between 1980 and 2015, the age-standardized prevalence of obesity increased by a factor of 2 or more in 13 of the 20 countries; only the Democratic Republic of Congo had no increase (Figs. S1 and S2 in the Supplementary Appendix). In 2015, China and India had the highest numbers of obese children, whereas the United States and China had the highest numbers of obese adults.

BURDEN OF DISEASE RELATED TO HIGH BMI (1990–2015)

Global Level

In 2015, high BMI contributed to 4.0 million deaths (95% uncertainty interval, 2.7 to 5.3), which represented 7.1% (95% uncertainty interval, 4.9 to 9.6) of the deaths from any cause; it also contributed to 120 million disability-adjusted life-years (95% uncertainty interval, 84 to 158), which represented 4.9% (95% uncertainty interval, 3.5 to 6.4) of disability-adjusted life-years from any cause among adults globally. A total of 39% of the deaths and 37% of the disability-adjusted life-years that were related to high BMI occurred in persons with a BMI of less than 30 (Fig. 3).

Cardiovascular disease was the leading cause of death and disability-adjusted life-years related to high BMI and accounted for 2.7 million deaths (95% uncertainty interval, 1.8 to 3.7) and 66.3 million disability-adjusted life-years (95% uncertainty interval, 45.3 to 88.5) (Table S4 in the Supplementary Appendix). Globally, 41% of BMI-related deaths and 34% of BMI-related disability-adjusted life-years were due to cardiovascular disease among obese persons. Diabetes was the second leading cause of BMI-related deaths in 2015 and contributed to 0.6 million deaths (95% uncertainty interval, 0.4 to 0.7) and

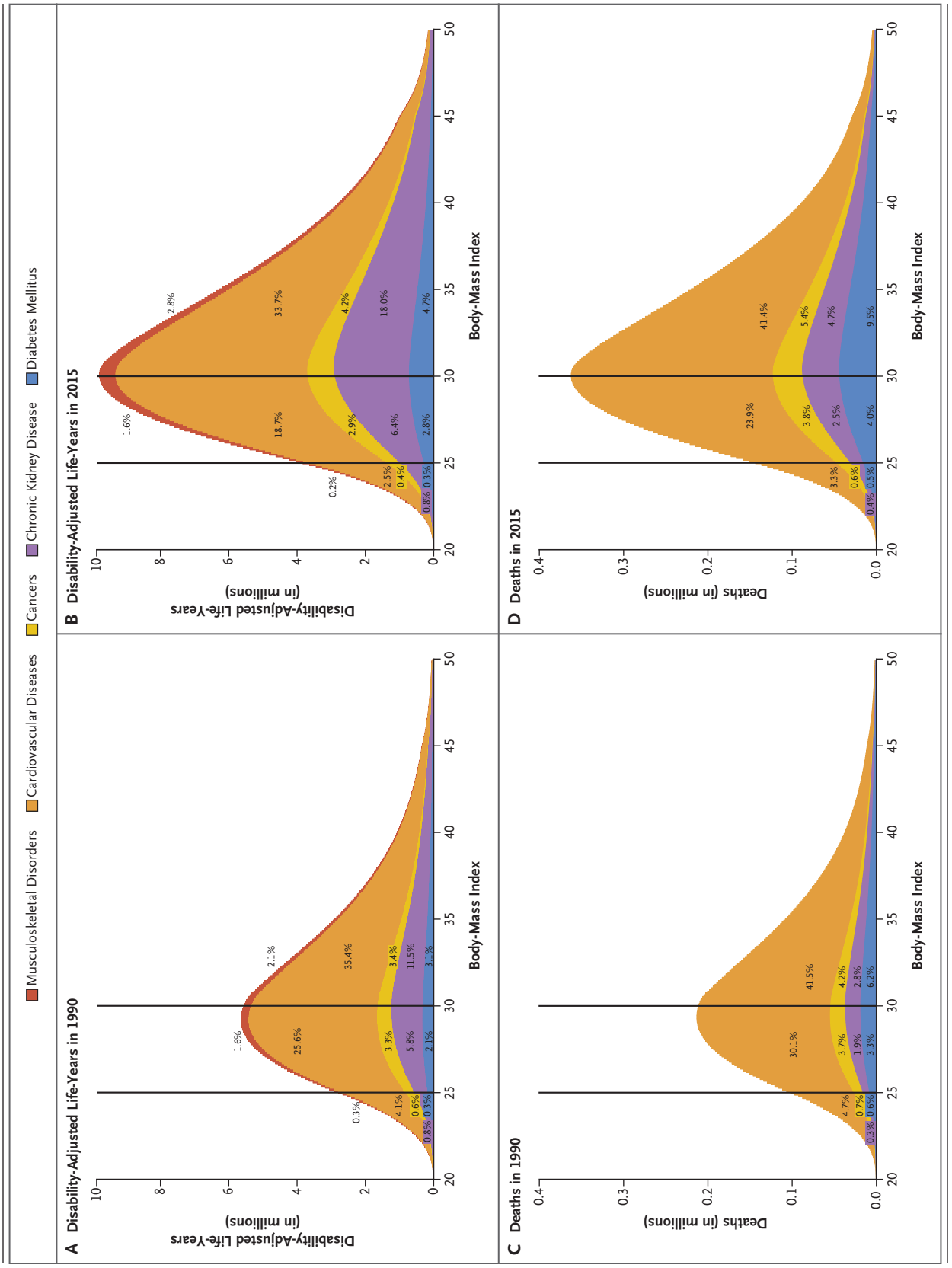


Figure 3 (facing page). Global Disability-Adjusted Life-Years and Deaths Associated with a High Body-Mass Index (1990–2015).

Shown are the number of global disability-adjusted life-years (in millions) related to a high body-mass index (BMI) among adults according to the cause and the level of BMI in 1990 (Panel A) and in 2015 (Panel B) and the number of global deaths (in millions) related to high BMI in 1990 (Panel C) and in 2015 (Panel D). The two vertical lines mark the BMI thresholds for overweight (25 to 29) and for obesity (≥30). The percentages indicate the proportion of the total number of disability-adjusted life-years or deaths that were contributed by each of the listed disorders.

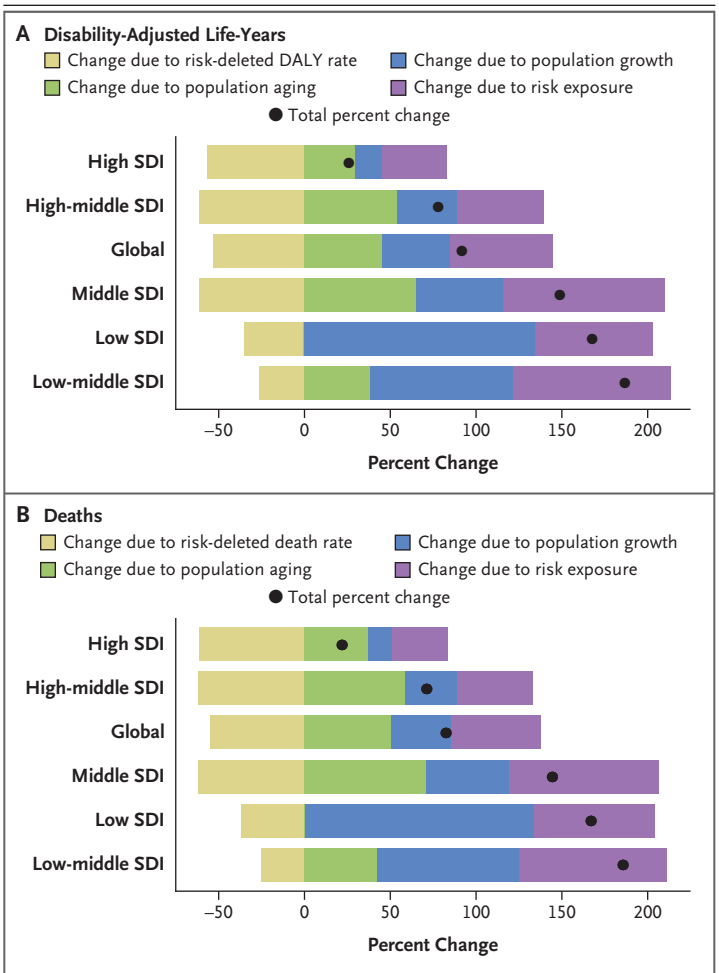


Figure 4. Percent Changes and Drivers of Change in Disability-Adjusted Life-Years and Deaths at the Global Level, According to SDI (1990–2015).

Shown is a breakdown in percent changes from 1990 to 2015 in disability-adjusted life-years (DALYs) from any cause (Panel A) and deaths (Panel B) related to a high BMI, according to whether the changes were attributed to population aging, population growth, exposure to high BMI, or risk-deleted rates of disability-adjusted life-years or death. (Risk-deleted rates are the underlying rates of disease that would have occurred in the absence of the risk factor.) The percent changes have been estimated according to SDI as well as at the global level. The black circles indicate the total percent change.

30.4 million disability-adjusted life-years (95% uncertainty interval, 21.5 to 39.9); among all BMI-related deaths that were due to diabetes, 9.5% occurred at a BMI of 30 or more and 4.5% occurred at a BMI of less than 30. Chronic kidney disease was the second leading cause of BMI-related disability-adjusted life-years in 2015; 18.0% of disability-adjusted life-years occurred at a BMI of 30 or more and 7.2% at a BMI of less than 30. Chronic kidney disease and cancers each accounted for less than 10% of all BMI-related deaths in 2015, whereas cancers, diabetes, and musculoskeletal disorders each contributed less than 10% of BMI-related disability-adjusted life-years (Fig. 3).

High BMI also accounted for 28.6 million years lived with disability (95% uncertainty interval, 17.8 to 41.4), which accounted for 3.6% (95% uncertainty interval, 2.7 to 4.6) of years lived with disability due to any cause globally. Diabetes was the leading cause of years lived with disability related to BMI (17.1 million; 95% uncertainty interval, 10.6 to 24.4), followed by musculoskeletal disorders (5.7 million; 95% uncertainty interval, 3.4 to 8.8) and cardiovascular disease (3.3 million; 95% uncertainty interval, 2.0 to 4.9).

From 1990 through 2015, there was a relative increase of 28.3% in the global rate of death related to high BMI, from 41.9 deaths per 100,000 population in 1990 to 53.7 deaths per 100,000 population in 2015. However, there was no significant change in age-standardized rates of death during this period, with a rate of 64.0 (95% uncertainty interval, 41.7 to 89.7) per 100,000 population in 1990 and 60.2 (95% uncertainty interval, 41.4 to 81.5) per 100,000 population in 2015. Similarly, during the same period, there was a relative increase of 35.8% in the rate of BMI-related disability-adjusted life-years, from 1200 per 100,000 population to 1630 per 100,000 population, whereas there was no significant change in age-standardized rates. Globally, the increases in BMI-related deaths and disability-adjusted life-years due to population growth, population aging, and increasing risk exposure were partially offset by reductions in underlying rates of death and disability-adjusted life-years (Fig. 4). Of the disease end points that

were considered in this study, decreases in risk-deleted rates of death from cardiovascular disease contributed the most to this pattern. Changes that were due to the risk of exposure to elevated BMI and aging of the population were roughly equal in terms of their contribution to the percent changes in BMI-related deaths and disability-adjusted life-years globally from 1990 through 2015.

SDI Level

In 2015, the age-standardized rates of BMI-related deaths and disability-adjusted life-years were greatest in countries with high-middle SDI levels, with a rate of death of 68.1 (95% uncertainty interval, 47.1 to 91.6) per 100,000 population and a rate of disability-adjusted life-years of 1890 (95% uncertainty interval, 1330 to 2460) per 100,000 population. The rates of both measures were lowest in countries with high SDI levels, with a rate of death of 52.6 (95% uncertainty interval, 38.7 to 67.9) per 100,000 population and a rate of disability-adjusted life-years of 1530 (95% uncertainty interval, 1160 to 1920) per 100,000 population. The rate of BMI-related deaths increased between 1990 and 2015 at all SDI levels, with the highest observed rate of 90.6 (95% uncertainty interval, 65.8 to 117.3) per 100,000 population occurring in countries with a high SDI in 2005. The age-standardized rates of death in countries with high or high-middle SDI decreased between 1990 and 2015; in the lowest quintiles of SDI, age-standardized BMI-related rates of death increased. With increasing SDI levels, the contribution of risk-deleted mortality to the percent change in BMI-related deaths increased, whereas the contribution of population growth to the percent change in BMI-related deaths decreased (Fig. 4). The contribution of risk exposure to the percent change in BMI-related deaths was also generally inversely related to the SDI. Patterns in the breakdown of the sources of change in BMI-related disability-adjusted life-years were parallel to those observed for mortality. In a disease-specific breakdown, risk-deleted mortality and disability-adjusted life-years showed a declining trend for most causes across all SDI levels (Table S5 in the Supplementary Appendix). The largest decreases in the risk-deleted rates of death and disability-adjusted life-years were observed for cardiovascular disease, whereas cancers and musculoskeletal disorders showed the least decline.

National Level

In 2015, among the 20 most populous countries, the highest rates of BMI-related death and disability-adjusted life-years were observed in Russia, and the lowest rates were observed in the Democratic Republic of Congo (Fig. S3 in the Supplementary Appendix). Between 1990 and 2015, the greatest percent changes in age-standardized BMI-related deaths and disability-adjusted life-years occurred in Bangladesh, with relative increases of 133.6% (95% uncertainty interval, 66.3 to 265.7) and 139.4% (95% uncertainty interval, 77.2 to 273.0), respectively. During the same period, Turkey had the largest significant decrease in age-standardized BMI-related burden, with a decrease of 43.7% (95% uncertainty interval, 36.9 to 49.8) in deaths and 37.2% (95% uncertainty interval, 29.9 to 44.0) in disability-adjusted life-years (Table S6 in the Supplementary Appendix).

DISCUSSION

In our systematic evaluation of the health effects of high BMI, we found that excess body weight accounted for about 4 million deaths and 120 million disability-adjusted life-years worldwide in 2015. Nearly 70% of the deaths that were related to high BMI were due to cardiovascular disease, and more than 60% of those deaths occurred among obese persons. The prevalence of obesity has increased during the past three decades and at a faster pace than the related disease burden. However, both the trend and magnitude of the BMI-related disease burden vary widely across countries.

Among the leading health risks that were assessed in the Global Burden of Disease 2015 study, high BMI continues to have one of the highest rates of increase. Across levels of development, the prevalence of obesity has increased over recent decades, which indicates that the problem is not simply a function of income or wealth.[13] Changes in the food environment and food systems are probably major drivers.[18] Increased availability, accessibility, and affordability of energy-dense foods, along with intense marketing of such foods, could explain excess energy intake and weight gain among different populations.[18] The reduced opportunities for physical activity that have followed urbanization and other changes in the built environment have also been considered as potential drivers; however,

these changes generally preceded the global increase in obesity and are less likely to be major contributors.[18]

During the past decade, researchers have proposed a range of interventions to reduce obesity.[19] Among such interventions are restricting the advertisement of unhealthy foods to children, improving school meals, using taxation to reduce consumption of unhealthy foods and providing subsidies to increase intake of healthy foods, and using supply-chain incentives to increase the production of healthy foods.[19] However, the effectiveness, feasibility of widespread implementation, and sustainability of such interventions need to be evaluated in various settings. In recent years, some countries have started to implement some of these policies,[1] but no major population success has yet been shown. Many of the countries with the highest increases in the prevalence of obesity are those that have a low or middle SDI and simultaneously have high rates of other forms of malnutrition. These countries generally have limited financial resources for nutrition programs and mostly rely on external donors whose programs often preferentially target undernutrition; consequently, food security frequently takes precedence over obesity in these countries.[20] In 2013, the World Health Organization (WHO) called for zero increase in the prevalence of overweight among children and in the prevalence of obesity among adults.[21] However, given the current pace of increase and the existing challenges in implementing food policies, achieving this goal appears unlikely in the near future.

Our study showed a greater increase in the rate of exposure to high BMI than in the rate of the related disease burden. This difference was driven mainly by the decline in risk-deleted mortality, particularly for cardiovascular disease; factors such as improved treatment or changes in other risks have resulted in decreases in the rate of cardiovascular disease despite increases in BMI. Existing evidence-based policies, even if fully implemented, are unlikely to rapidly reduce the prevalence of obesity. Clinical interventions, however, have proved to be effective in controlling high levels of systolic blood pressure, cholesterol, and fasting plasma glucose — the major risk factors for cardiovascular disease.[22] The expanded use of such interventions among overweight and obese persons could effectively reduce the disease burden related to high BMI. A recent pooled cohort analysis involving 1.8 million participants showed that nearly half the excess risk for ischemic heart disease and more than 75% of the excess risk for stroke that was related to high BMI were mediated through a combination of raised levels of blood pressure, total serum cholesterol, and fasting plasma glucose.[23] Together, these findings suggest that clinical interventions to reduce the underlying rate of cardiovascular disease could substantially reduce the burden of disease related to high BMI, although maintaining a normal body weight remains necessary to achieve full benefit.

Globally, 39% of deaths and 37% of disability-adjusted life-years that were related to high BMI occurred among nonobese persons. Although some studies have suggested that overweight is associated with a lower risk of death from any cause than is a normal range of BMI (18 to 25),[2,10] recent evidence from a meta-analysis[14] and pooled analysis[9] of prospective observational studies showed a continuous increase in the risk of death associated with a BMI of more than 25. These studies are particularly notable since they addressed major sources of bias in previous studies (i.e., residual confounding due to smoking and reverse causation due to preexisting chronic disease) by restricting the analysis to persons who had never smoked and who did not have chronic diseases. In addition, the pooled-cohort analysis controlled for the same set of covariates, provided cause-specific relative risks, and evaluated the relationship between BMI and mortality across different regions. The balance of evidence thus supports our minimum risk level of 20 to 25 for BMI. At the same time, to date, there remains insufficient evidence to support the argument that the most beneficial level of BMI should vary according to geographic location or ethnic group[9] because of differences in the relationship between BMI and body-fat distribution.

We found that 5% of the disability-adjusted life-years that were related to high BMI were from musculoskeletal disorders. Although high BMI is a major risk factor contributing to years lived with disability globally, and the economic costs associated with treatment are substantial,[24] these nonfatal but debilitating health outcomes have received comparatively little policy attention. Weight loss is beneficial in the prevention and treatment of musculoskeletal pain.[25] A combina-

tion of modest weight loss and moderate exercise provides better overall improvement in musculoskeletal pain than either intervention alone[26]; however, surgical interventions may be most effective for the morbidly obese.[27]

Our systematic evaluation of prospective observational studies showed sufficient evidence supporting a causal relationship between high BMI and cancers of the esophagus, colon and rectum, liver, gallbladder and biliary tract, pancreas, breast, uterus, ovary, kidney, and thyroid, along with leukemia. A recent review by the International Agency for Research on Cancer (IARC)[4] comes to largely similar conclusions, except with respect to leukemia. (We included leukemia on the basis of a systematic review and meta-analysis of 21 prospective cohort studies.[28]) In addition, even though the IARC report acknowledged consistent inverse associations between BMI and the risk of premenopausal breast cancer, inconsistent findings from studies that evaluated the effect of waist circumference or body-weight gain resulted in the exclusion of premenopausal breast cancer from its list. However, since high BMI was the exposure of interest in our analysis, we included the protective effect of high BMI on breast cancer in premenopausal women. We did not evaluate the effect of high BMI on gastric cancer (cardia) and meningioma because of a lack of sufficient data to separately estimate the incidence and mortality of these cancers at the population level.

Our study has several important strengths. We have addressed the major limitations of previous studies by including more data sources and quantifying the prevalence of obesity among children. We also systematically evaluated the strength of evidence for the causal relationship between high BMI and health outcomes and included all BMI–outcome pairs for which sufficient evidence with respect to causal relationship was available. We used a beta distribution to characterize the distribution of BMI at the population level, a method that captures the proportion of the population with high BMI more accurately than other distributions.[12] We used the best available evidence to determine the lowest-risk BMI. We quantified the trends in high BMI and the associated disease burden across levels of development and estimated the contribution of demographic transition and epidemiologic transition to changes in BMI-related burden.

The potential limitations of our study should also be considered. We used both self-reported and measured data with respect to height and weight and corrected the bias in self-reported data using measured data at each age, sex, and geographic region. To apply a consistent definition for childhood overweight and obesity across sources, we used the definition of the International Obesity Task Force and excluded studies that used the WHO definition. We did not propagate the uncertainty in the age pattern and sex pattern that were used to split the aggregated data. We did not incorporate the uncertainty of the BMI regression coefficients in our analysis. Data were sparse for some locations, particularly in earlier years, and estimates in these locations were based on country-level covariates and regional data. We did not identify a consistent pattern in the relationship between nationally representative data and data representing only urban or rural areas and were not able to correct those data for potential bias. We did not evaluate the trends in other measures of adiposity that may better relate to specific health outcomes, including waist circumference and waist-to-hip ratio. Since we obtained the effect size of BMI on health outcomes from prospective observational studies, the possibility of confounding by lifestyle habits cannot be excluded. Our estimation of relative risks did not capture possible differences owing to ethnic group and did not account for the possibility of geographic variation in relative-risk curves or the lowest-risk BMI. In addition, these studies generally excluded people with prevalent chronic diseases from the analysis of relative-risk estimation. Thus, our estimates represent the effect of BMI among persons without underlying diseases. This issue might be particularly important for older age groups, in which the prevalence of chronic disease increases. Finally, other probable complications or forms of BMI-related burden (e.g., disease burden in children) were not included.

In conclusion, our study provides a comprehensive assessment of the trends in high BMI and the associated disease burden. Our results show that both the prevalence and disease burden of high BMI are increasing globally. These findings highlight the need for implementation of multicomponent interventions to reduce the prevalence and disease burden of high BMI.

Supported by a grant (OPP1070441) from the Bill and Melinda Gates Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Ashkan Afshin, M.D., Sc.D., Mohammad H. Forouzanfar, Ph.D., M.D., Marissa B. Reitsma, B.S., Patrick Sur, B.A., Kara Estep, M.P.A., Alex Lee, B.A., Laurie Marczak, Ph.D., Ali H. Mokdad, Ph.D., Maziar Moradi-Lakeh, M.D., Ph.D., Mohsen Naghavi, M.D., Ph.D., Joseph S. Salama, M.Sc., Theo Vos, Ph.D., Kalkidan H. Abate, M.S., Cristiana Abbafati, Ph.D., Muktar B. Ahmed, M.P.H., Ziyad Al-Aly, M.D., Ala'a Alkerwi, Ph.D., Rajaa Al-Raddadi, Ph.D., Azmeraw T. Amare, M.P.H., Alemayehu Amberbir, Ph.D., Adeladza K. Amegah, Ph.D., 0000-0001-9647-0047Erfan Amini, M.D., Stephen M. Amrock, M.D., Ranjit M. Anjana, M.D., Ph.D., Johan Ärnlöv, Ph.D., Hamid Asayesh, Ph.D., Amitava Banerjee, D.Phil., Aleksandra Barac, M.D., Ph.D., Estifanos Baye, M.P.H., Derrick A. Bennett, Ph.D., Addisu S. Beyene, M.P.H., Sibhatu Biadgilign, M.P.H., Stan Biryukov, B.S., Espen Bjertness, Ph.D., Dube J. Boneya, M.P.H., Ismael Campos-Nonato, M.D., Juan J. Carrero, Ph.D., Pedro Cecilio, M.S., Kelly Cercy, B.A., Liliana G. Ciobanu, M.S., Leslie Cornaby, B.S., Solomon A. Damtew, M.P.H., Lalit Dandona, M.D., Rakhi Dandona, Ph.D., Samath D. Dharmaratne, M.D., Bruce B. Duncan, Ph.D., Babak Eshrati, Ph.D., Alireza Esteghamati, M.D., Valery L. Feigin, M.D., Ph.D., João C. Fernandes, Ph.D., Thomas Fürst, Ph.D., Tsegaye T. Gebrehiwot, M.P.H., Audra Gold, M.Sc., Philimon N. Gona, Ph.D., Atsushi Goto, M.D., Ph.D., Tesfa D. Habtewold, M.S., Kokeb T. Hadush, M.P.H., Nima Hafezi-Nejad, M.D., Simon I. Hay, D.Sc., Masako Horino, M.P.H., Farhad Islami, M.D., Ph.D., Ritul Kamal, M.Sc., Amir Kasaeian, Ph.D., Srinivasa V. Katikireddi, Ph.D., Andre P. Kengne, Ph.D., Chandrasekharan N. Kesavachandran, Ph.D., Yousef S. Khader, Sc.D., Young-Ho Khang, M.D., Ph.D., Jagdish Khubchandani, Ph.D., Daniel Kim, M.D., Dr.P.H., Yun J. Kim, M.D., Ph.D., Yohannes Kinfu, Ph.D., Soewarta Kosen, M.D., Tiffany Ku, B.A., Barthelemy Kuate Defo, Ph.D., G. Anil Kumar, Ph.D., Heidi J. Larson, Ph.D., Mall Leinsalu, Ph.D., Xiaofeng Liang, M.D., Stephen S. Lim, Ph.D., Patrick Liu, B.A., Alan D. Lopez, Ph.D., Rafael Lozano, Ph.D., Azeem Majeed, M.D., Reza Malekzadeh, M.D., Deborah C. Malta, Ph.D., Mohsen Mazidi, Ph.D., Colm McAlinden, M.D., Ph.D., Stephen T. McGarvey, Ph.D., Desalegn T. Mengistu, M.S., George A. Mensah, M.D., 0000-0001-6268-5998Gert B.M. Mensink, Ph.D., Haftay B. Mezgebe, M.S., Erkin M. Mirrakhimov, Ph.D., Ulrich O. Mueller, M.D., Ph.D., Jean J. Noubiap, M.D., Carla M. Obermeyer, D.C.A., Felix A. Ogbo, M.P.H., M.D., Mayowa O. Owolabi, Dr.Med., George C. Patton, M.D., Farshad Pourmalek, M.D., Ph.D., Mostafa Qorbani, Ph.D., Anwar Rafay, M.S., Rajesh K. Rai, M.P.H., Chhabi L. Ranabhat, Ph.D., Nikolas Reinig, B.S., Saeid Safiri, Ph.D., Joshua A. Salomon, Ph.D., Juan R. Sanabria, M.D., Itamar S. Santos, M.D., Ph.D., Benn Sartorius, Ph.D., Monika Sawhney, Ph.D., Josef Schmidhuber, Ph.D., Aletta E. Schutte, Ph.D., Maria I. Schmidt, M.D., Sadaf G. Sepanlou, M.D., Ph.D., Moretza Shamsizadeh, M.P.H., Sara Sheikhbahaei, M.D., Min-Jeong Shin, Ph.D., Rahman Shiri, Ph.D., Ivy Shiue, Ph.D., Hirbo S. Roba, M.P.H., Diego A.S. Silva, Ph.D., Jonathan I. Silverberg, M.D., Ph.D., Jasvinder A. Singh, M.D., Saverio Stranges, M.D., Ph.D., Soumya Swaminathan, M.D., Rafael Tabarés-Seisdedos, Ph.D., M.D., Fentaw Tadese, M.P.H., Bemnet A. Tedla, B.S., Balewgizie S. Tegegne, M.P.H., Abdullah S. Terkawi, M.D., J.S. Thakur, M.D., Marcello Tonelli, M.D., Roman Topor-Madry, Ph.D., Stefanos Tyrovolas, Ph.D., Kingsley N. Ukwaja, M.D., Olalekan A. Uthman, Ph.D., Masoud Vaezghasemi, Ph.D., Tommi Vasankari, M.D., Ph.D., Vasiliy V. Vlassov, M.D., Stein E. Vollset, M.D., Dr.P.H., Elisabete Weiderpass, Ph.D., Andrea Werdecker, Ph.D., Joshua Wesana, M.P.H., Ronny Westerman, Ph.D., Yuichiro Yano, M.D., Ph.D., Naohiro Yonemoto, M.P.H., Gerald Yonga, M.D., Zoubida Zaidi, Ph.D., M.D., Zerihun M. Zenebe, M.S., Ben Zipkin, B.S., and Christopher J.L. Murray, M.D., D.Phil.

The authors' affiliations are as follows: the University of Washington, Institute for Health Metrics and Evaluation, Seattle (A. Afshin, M.H.F., M.B.R., P.S., K.E., A.L., L.M., A.H.M., M.M.-L., M.N., J.S.S., T. Vos, S. Biryukov, K.C., L.C., L.D., R.D., V.L.F., A. Gold, S.I.H., T.K., H.J.L., S.S.L., P.L., N.R., S.E.V., B.Z., C.J.L.M.); Jimma University, Jimma (K.H.A., M.B.A., T.T.G.), Wollo University, Department of Public Health, Dessie (E. Baye, F.T.), Haramaya University, College of Health and Medical Sciences, Harar (A.S.B., H.S.R., B.S.T.), Independent Public Health Consultants (S. Biadgilign), Addis Ababa University (S.A.D.), Addis Ababa, Wolaita Sodo University, College of Health Sciences and Medicine, Wolaita (S.A.D.), Ambo University, Ambo (K.T.H.), Debre Markos University, Department of Public Health, Debre Markos (D.J.B.), Mekelle University, Mekelle (D.T.M., H.B.M., Z.M.Z.), University of Gondar, Gondar (B.A.T.), Debre Berhan University, Debre Berhan (T.D.H.), and Bahir Dar University, College of Medicine and Health Sciences, Bahir Dar (A.T.A.) — all in Ethiopia; Sapienza University of Rome (C.A.), and Food and Agriculture Organization, Global Perspective Studies Unit (J. Schmidhuber), Rome; Washington University School of Medicine, St. Louis (Z.A.-A.); Luxembourg Institute of Health, Department of Population Health, Strassen (A. Alkerwi, S. Stranges); Joint Program of Family and Community Medicine, Jeddah (R.A.-R.), and King Fahad Medical City, Department of Anesthesiology, Riyadh (A.S.T.) — both in Saudi Arabia; the University of Adelaide, School of Medicine, Adelaide, SA (A.T.A., L.G.C.), University of Canberra, Centre for Research and Action in Public Health, Canberra, ACT (Y.K.), University of Melbourne, Melbourne School of Population and Global Health, Melbourne, VIC (A.D.L.), University of Melbourne, Department of Pediatrics, Murdoch Childrens Research Institute, Melbourne, VIC (G.C.P.), Western Sydney University, Centre for Health Research–School of Medicine, Sydney, NSW (F.A.O.), James Cook University, Cairns, QLD (B.A.T.), and Monash University, School of Public Health and Preventive Medicine, Melbourne, VIC (E. Baye) — all in Australia; University of Cape Coast, Cape Coast, Ghana (A.K.A.); Tehran University of Medical Sciences, Uro-Oncology Research Center (E.A.), Endrocrinology and Metabolism Population Sciences Institute (A.K.), Endocrinology and Metabolism Research Center (A.E., N.H.-N., S. Sheikhbahaei), Digestive Diseases Research Institute (R.M., S.G.S.), Non-Communicable Diseases Research Center (E.A.), Hematology-Oncology and Stem Cell Transplantation Research Center (A.K.), Iran University of Medical Sciences, Department of Community Medicine, Gastrointestinal and Liver Disease Research Center, Preventative Medicine and Public Health Research Center (M.M.-L.), Tehran, Qom University of Medical Sciences, Department of Medical Emergency, Qom (H.A.), Arak University of Medical Sciences, Arak (B.E.), Shiraz University of Medical Sciences, Non-Communicable Diseases Research Center, Shiraz (R.M.), Alborz University of Medical Sciences, Non-Communicable Diseases Research Center, Karaj (M.Q.), Maragheh University of Medical Sciences, Managerial Epidemiology Research Center, Department of Public Health, School of Nursing and Midwifery, Maragheh (S. Safiri), and Hamadan University of Medical Sciences, Department of Medical Surgical Nursing, School of Nursing and Midwifery, Hamadan (M. Shamsizadeh) — all in Iran; Dignitas International, Zomba, Malawi (A. Amberbir); Oregon Health and Science University, Portland (S.M.A.); Madras Diabetes Research Foundation, Chennai (R.M.A.), Dr. Mohans Diabetes Specialities Centre, Chennai (R.M.A.), Public Health Foundation of India, Gurgaon (L.D., R.D., G.A.K.,), Indian Council of Medical Research, Chennai (S. Swaminathan), CSIR-Indian Institute of Toxicology Research, Epidemiology Division, Lucknow (R.K., C.N.K.), Society for Health and Demographic Surveillance, Suri (R.K.R.), and Post Graduate Institute of Medical Education and Research, School of Public Health, Chandigarh (J.S.T.) — all in India; Dalarna University, School of Health and Social Sciences, Falun (J.Å.), Karolinska Institutet, Department of Medical Epidemiology and Biostatistics (J.J.C., E.W.), Karolinska Institutet,

Department of Neurobiology, Care Sciences and Society, Division of Family Medicine and Primary Care (J.Å.), Stockholm, Södertörn University, Stockholm Center for Health and Social Change, Huddinge (M.L.), Umeå University, Department of Public Health and Clinical Medicine, Umea (M.V.) — all in Sweden; University College London, Farr Institute of Health Informatics Research (A. Banerjee), Imperial College London, Department of Primary Care and Public Health (A.M.), Imperial College London, Department of Infectious Disease Epidemiology (T.F.), and London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology (H.J.L.), London, University of Oxford, Nuffield Department of Population Health (D.A.B.), and University of Oxford, Oxford Big Data Institute, Li Ka Shing Centre for Health Information and Discovery (S.I.H.), Oxford, University of Glasgow, MRC/CSO Social and Public Health Sciences Unit, Glasgow (S.V.K.), University Hospitals Bristol NHS Foundation Trust, Bristol (C.M.), Public Health Wales, Swansea (C.M.), Northumbria University, Faculty of Health and Life Sciences, Newcastle upon Tyne (I.S.), University of Edinburgh, Alzheimer Scotland Dementia Research Centre, Edinburgh (I.S.), and University of Warwick, Warwick Centre for Applied Health Research and Delivery, Division of Health Sciences, Warwick Medical School Coventry (O.A.U.) — all in the United Kingdom; University of Belgrade, Faculty of Medicine, Belgrade, Serbia (A. Barac); Nevada Division of Public and Behavioral Health, Bureau of Child, Family and Community Wellness, Carson City (M.H.); University of Oslo, Department of Community Medicine and Global Health (E. Bjertness), and Institute of Population-Based Cancer Research, Department of Research, Cancer Registry of Norway (E.W.), Oslo, Norwegian Institute of Public Health and Department of Global Public Health and Primary Care, University of Bergen (S.E.V.), Bergen, and University of Tromsø, Arctic University of Norway, Department of Community Medicine, Tromsø (E.W.) — all in Norway; National Institute of Public Health, Cuernavaca, Mexico (I.C.-N., R.L.); Universidade do Porto, Departamento de Ciências Biológicas, Faculdade de Farmácia (P.C.), Catholic University of Portugal, Center for Biotechnology and Fine Chemistry–Associate Laboratory, Faculty of Biotechnology (J.C.F.), and Independent Collaborator (P.C.) — all in Porto, Portugal; University of Peradeniya, Department of Community Medicine, Faculty of Medicine, Peradeniya, Sri Lanka (S.D.D.); Universidade Federal do Rio Grande do Sul, Porto Alegre (B.B.D., M.I.S.), Universidade Federal de Minas Gerais, Minas Gerais (D.C.M.), University of São Paulo, São Paulo (I.S.S.), and Federal University of Santa Catarina, Florianopolis (D.A.S.S.) — all in Brazil; National Institute for Stroke and Applied Neurosciences, Auckland University of Technology, Auckland, New Zealand (V.L.F.); University of Massachusetts Boston (P.N.G.), Northeastern University, Department of Health Sciences (D.K.), and Harvard University, Harvard T.H. Chan School of Public Health (I.C.-N.), Department of Global Health and Population (J.A. Salomon) — all in Boston; National Cancer Center, Division of Epidemiology, Center for Public Health Sciences, Tokyo (A. Goto), and Kyoto University, Department of Biostatistics, School of Public Health, Kyoto (N.Y.) — both in Japan; University of Groningen (T.D.H.), University Medical Centrum Groningen (B.S.T.), Groningen, the Netherlands; American Cancer Society, Surveillance and Health Services Research, Atlanta (F.I.); South African Medical Research Council (A.P.K., A.E.S., B.S.), Groote Schuur Hospital and University of Cape Town (J.J.N.), University of Cape Town (A.P.K.), Cape Town, North-West University, Hypertension in Africa Research Team, Potchefstroom (A.E.S.), and University of KwaZulu-Natal, Public Health Medicine, School of Nursing and Public Health, Durban (B.S.) — all in South Africa; Jordan University of Science and Technology, Department of Community Medicine, Public Health and Family Medicine, Irbid, Jordan (Y.S.K.); Seoul National University College of Medicine, Department of Health Policy and Management (Y.-H.K.) and Seoul National University Medical Center, Institute of Health Policy and Management (Y-.H.K.) and Korea University, Department of Public Health Sciences (M.-J.S.), Seoul, and Yonsei University, Department of Preventative Medicine, Wonju College of Medicine, Wonju (C.L.R.) — all in South Korea; Ball State University, Department of Nutrition and Health Science, Muncie, IN (J.K.); Southern University College, Faculty of Chinese Medicine, Johor, Malaysia (Y.J.K.); National Institute of Health Research and Development, Jakarta, Indonesia (S.K.); University of Montreal, Departments of Social and Preventive Medicine, and Demography and the Public Health Research Institute, School of Public Health, Montreal (B.K.D.), University of British Columbia, Vancouver (F.P.), Western University, Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, London, ON (S. Stranges), and University of Calgary, Calgary, AB (M.T.) — all in Canada; Chinese Academy of Sciences, Key State Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology (M.M.), Chinese Center for Disease Control and Prevention (X.L.), Beijing; Brown University School of Public Health, Providence, RI (S.T.M.); National Institutes of Health, Center for Translation Research and Implementation Science, National Heart, Lung, and Blood Institute, Bethesda, MD (G.A.M.); Robert Koch Institute, Department of Epidemiology and Health Monitoring, Berlin (G.B.B.M.), and Federal Institute for Population Research, Wiesbaden (U.O.M., A.W., R.W.) — both in Germany; National Center of Cardiology and Internal Disease and Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan (E.M.M.); American University of Beirut, Center for Research on Population and Health, Faculty of Health Sciences, Beirut, Lebanon (C.M.O.); University of Ibadan, Department of Medicine, and Blossom Specialist Medical Center, Ibadan (M.O.O.), and Federal Teaching Hospital, Department of Internal Medicine, Abakaliki (K.N.U.) — both in Nigeria; Contech School of Public Health, Lahore, Pakistan (A.R.); Case Western Reserve University School of Medicine, Comprehensive Cancer Center (J.R.S.), and Cleveland Clinic, Outcomes Research Consortium (A.S.T.), Cleveland; the Department of Public Health (M. Sawhney), and the Joan C. Edwards School of Medicine (J.R.S.), Marshall University, Huntington, WV; Finnish Institute of Occupational Health (R.S.) and Folkhälsan Research Center, Genetic Epidemiology Group (E.W.), Helsinki, and the UKK Institute for Health Promotion Research, Tampere (T. Vasankari) — all in Finland; Feinberg School of Medicine (J.I.S.) and Department of Preventive Medicine, Northwestern University (Y.Y.), Chicago; University of Alabama at Birmingham, Birmingham (J.A. Singh); University of Valencia, Department of Medicine, Valencia (R.T.-S.), and Universitat de Barcelona, CIBERSAM, Parc Sanitari Sant Joan de Deu, Fundació Sant Joan de Déu, Barcelona (S.T.) — both in Spain; Department of Anesthesiology, University of Virginia, Charlottesville (A.S.T.); Jagiellonian University Medical College, Institute of Public Health, Faculty of Health Sciences, Krakow, and Wroclaw Medical University, Faculty of Health Sciences, Wroclaw (R.T.-M.) — both in Poland; National Research University Higher School of Economics, Moscow (V.V.V.); Ghent University, Faculty of Bioscience Engineering, Ghent, Belgium (J.W.); Aga Khan University, East Africa, NCD Research to Policy Unit, Nairobi, Kenya (G.Y.); University Hospital, Setif, Algeria (Z.Z.); Swiss Tropical and Public Health Institute, Department of Epidemiology and Public Health, and University of Basel, Basel (T.F.) — both in Switzerland; National Institute for Health Development, Tallinn, Estonia (M.L.); and Health Science Foundation and Study Center, Kathmandu, Nepal (C.L.R.).

REFERENCES

1. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet 2015;385:2400-9.
2. Singh GM, Danaei G, Farzadfar F, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLoS One 2013;8(7):e65174.
3. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011;377:1085-95.
4. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer — viewpoint of the IARC Working Group. N Engl J Med 2016;375:794-8.
5. Jiang L, Rong J, Wang Y, et al. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2011;78:150-5.
6. Jiang L, Tian W, Wang Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79:291-7.
7. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016;387:1377-96.
8. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766-81.
9. Di Angelantonio E, Bhupathiraju ShN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-86.
10. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71-82.
11. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA 2014;311:183-92.
12. Ng M, Liu P, Thomson B, Murray CJL. A novel method for estimating distributions of body mass index. Popul Health Metr 2016;14:6.
13. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1659-724.
14. Xia X, Chen W, Li J, et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Scientific Reports. December 15, 2014 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265780/).
15. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.
16. Estimating attributable burden of disease from exposure and hazard data — comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization, 2004:2129-40.
17. Das Gupta P. Standardization and decomposition of rates: a user's manual. Washington, DC: Bureau of the Census, 1993.
18. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378:804-14.
19. Hawkes C, Smith TG, Jewell J, et al. Smart food policies for obesity prevention. Lancet 2015;385:2410-21.
20. Global nutrition policy review: what does it take to scale up nutrition action? Geneva: World Health Organization, 2013.
21. Comprehensive implementation plan on maternal, infant, and young child nutrition. Geneva: World Health Organization, 2014 (http://apps.who.int/iris/bitstream/10665/113048/1/WHO_NMH_NHD_14.1_eng.pdf?ua=1).
22. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388-98.
23. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. Lancet 2014;383:970-83.
24. Kleinman N, Abouzaid S, Andersen L, Wang Z, Powers A. Cohort analysis assessing medical and nonmedical cost associated with obesity in the workplace. J Occup Environ Med 2014;56:161-70.
25. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women: the Framingham Study. Ann Intern Med 1992;116:535-9.
26. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004;50:1501-10.
27. Peltonen M, Lindroos AK, Torgerson JS. Musculoskeletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. Pain 2003;104:549-57.
28. Castillo JJ, Reagan JL, Ingham RR, et al. Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. Leuk Res 2012;36:868-75.

Annals of Internal Medicine | ARTICLE

Body Mass Index and Risk for End-Stage Renal Disease

Chi-yuan Hsu, MD, MSc; Charles E. McCulloch, PhD; Carlos Iribarren, MD, MPH, PhD; Jeanne Darbinian, MPH; and Alan S. Go, MD

Background: Although interest in the relationship between obesity and kidney disease is increasing, few epidemiologic studies have examined whether excess weight is an independent risk factor for end-stage renal disease (ESRD).

Objective: To determine the association between increased body mass index (BMI) and risk for ESRD.

Design: Historical (nonconcurrent) cohort study.

Setting: A large integrated health care delivery system in northern California.

Participants: 320 252 adult members of Kaiser Permanente who volunteered for screening health checkups between 1964 and 1985 and who had height and weight measured.

Measurements: The authors ascertained ESRD cases by matching data with the U.S. Renal Data System registry through 2000.

Results: A total of 1471 cases of ESRD occurred during 8 347 955 person-years of follow-up. Higher BMI was a risk factor for ESRD in multivariable models that adjusted for age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, urinalysis proteinuria, urinalysis hematuria, and serum creatinine level. Compared with persons who had normal weight (BMI, 18.5 to 24.9 kg/m^2), the adjusted relative risk for ESRD was 1.87 (95% CI, 1.64 to 2.14) for those who were overweight (BMI, 25.0 to 29.9 kg/m^2), 3.57 (CI, 3.05 to 4.18) for those with class I obesity (BMI, 30.0 to 34.9 kg/m^2), 6.12 (CI, 4.97 to 7.54) for those with class II obesity (BMI, 35.0 to 39.9 kg/m^2), and 7.07 (CI, 5.37 to 9.31) for those with extreme obesity (BMI $\geq$ 40 kg/m^2). Higher baseline BMI remained an independent predictor for ESRD after additional adjustments for baseline blood pressure level and presence or absence of diabetes mellitus.

Limitations: Primary analyses were based on single measurements of exposures.

Conclusions: High BMI is a common, strong, and potentially modifiable risk factor for ESRD.

Ann Intern Med. 2006;144:21-28. www.annals.org

For author affiliations, see end of text.

The increasing prevalence of end-stage renal disease (ESRD), with its associated high annual rates of mortality and cardiovascular complications, is a worldwide problem. In the United States alone, the prevalence of ESRD has more than doubled in the past decade (1), and the population living with ESRD is projected to increase to 650 000 persons by the year 2010, with associated Medicare expenditures of $28 billion (2). Identifying new and potentially modifiable risk factors for ESRD is critical in order to devise effective, population-based preventive strategies.

Obesity is also a major worldwide public health problem (3). However, few studies have examined the relationship between excess weight and risk for ESRD (4–8). Previous studies have shown that obese patients are at higher risk for glomerulomegaly and focal segmental glomerulosclerosis (9–11). Studies have also reported that obesity was associated with more rapid loss of renal function among patients who underwent uninephrectomy (12) or who have IgA nephropathy (13).

We examined the hypothesis that overweight and obesity are risk factors for developing ESRD among a large, community-based sample of men and women.

METHODS

Study Sample

Our study is based on a large, well-characterized cohort of members of Kaiser Permanente of Northern California who participated in a Multiphasic Health Testing Services Program in Oakland and San Francisco medical centers between 1964 and 1985 (14). Kaiser Permanente of Northern California is a large, integrated health care delivery system that currently cares for more than 35% of the insured adult population in the greater San Francisco Bay area (15). The Multiphasic Health Checkup was a voluntary health assessment offered at initial and yearly open enrollment periods (14). Analyzable data were available for 3 Multiphasic Health Checkup periods: June 1964 to August 1973, September 1973 to December 1977, and January 1978 to March 1985.

We studied all individuals who participated in the Multiphasic Health Checkups from 1964 to 1985; who were 18 years of age or older; and who had at least 1 concurrent measurement (that is, done at the same visit) of height, weight, blood pressure, serum creatinine level, and dipstick urinalysis. We excluded persons who had a baseline serum creatinine level greater than 884 μmol/L (>10 mg/dL) because they might already have ESRD. The final study sample included 320 252 eligible persons.

Institutional review boards at the collaborating institutions approved the study. Because of the low-risk nature of

See also:

Print
Editors' Notes 22
Summary for Patients I-28

Web-Only
Conversion of figure and tables into slides

Context

Few studies have asked whether obesity affects the risk for end-stage renal disease (ESRD).

Contribution

In this retrospective cohort study of 320 252 adults who were followed for 15 to 35 years, the rate of ESRD increased in a stepwise manner as body mass index (BMI) increased. Age-, sex-, and race-adjusted rates of ESRD increased from 10 per 100 000 person-years among those with normal weight (BMI, 18.5 to 24.9 kg/m^2) to 108 per 100 000 among those with extreme obesity (BMI ≥ 40 kg/m^2). This relationship was not affected by blood pressure levels or diabetes.

Cautions

Body mass index and potential confounders were measured only at baseline.

Implications

High BMI is a potentially modifiable risk factor for ESRD.

—The Editors

our study and the use of existing data, the need for obtaining informed consent was waived.

Assessment of Obesity

We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared. Following National Heart, Lung, and Blood Institute guidelines (7), we defined overweight as a BMI of 25.0 to 29.9 kg/m^2, class I obesity as a BMI of 30.0 to 34.9 kg/m^2, class II obesity as a BMI of 35.0 to 39.9 kg/m^2, and class III obesity (extreme) as a BMI of 40 kg/m^2 or greater. Underweight was defined as a BMI less than 18.5 kg/m^2. We conducted all analyses relative to a normal BMI (18.5 to 24.9 kg/m^2).

Assessment of Covariates

We obtained information about relevant covariates (such as history of myocardial infarction) from self-completed questionnaires administered within 45 days of laboratory tests. Medical history data were not available in an electronic format for participants from the second period (September 1973 to December 1977), and we classified these persons as missing those data elements.

We classified self-reported race as white, black, Asian, or other. We categorized education level as high school or less, some college, or college graduate or higher. We classified cigarette smoking status as never, former, or current (14). Dipstick urinalysis quantified urine protein as negative, trace, 1+ to 2+, or 3+ to 4+ and urine hemoglobin as negative, small, moderate, or large.

We measured sitting blood pressure once on the basis of the acoustic detection of the onset (systolic point) and disappearance (diastolic point) of Korotkoff sounds. We classified participants' blood pressure by using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) criteria for normal (systolic blood pressure < 120 mm Hg and diastolic blood pressure < 80 mm Hg), prehypertension (systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg), stage 1 hypertension (systolic blood pressure of 140 to 159 mm Hg or diastolic blood pressure of 90 to 99 mm Hg), and stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg) (16).

Information available for defining the presence or absence of diabetes mellitus varied across the 3 periods. Participant self-report of diagnosis or treatment of diabetes was available in the first and third periods. Blood glucose measurements were available for all periods but were done in the context of oral glucose challenge tests during the first period. We defined diabetes mellitus initially by either self-report or blood glucose measurement of 11.1 mmol/L or greater (≥200 mg/dL). We then considered several alternative definitions of diabetes in sensitivity analyses, including relying on only self-report (using data from the first and third periods), relying on only blood glucose measurements that were done outside the context of oral glucose challenge tests (from the first and third periods), and using 11.1 mmol/L (200 mg/dL) or 7.0 mmol/L (126 mg/dL) as the cutoff value to define the presence of diabetes mellitus.

Identification of Outcomes of ESRD and Death

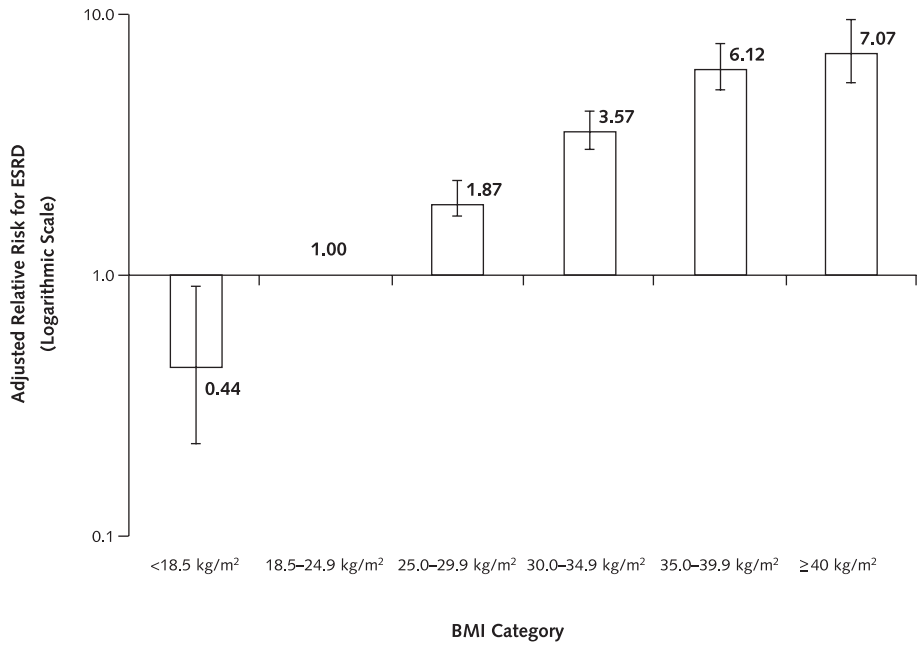
We defined ESRD as the receipt of renal transplantation or maintenance hemodialysis or peritoneal dialysis. We identified cases of ESRD by matching our cohort against the nationally comprehensive U.S. Renal Data System registry data (1). We performed matching, blinded to exposure status, by using Social Security number, first and last name, sex, and date of birth. We ascertained deaths by using the California Automated Mortality Linkage System, which has a sensitivity of 97% and a specificity of 93% compared with the U.S. National Death Index (17). We assessed both ESRD and death through 31 December 2000, the most recent date that data were available for both outcomes when this project was initiated.

We calculated person-years as years from baseline (date of Multiphasic Health Checkup) until death, development of ESRD, or the end of follow-up on 31 December 2000, whichever occurred first.

Statistical Analysis

We based main analyses on data collected at the first eligible Multiphasic Health Checkup examination for each person. We calculated age-, sex-, and race-adjusted rates of ESRD by using the direct method. We analyzed the relationship between category of BMI and subsequent risk for ESRD by using time-to-event methods (18). We conducted multivariable analyses by using Cox proportional hazards models. We confirmed that the proportional hazards assumption was not violated for BMI categories and

Figure. **Adjusted relative risk for end-stage renal disease (*ESRD*) by body mass index (*BMI*).**



Model adjusted for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, hematuria, and serum creatinine level. Error bars represent 95% CIs.

risk for ESRD by using a graph of estimated ln(−ln) survival, stratified by BMI category (19). In all multivariable analyses, we adjusted for the Multiphasic Health Checkup period when baseline assessment occurred. All variables included a missing value category when needed.

Since hypertension and diabetes are likely to be intermediate variables in the pathway between increased BMI and ESRD, our main multivariable analysis did not include baseline blood pressure level or presence or absence of diabetes mellitus as exposures. We then compared this analysis with the results of multivariable analysis, which adjusted for baseline blood pressure level and presence or absence of diabetes.

We also performed stratified analyses by sex, race, age, diabetes mellitus, hypertension, and presence or absence of baseline kidney disease. Baseline kidney disease was defined as an estimated glomerular filtration rate less than 0.58 $mL \cdot s^{-2} \cdot m^{-2}$ (<60 mL/min per 1.73 m^2) calculated with the Modification of Diet in Renal Disease Study formula (20, 21) or as the presence of urinalysis proteinuria or hematuria (22). Hazard ratios are reported as relative risks.

Secondary Analysis among Persons with More than 1 Measurement of BMI

To assess the robustness of our findings, we conducted additional analyses among the subset of study cohort members who returned for at least 1 additional Multiphasic Health Checkup with repeated assessment of BMI, blood pressure, and diabetes status (n = 134 705). In this subset, we first repeated our Cox regression analyses by using only baseline exposures and then compared those findings with the results obtained by using time-dependent exposures, updating BMI and other covariates (excluding blood pressure and diabetes status) for each person.

Role of the Funding Source

The National Institutes of Health funded our study (grants HL71074 and DK61520). The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication. The authors had full access to the data files for the study.

RESULTS

The mean BMI in the study sample was 24.5 kg/m^2 (SD, 4.3) (**Table 1**). Of the participants, 58% had normal weight (BMI, 18.5 to 24.9 kg/m^2) and 39% had a BMI of 25.0 kg/m^2 or greater. Higher BMI was associated with black race, presence of diabetes mellitus, and higher blood pressure level. The higher proportion of missing data on education level, smoking status, and history of myocardial infarction was due to the fact that medical history data were not available in an electronic format for participants from the second period (September 1973 to December 1977).

A total of 1471 cases of ESRD (and 56 336 deaths) occurred during 8 347 955 person-years of observation. We found a stepwise increase in the rate of ESRD with higher BMI (**Table 2**). The age-, sex-, and race-adjusted

Table 1. **Baseline Characteristics of 320 252 Adults Stratified by Baseline Body Mass Index***

Characteristic	BMI Category					
	Underweight (*n* = 10 352)	Normal Weight (*n* = 186 730)	Overweight (*n* = 93 357)	Class I Obesity (*n* = 21 856)	Class II Obesity (*n* = 5540)	Class III Obesity (*n* = 2417)
BMI, *kg/m²*	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0
Mean (SD) height, *cm*	164.9 (8.7)	167.5 (9.6)	169.6 (9.8)	167.6 (10.0)	165.1 (10.4)	162.3 (11.8)
Mean (SD) weight, *kg*	48.1 (5.5)	62.4 (9.1)	77.9 (9.7)	89.9 (11.1)	101.3 (13.1)	116.4 (17.5)
Mean (SD) age, *y*	31 (12)	36 (13)	42 (14)	43 (14)	42 (13)	40 (13)
Women, *n (%)*	8644 (84)	112 784 (60)	35 002 (37)	11 005 (50)	3789 (68)	1915 (79)
Race, *n (%)*						
White	6285 (61)	132 647 (71)	65 021 (70)	13 414 (61)	3084 (56)	1235 (51)
Black	1766 (17)	28 982 (16)	19 193 (21)	6683 (31)	2032 (37)	1033 (43)
Asian	1499 (14)	13 048 (7)	2885 (3)	300 (1)	45 (1)	16 (1)
Other	800 (8)	11 981 (6)	6238 (7)	1446 (7)	378 (7)	133 (6)
Unknown	2 (0)	72 (0)	20 (0)	13 (0)	1 (0)	0 (0)
Education, *n (%)*						
≤High school	2895 (28)	57 820 (31)	37 473 (40)	9805 (45)	2447 (44)	1065 (44)
Some college	2629 (25)	44 860 (24)	19 722 (21)	4316 (20)	1100 (20)	538 (22)
≥College graduate	2069 (20)	38 326 (21)	15 044 (16)	2445 (11)	548 (10)	206 (9)
Unknown	2759 (27)	45 724 (24)	21 118 (23)	5290 (24)	1445 (26)	608 (25)
Cigarette smoking history, *n (%)*						
Never	3546 (34)	60 754 (33)	29 116 (31)	7320 (33)	1939 (35)	871 (36)
Former	795 (8)	22 754 (12)	15 223 (16)	3255 (15)	757 (14)	305 (12)
Current	3130 (30)	54 118 (29)	26 130 (28)	5792 (27)	1355 (24)	621 (26)
Unknown	2881 (28)	49 104 (26)	22 888 (25)	5489 (25)	1489 (27)	620 (26)
Diabetes mellitus, *n (%)*						
No	9407 (87)	156 309 (84)	74 686 (80)	17 423 (80)	4394 (79)	1916 (79)
Yes	1304 (13)	30 418 (16)	18 671 (20)	4433 (20)	1146 (21)	501 (21)
Unknown	1 (0.01)	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Previous MI, *n (%)*						
No	7685 (74)	143 412 (77)	73 027 (78)	16 587 (76)	4088 (74)	1801 (75)
Yes	145 (1)	3069 (2)	2585 (3)	702 (3)	187 (3)	78 (3)
Unknown	2522 (24)	40 249 (22)	17 745 (19)	4567 (21)	1265 (23)	538 (22)
Mean (SD) systolic BP, *mm Hg*	117 (17)	125 (18)	134 (20)	140 (22)	142 (23)	144 (24)
Mean (SD) diastolic BP, *mm Hg*	69 (12)	73 (12)	79 (13)	84 (13)	87 (15)	87 (16)
Mean (SD) serum cholesterol level						
mmol/L	5.02 (1.0)	5.34 (1.1)	5.78 (1.2)	5.88 (1.2)	5.78 (1.2)	5.67 (1.2)
mg/dL	194 (40)	206 (43)	223 (45)	227 (46)	223 (46)	219 (46)
Urine protein, *n (%)*						
Negative	9802 (95)	179 866 (96)	89 662 (96)	20 717 (95)	5141 (93)	2220 (92)
Trace	288 (3)	3805 (2)	2070 (2)	564 (3)	184 (3)	96 (4)
1–2+	223 (2)	2721 (1)	1471 (2)	497 (2)	192 (3)	89 (4)
3–4+	39 (0.4)	338 (0.2)	194 (0.2)	78 (0.4)	23 (0.4)	12 (0.5)
Urine hemoglobin, *n (%)*						
Negative	9634 (93)	177 203 (95)	89 639 (96)	20 762 (95)	5155 (93)	2232 (92)
Small	452 (4)	6456 (3)	2600 (3)	737 (3)	228 (4)	105 (4)
Moderate	155 (2)	1878 (1)	706 (1)	224 (1)	90 (2)	40 (2)
Large	111 (1)	1193 (1)	412 (0.4)	133 (1)	67 (1)	40 (2)
Mean (SD) serum creatinine level						
μmol/L	71 (18)	80 (18)	88 (18)	88 (18)	80 (27)	80 (27)
mg/dL	0.8 (0.2)	0.9 (0.2)	1.0 (0.2)	1.0 (0.2)	0.9 (0.3)	0.9 (0.3)

* BMI = body mass index; BP = blood pressure; MI = myocardial infarction.

rate of ESRD increased from 10 per 100 000 person-years among those with normal weight (BMI, 18.5 to 24.9 kg/m^2) to 108 per 100 000 person-years among those with extreme obesity (BMI $\geq$ 40 kg/m^2) (**Table 2**).

This relationship between BMI and risk for ESRD persisted in multivariable analyses after adjustment for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, urinalysis proteinuria, urinalysis hematuria, and serum creatinine level (**Figure**). Compared with persons with normal weight (BMI, 18.5 to 24.9 kg/m^2), the adjusted relative risk for ESRD was 1.87 (95% CI, 1.64 to 2.14) for those who were overweight (BMI, 25.0 to 29.9 kg/m^2), 3.57 (CI, 3.05 to 4.18) for those with class I obesity (BMI, 30.0 to 34.9 kg/m^2), 6.12 (CI, 4.97 to 7.54) for those with class II obesity (BMI, 35.0 to 39.9 kg/m^2), and 7.07 (CI, 5.37 to 9.31) for those with extreme obesity (BMI $\geq$ 40 kg/m^2). Higher BMI was independently associated with higher ESRD risk in all subgroups analyzed (**Table 3**).

Analyses that Adjusted for Baseline Blood Pressure and Diabetes Status

Additional adjustment for baseline blood pressure and presence or absence of diabetes attenuated the association between higher BMI and risk for ESRD, but the relationship remained strong. Compared with persons with normal weight (BMI, 18.5 to 24.9 kg/m^2), the adjusted relative risk for ESRD was 1.72 (CI, 1.50 to 1.96) for those who are overweight (BMI, 25.0 to 29.9 kg/m^2), 2.98 (CI, 2.54 to 3.49) for those with class I obesity (BMI, 30.0 to 34.9 kg/m^2), 4.68 (CI, 3.79 to 5.79) for those with class II obesity (BMI, 35.0 to 39.9 kg/m^2), and 4.99 (CI, 3.77 to 6.60) for those with extreme obesity (BMI $\geq$ 40 kg/m^2).

Elevated BMI remained a risk factor for ESRD if we alternatively defined diabetes mellitus status by relying on only self-report (that is, using data from only the first and third Multiphasic Health Checkup periods), with adjusted relative risks of 1.6 for those who were overweight, 2.9 for those with class I obesity, 4.2 for those with class II obesity, and 4.7 for those with extreme obesity ($P < 0.001$ for all). Elevated BMI remained a risk factor for ESRD if we alternatively defined diabetes mellitus status by using only blood glucose measurements performed outside the context of oral glucose challenge tests (that is, using data from only the second and third Multiphasic Health Checkup periods) with adjusted corresponding relative risks of 1.7, 2.2, 4.3, and 2.9, respectively ($P < 0.001$ for all). Finally, elevated BMI remained a risk factor for ESRD if we alternatively defined diabetes mellitus status by using only blood glucose measurements performed outside the context of oral glucose challenge tests (that is, using data from only the second and third Multiphasic Health Checkup periods) but using 7.0 mmol/L (126 mg/dL) instead of 11.1 mmol/L (200 mg/dL) as the cutoff value, with adjusted corresponding relative risks of 1.7, 2.1, 4.1, and 2.8, respectively ($P < 0.001$ for all).

Higher BMI also predicted risk for ESRD in analyses that excluded persons with an estimated glomerular filtration rate less than 0.14 mL $\cdot$ s^{-2} $\cdot$ m^{-2} (<15 mL/min per 1.73 m^2); in analyses that excluded participants with any missing data; in analyses that did not adjust for education level, smoking status, and history of myocardial infarction (which are the 3 covariates with the most missing data); and in analyses that were limited to each of the 3 individual Multiphasic Health Checkup periods (data not shown).

Secondary Analysis

Participants with 2 or more Multiphasic Health Checkup visits (n = 134 705) were similar to participants with only 1 Multiphasic Health Checkup visit (n = 185 547) in terms of sex distribution (55% vs. 53% women), mean BMI (24.7 kg/m^2 vs. 24.3 kg/m^2), mean blood pressure (130/77 mm Hg vs. 128/75 mm Hg), mean serum creatinine level (84.8 μmol/L [0.96 mg/dL] vs. 83.1 μmol/L [0.94 mg/dL]), and prevalence of proteinuria (4% in both groups). However, persons with more than 1 visit were more likely than those with 1 visit to be older (mean, 41 years vs. 36 years) and to have diabetes (23% vs. 14%). In this subgroup, using baseline exposure information only, we found a similar relationship between each category of increased BMI and the risk for ESRD, with relative risks of 1.8, 3.8, 6.5, and 9.3, respectively ($P < 0.001$ for all). Our results were similar when we updated BMI and other covariates in our multivariable models with relative

Table 2. **Age-, Sex-, and Race-Adjusted Rates of End-Stage Renal Disease for Each Category of Body Mass Index***

BMI Category	Persons, *n*	Mean (SD) BMI, kg/m^2	ESRD Events, *n*	Person-Years of Observation	Adjusted Rate per 100 000 Person-Years (95% CI)
Underweight (<18.5 kg/m^2)	10 352	17.6 (0.8)	8	264 280	7 (0.2–13)
Normal weight (18.5–24.9 kg/m^2)	186 730	22.1 (1.7)	414	4 921 700	10 (9–12)
Overweight (25.0–29.9 kg/m^2)	93 357	27.0 (1.4)	575	2 426 966	20 (18–22)
Class I obesity (30.0–34.9 kg/m^2)	21 856	31.9 (1.4)	291	543 835	46 (40–53)
Class II obesity (35.0–39.9 kg/m^2)	5540	37.0 (1.4)	122	134 006	76 (60–91)
Class III obesity (≥40.0 kg/m^2)	2417	44.1 (4.6)	61	57 169	108 (72–143)
Total	320 252		1471	8 347 955	

* BMI = body mass index; ESRD = end-stage renal disease.

Table 3. **Multivariable Associations between Categories of Body Mass Index and Risk for End-Stage Renal Disease in Subgroups of Participants***

Variable	Relative Risk (95% CI)					
	Underweight	Normal	Overweight	Class I Obesity	Class II Obesity	Class III Obesity
Sex						
Women	0.6 (0.3–1.2)	1.0	2.2 (1.7–2.7)	3.6 (2.8–4.6)	5.4 (4.1–7.3)	6.5 (4.6–9.3)
Men	0.2 (0.0–1.4)	1.0	1.8 (1.5–2.1)	3.6 (2.9–4.4)	7.3 (5.4–9.9)	9.4 (6.0–14.7)
Race						
Black	0.1 (0.0–1.0)	1.0	2.2 (1.8–2.7)	3.4 (2.7–4.3)	5.5 (4.1–7.5)	7.2 (5.0–10.4)
White	1.0 (0.4–2.2)	1.0	1.5 (1.2–1.8)	3.4 (2.7–4.4)	7.2 (5.2–10.0)	8.0 (5.0–12.8)
Age†						
<40 y	0.2 (0.1–0.8)	1.0	1.8 (1.4–2.2)	4.4 (3.5–5.7)	7.3 (5.3–10.1)	11.6 (8.0–16.9)
≥40 y	0.8 (0.3–2.0)	1.0	1.9 (1.6–2.2)	3.1 (2.5–3.8)	5.5 (4.2–7.2)	4.8 (3.2–7.2)
Diabetes						
Yes	1.3 (0.6–3.0)	1.0	1.9 (1.5–2.4)	3.3 (2.5–4.4)	5.0 (3.5–7.1)	3.6 (2.3–5.9)
No	0.1 (0.0–0.6)	1.0	1.9 (1.6–2.2)	3.4 (2.8–4.1)	5.7 (4.3–7.4)	7.6 (5.4–10.8)
Hypertension‡						
Yes	0.4 (0.1–1.5)	1.0	1.6 (1.3–1.9)	2.7 (2.2–3.4)	4.7 (3.7–6.1)	5.3 (3.9–7.3)
No	0.5 (0.2–1.1)	1.0	1.9 (1.6–2.3)	3.6 (2.8–4.7)	5.0 (3.3–7.5)	5.6 (3.1–10.2)
Baseline kidney disease§						
Yes	0.4 (0.1–1.3)	1.0	1.5 (1.2–2.0)	2.7 (2.0–3.6)	4.7 (3.3–6.8)	3.1 (1.8–5.3)
No	0.4 (0.2–1.0)	1.0	2.1 (1.8–2.4)	4.1 (3.4–5.0)	7.3 (5.6–9.4)	10.3 (7.5–14.1)

* Models adjusted for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, hematuria, and serum creatinine level. Body mass index (BMI) categories were as follows: underweight (BMI < 18.5 kg/m^2), normal (BMI, 18.5–24.9 kg/m^2), overweight (BMI, 25.0–29.9 kg/m^2), class I obesity (BMI, 30.0–34.9 kg/m^2), class II obesity (BMI, 35.0–39.9 kg/m^2), and class III obesity (BMI ≥ 40 kg/m^2).
† Stratified models also adjusted for age.
‡ Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.
§ Defined as an estimated glomerular filtration rate < 0.58 mL · s^{-2} · m^{-2} (<60 mL/min per 1.73 m^2) (by using the Modification of Diet in Renal Disease Study formula [20, 21]) or as the presence of urinalysis proteinuria or hematuria (22). These stratified models also adjusted for serum creatinine level and urinalysis proteinuria and hematuria.

risks of 1.7, 2.6, 4.2, and 6.5, respectively ($P < 0.001$ for all).

DISCUSSION

In our large cohort study, we observed a graded, strong relationship between the risk for ESRD and elevated BMI starting at a BMI of 25.0 kg/m^2. We consistently observed this association in men and women; younger and older persons; persons of different races; and persons with or without baseline kidney disease, diabetes, or hypertension.

Our findings are consistent with recently published data from the Framingham Offspring Study, which show that higher BMI is a risk factor for development of new-onset kidney disease (23). In that study, each SD increase in BMI was associated with an odds ratio of 1.23 (CI, 1.08 to 1.41) for "new-onset kidney disease," defined as a decrease in glomerular filtration rate to 0.57 mL · s^{-2} · m^{-2} or less (≤59 mL/min per 1.73 m^2) in women and 0.62 mL · s^{-2} · m^{-2} or less (≤64 mL/min per 1.73 m^2) in men.

Few studies have examined the association between BMI and future risk for ESRD. Perry and colleagues (8) reported no association between baseline BMI and future risk for ESRD in their study of 11 912 male veterans with hypertension. Iseki and colleagues (5, 6) found that, among 100 753 members of a screened Japanese cohort, baseline BMI predicted future risk for ESRD in men but not women. Compared with our study, these earlier studies had fewer persons with high BMI and fewer ESRD cases ($n = 245$ and 404). Stengel and colleagues (24) investigated the relationship between baseline BMI and risk for "chronic kidney disease" by using Second National Health and Nutrition Examination Survey (NHANES II) data. "Chronic kidney disease" was defined as the receipt of treatment for ESRD ($n = 44$) or "death related to chronic kidney disease" ($n = 145$) assessed by using death certificate codes of the International Classification of Diseases, Ninth Revision. They found an increased risk only for persons with a baseline BMI of 35 kg/m^2 or greater.

In contrast, we found a robust association between baseline BMI and risk for ESRD. Several possible pathophysiologic pathways may underlie this association. One possibility is that overweight patients are more likely to also have diabetes and hypertension, which are 2 well-established risk factors for ESRD. In our analysis, we found that baseline BMI remained a risk factor even after adjustment for baseline blood pressure and diabetes status. (However, as we later acknowledge, ascertainment of diabetes mellitus is not uniform in our cohort and a single

blood pressure measurement is associated with measurement error.) Another possibility is that patients with elevated BMI at baseline are more likely to develop new cases of diabetes and hypertension in the future, and these are the steps in the causal pathway linking elevated BMI to ESRD. A third possibility is that beyond high BMI being a risk factor for diabetes and hypertension, it also leads to renal failure through other mechanisms. Biopsy studies from humans have clearly established that obese patients have renal lesions that are distinct from diabetic nephropathy or hypertensive nephrosclerosis (9–11). Both animal and human studies have demonstrated that overweight leads to renal hyperperfusion and glomerular hyperfiltration, which, in turn, cause proteinuria and focal segmental glomerulosclerosis (25–31). More recently, some investigators have suggested that leptin produced from adipose tissue may directly lead to renal fibrosis (32). Although the exact mechanisms by which excessive weight leads to kidney disease are still being investigated (33, 34), our study provides epidemiologic support for their importance.

Our findings that underweight participants had the lowest risk for ESRD should be interpreted with caution, since the 95% CI for the multivariable risk estimate extended nearly to 1.0 (**Figure**). Few studies have examined the association between low body weight and future risk for renal disease (6). Ramirez and colleagues (35) noted that, among a sample of persons from Singapore, the relationship between proteinuria and BMI was J-shaped because those with a BMI of 18 kg/m^2 or less (and those with a BMI $\geq$ 25 kg/m^2) were more likely to have proteinuria than those with a BMI of 18.01 to 22.99 kg/m^2. However, because that study was cross-sectional, preceding illness may have led to both proteinuria and malnutrition.

Our study is strengthened by the broad distribution of BMI among a large, diverse sample of screened ambulatory adults with comprehensive, longitudinal follow-up for ESRD. We could also control for important clinical and sociodemographic characteristics.

A limitation of our study is that many persons had only 1 measurement of BMI. However, within-person correlation of BMI over time is high (36). In addition, we confirmed our main conclusions in the secondary analysis of the subgroup of persons (42% of the cohort) who had at least 2 determinations of BMI. As detailed, availability of data to ascertain the presence or absence of diabetes was not uniform throughout the 3 Multiphasic Health Checkup periods. However, in sensitivity analysis, the strong association between elevated BMI and risk for ESRD seemed robust to alternate definitions of diabetes mellitus. We assessed blood pressure only once, and details about the standardization of this measurement were not available. We did not have complete information on use and type of antihypertensive and hypoglycemic medications and therefore could not evaluate the extent to which medical interventions confounded the reported associations. These limitations diminished our ability to determine the extent to which hypertension and diabetes mediated the association between excess weight and kidney failure. However, we believe that the overall association between increased BMI and risk for ESRD is the important finding in our study, more so than quantifying how much of this association is independent of hypertension or diabetes. We used a missing data category in our statistical analysis, and this approach is problematic in most instances. However, since data on education level, smoking status, and history of myocardial infarction are missing because medical history data were not available in an electronic format from the second Multiphasic Health Checkup period, this represents an uncommon instance when data are missing nearly at random. Since our study was conducted among insured members of a northern California integrated health care delivery system, our results may not be generalizable to other populations. Because this is an observational study, we could not assess whether intentional weight loss will reduce the risk for ESRD. Previous studies have shown that obese persons who lose weight have a reduction of absolute glomerular filtration rate, consistent with reversal of glomerular hyperfiltration (37, 38). Other studies have shown that weight loss is associated with a decrease in proteinuria, a major risk factor for future loss of glomerular filtration rate (39).

In summary, we have identified overweight or obesity as a strong and potentially modifiable risk factor for the development of ESRD. Conversely, kidney failure should be added to the list of adverse consequences of obesity. Given the rapidly increasing incidence of obesity and ESRD in the United States and internationally (1, 40), the confluence of these 2 public health problems is alarming. Vigorous efforts are needed to combat the epidemic of obesity and its complications.

From the University of California, San Francisco, San Francisco, California, and Kaiser Permanente of Northern California, Oakland, California.

Disclaimer: Some data were supplied by the U.S. Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government.

Acknowledgment: The authors thank Mr. Shu-Cheng Chen of the U.S. Renal Data System for his assistance.

Grant Support: By the National Institutes of Health (grants HL71074 and DK61520).

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Chi-yuan Hsu, MD, MSc, Division of Nephrology, University of California, San Francisco, 513 Parnassus Avenue, 672 HSE, Box 0532, San Francisco, CA 94143-0532; e-mail, hsuchi@medicine.ucsf.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. USRDS: the United States Renal Data System. Am J Kidney Dis. 2003;42:1-230. [PMID: 14655174]

2. **Xue JL, Ma JZ, Louis TA, Collins AJ.** Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. J Am Soc Nephrol. 2001;12:2753-8. [PMID: 11729245]

3. **Ogden CL, Carroll MD, Flegal KM.** Epidemiologic trends in overweight and obesity. Endocrinol Metab Clin North Am. 2003;32:741-60, vii. [PMID: 14711060]

4. **Manson JE, Skerrett PJ, Greenland P, VanItallie TB.** The escalating pandemics of obesity and sedentary lifestyle. A call to action for clinicians. Arch Intern Med. 2004;164:249-58. [PMID: 14769621]

5. **Iseki K, Ikemiya Y, Fukiyama K.** Predictors of end-stage renal disease and body mass index in a screened cohort. Kidney Int Suppl. 1997;63:S169-70. [PMID: 9407450]

6. **Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S.** Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65:1870-6. [PMID: 15086929]

7. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults: The Evidence Report. NIH publication no. 98-4083. Bethesda, MD: National Institutes of Health; 1998.

8. **Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, et al.** Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension. 1995;25:587-94. [PMID: 7721402]

9. **Cohen AH.** Massive obesity and the kidney. A morphologic and statistical study. Am J Pathol. 1975;81:117-30. [PMID: 1180328]

10. **Kasiske BL, Crosson JT.** Renal disease in patients with massive obesity. Arch Intern Med. 1986;146:1105-9. [PMID: 3718096]

11. **Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD.** Obesity-related glomerulopathy: an emerging epidemic. Kidney Int. 2001;59:1498-509. [PMID: 11260414]

12. **Praga M, Hernández E, Herrero JC, Morales E, Revilla Y, Díaz-González R, et al.** Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. Kidney Int. 2000;58:2111-8. [PMID: 11044232]

13. **Bonnet F, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezène F, et al.** Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. Am J Kidney Dis. 2001;37:720-7. [PMID: 11273871]

14. **Collen MF, ed.** Multiphasic Health Testing Services. New York: J Wiley; 1978.

15. **Krieger N.** Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992;82:703-10. [PMID: 1566949]

16. **Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al.** Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206-52. [PMID: 14656957]

17. **Arellano MG, Petersen GR, Petitti DB, Smith RE.** The California Automated Mortality Linkage System (CAMLIS). Am J Public Health. 1984;74:1324-30. [PMID: 6507683]

18. **Fisher LD, van Belle G.** Biostatistics: A Methodology for the Health Sciences. New York: Wiley; 1996.

19. **Kalbfleisch JD, Prentice RL.** The Statistical Analysis of Failure Time Data. 2nd ed. Hoboken, NJ: Wiley-Interscience; 2002.

20. **Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D.** A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70. [PMID: 10075613]

21. **Levey AS, Greene T, Kusek JW, Beck GJ.** A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. J Am Soc Nephrol. 2000;11:155A.

22. **Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al.** National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137-47. [PMID: 12859163]

23. **Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D.** Predictors of new-onset kidney disease in a community-based population. JAMA. 2004;291: 844-50. [PMID: 14970063]

24. **Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL.** Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology. 2003; 14:479-87. [PMID: 12843775]

25. **Ribstein J, du Cailar G, Mimran A.** Combined renal effects of overweight and hypertension. Hypertension. 1995;26:610-5. [PMID: 7558220]

26. **Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U.** Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol. 2000; 278:F817-22. [PMID: 10807594]

27. **Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE.** Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001;12:1211-7. [PMID: 11373344]

28. **Adelman RD.** Obesity and renal disease. Curr Opin Nephrol Hypertens. 2002;11:331-5. [PMID: 11981264]

29. **de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL.** Obesity and target organ damage: the kidney. Int J Obes Relat Metab Disord. 2002;26 Suppl 4:S21-4. [PMID: 12457295]

30. **Praga M.** Obesity—a neglected culprit in renal disease [Editorial]. Nephrol Dial Transplant. 2002;17:1157-9. [PMID: 12105233]

31. **Bosma RJ, van der Heide JJ, Oosterop EJ, de Jong PE, Navis G.** Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects. Kidney Int. 2004;65:259-65. [PMID: 14675058]

32. **Wolf G, Chen S, Han DC, Ziyadeh FN.** Leptin and renal disease. Am J Kidney Dis. 2002;39:1-11. [PMID: 11774095]

33. **Hall JE, Henegar JR, Dwyer TM, Liu J, Da Silva AA, Kuo JJ, et al.** Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther. 2004; 11:41-54. [PMID: 14730537]

34. **Abrass CK.** Overview: obesity: what does it have to do with kidney disease? J Am Soc Nephrol. 2004;15:2768-72. [PMID: 15504929]

35. **Ramirez SP, McClellan W, Port FK, Hsu SI.** Risk factors for proteinuria in a large, multiracial, southeast Asian population. J Am Soc Nephrol. 2002;13: 1907-17. [PMID: 12089388]

36. **Brancati FL, Wang NY, Mead LA, Liang KY, Klag MJ.** Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. Arch Intern Med. 1999;159:957-63. [PMID: 10326937]

37. **Brøchner-Mortensen J, Rickers H, Balslev I.** Renal function and body composition before and after intestinal bypass operation in obese patients. Scand J Clin Lab Invest. 1980;40:695-702. [PMID: 7280549]

38. **Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y.** The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol. 2003;14:1480-6. [PMID: 12761248]

39. **Morales E, Valero MA, León M, Hernández E, Praga M.** Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. Am J Kidney Dis. 2003;41:319-27. [PMID: 12552492]

40. **Flegal KM, Carroll MD, Ogden CL, Johnson CL.** Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002;288:1723-7. [PMID: 12365955]

Current Author Addresses: Dr. Hsu: Division of Nephrology, University of California, San Francisco, 513 Parnassus Avenue, 672 HSE, Box 0532, San Francisco, CA 94143-0532.
Dr. McCulloch: Department of Epidemiology and Biostatistics, University of California, San Francisco, 500 Parnassus Avenue, San Francisco, CA 94143.
Drs. Iribarren and Go and Ms. Darbinian: Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612.

Author Contributions: Conception and design: C.-Y. Hsu, C. Iribarren, A.S. Go.
Analysis and interpretation of the data: C.-Y. Hsu, C.E. McCulloch, J. Darbinian, A.S. Go.
Drafting of the article: C.-Y. Hsu.
Critical revision of the article for important intellectual content: C.-Y. Hsu, C.E. McCulloch, C. Iribarren, J. Darbinian, A.S. Go.
Final approval of the article: C.-Y. Hsu, C.E. McCulloch, C. Iribarren, J. Darbinian, A.S. Go.
Statistical expertise: C.-Y. Hsu, C.E. McCulloch.
Obtaining of funding: C.-Y. Hsu, C. Iribarren, A.S. Go.
Administrative, technical, or logistic support: C.-Y. Hsu, A.S. Go.

Ethiek van medisch-wetenschappelijk onderzoek: informed consent en de therapeutische misconceptie

M.C.de Vries en E.van Leeuwen

Zie ook de artikelen op bl. 666, 668, 674 en 685.

– De medisch-ethische beoordeling van onderzoek met proefpersonen is gebaseerd op 2 pijlers: enerzijds 'toezicht' door een medisch-ethische toetsingscommisie (METC) of de Centrale Commisie Mensgebonden Onderzoek (CCMO) op de wetenschappelijke deugdelijkheid van het onderzoek en op de risico's en belasting voor de proefpersonen en anderzijds 'informed consent' door de proefpersoon of diens wettelijke vertegenwoordigers.
– Wanneer er gediscussieerd wordt over de ethische aanvaardbaarheid van onderzoek, dan gaat het meestal om de 1e pijler, het toezicht. Veel minder vaak worden vragen gesteld bij de 2e pijler, het verkrijgen van informed consent voor het door de toetsende instantie goedgekeurde onderzoek.
– Een aantal ethische concepten speelt een rol bij de pijler 'informed consent'. Het belangrijkste is het concept 'therapeutische misconceptie': de misvatting dat deelname aan onderzoek hetzelfde is als het krijgen van een op de persoon afgestemde behandeling door een arts.
– Van belang hierbij is het fundamentele verschil tussen de behandelrelatie (tussen arts en patiënt) en de onderzoeksrelatie (tussen onderzoeker en proefpersoon).
– Kennis van het concept 'therapeutische misconceptie' is essentieel om te verklaren waarom het vaak zo moeilijk is om valide toestemming van proefpersonen te verkrijgen voor medisch onderzoek.

Ned Tijdschr Geneeskd. 2008;152:679-83

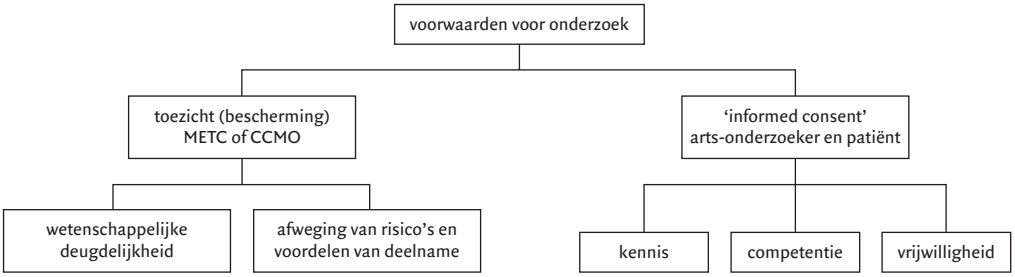
Op 23 januari 2008 maakte het Universitair Medisch Centrum (UMC) Utrecht bekend dat bij een gerandomiseerd onderzoek naar de werking van probiotica bij patiënten met acute pancreatitis onverwacht een hogere sterfte was opgetreden in de groep die de probiotica had gekregen (www.umcutrecht.nl/zorg/nieuws/2008/01/onverwacht-hogere-sterfte-in-onderzoek.htm). In totaal overleden 24 patiënten (16%) in de onderzoeksgroep en 9 patiënten (6%) in de controlegroep.[1,2]

In de media kwamen direct 2 verschillende soorten reacties op het nieuwsbericht: aan de ene kant twijfel over de opzet van het onderzoek, aan de andere kant twijfel over de informatievoorziening aan de proefpersonen. Alleen wetenschappers vroegen zich af of er bij de inclusie wellicht een stratificatieprobleem was opgetreden. De media stelden de vraag of deze uitkomst had kunnen worden voorkomen en of het onderzoek op de juiste wijze was uitgevoerd. De Inspectie voor de Volksgezondheid kondigde een onderzoek aan naar de uitvoering van de studie. Bij het tv-programma *Pauw & Witteman* vertelde een patiënt die had deelgenomen aan het onderzoek dat de informatievoorziening tijdens de 'informed consent'-procedure onvoldoende was geweest (aflevering van 24 januari 2008; http://pauwenwitteman.vara.nl). Hij had in zijn beleving niets gehoord over mogelijke risico's van deelname aan het onderzoek. Naar eigen zeggen had hij van de artsen te horen gekregen dat het medicijn zo 'veilig was als een probioticadrankje uit de supermarkt'. Bovendien had hij 'net zo goed een huis gekocht kunnen hebben', toen hij het informed-consentformulier ondertekende.

De reacties in de media op het nieuws uit het UMC Utrecht weerspiegelen de 2 pijlers waarop de medisch-ethische beoordeling van onderzoek met proefpersonen is gebaseerd: enerzijds toezicht door een toetsende instantie zoals een medisch-ethische toetsingscommissie (METC) of de Centrale Commissie Mensgebonden Onderzoek (CCMO) op de wetenschappelijke deugdelijkheid van het onderzoek en op de risico's en de belasting voor de proefpersonen en anderzijds informed consent (geïnformeerde toestemming) door de proefpersoon of diens wettelijke vertegenwoordigers (figuur). Deze 2 pijlers zijn verankerd in de Wet Medisch-wetenschappelijk Onderzoek met Mensen (WMO).

In dit artikel gaan wij in op enkele ethische concepten die een rol spelen bij de pijler informed consent. De nadruk ligt daarbij op het concept 'therapeutische misconceptie'. Dit concept is essentieel om te verklaren waarom het zo moeilijk is om valide toestemming van proefpersonen te verkrijgen voor medisch onderzoek.

Leids Universitair Medisch Centrum, sectie Ethiek & Recht van de Gezondheidszorg, Postbus 9600, 2300 RC Leiden.
Mw.M.C.de Vries, arts in opleiding tot kinderarts en medisch ethicus.
Universitair Medisch Centrum St Radboud, sectie Ethiek, Filosofie en Geschiedenis van de Geneeskunde, afd. Kwaliteit van Zorg, Nijmegen.
Hr.prof.dr.E.van Leeuwen, medisch ethicus.
Correspondentieadres: mw.M.C.de Vries (m.c.de_vries@lumc.nl).



De 2 pijlers van ethische aanvaardbaarheid van onderzoek. Toezicht wordt gehouden door een lokale medisch-ethische toetsingscommissie (METC) of de Centrale Commissie Mensgebonden Onderzoek (CCMO). 'Informed consent' komt tot stand in de relatie tussen arts-onderzoeker en patiënt.

INFORMED CONSENT ALS PIJLER VAN ETHISCHE AANVAARDBAARHEID VAN ONDERZOEK

Wanneer er gediscussieerd wordt over de ethische aanvaardbaarheid van onderzoek, dan gaat het meestal om de 1e pijler: het toezicht van de toetsende instantie. Veel minder vaak worden vragen gesteld bij de 2e pijler, het verkrijgen van informed consent voor het door de toetsende instantie goedgekeurde onderzoek. Maar juist ook over deze 2e pijler moet gediscussieerd worden. Begrijpen proefpersonen bijvoorbeeld wel wat het onderzoek inhoudt? Kunnen zij de risico's en de belasting zelf afwegen? Is het wel mogelijk om valide toestemming te verkrijgen in acute situaties?

Volgens de onderzoekers uit het UMC Utrecht is hun onderzoek uitgevoerd volgens de regels van de kunst en volgens de wet. Zij wijzen er daarbij op dat het onderzoek methodologisch goed in elkaar zat en dat in ieder participerend ziekenhuis het onderzoek was goedgekeurd door een lokale toetsingscommissie. De onderzoekers beroepen zich dus vooral op de 1e pijler. Zij worden hierin gesteund door 'peer reviewers' van het wetenschappelijke artikel over de resultaten van het onderzoek.[3] Maar hoe zat het met de 2e pijler, de geïnformeerde toestemming?

Criteria voor informed consent. Met geïnformeerde toestemming wordt recht gedaan aan het ethische ideaal van respect voor de autonomie van de patiënt. Een valide informed consent voldoet aan 3 criteria (zie de figuur): kennis, competentie en vrijwilligheid.

Kennis vereist dat er voldoende informatie gegeven is om een weloverwogen keuze te maken. Kennisoverdracht kan echter problematisch zijn. Uit onderzoek blijkt bijvoorbeeld dat veel patiënten de ontvangen informatiebrieven moeilijk leesbaar en te begrijpen vinden.[4-6] Ook na mondelinge uitleg blijken veel patiënten die instemmen met deelname, misvattingen te hebben over het onderzoeksproces.[7 8] Zij hebben vaak onvoldoende inzicht in een aantal van de noodzakelijke elementen van geïnformeerde toestemming, zoals risico's, procedures, mogelijkheid van alternatieve behandelingen, duur van de participatie, recht om zich terug te trekken en vrijwilligheid van participatie.

Competentie of wilsbekwaamheid betekent dat proefpersonen de aangeboden informatie kunnen bevatten en de gevolgen kunnen inzien van hun keuze om wel of niet deel te nemen aan het onderzoek. Wanneer onderzoeksbeslissingen zich aandienen bij het begin van het behandeltraject, kunnen patiënten onder bijzonder hoge psychologische en emotionele druk staan. Dan kan zelfs twijfel ontstaan over deze wilsbekwaamheid. De proefpersonen aan het onderzoek van het UMC Utrecht presenteerden zich allemaal met een eerste episode van een acute pancreatitis met een voorspeld ernstig verloop. Geen ideale situatie om informatie af te wegen en een doelbewuste keuze te maken. Achteraf kunnen deelnemers dan gaan twijfelen aan hun ogenschijnlijke wilsbekwaamheid op dat moment.

Vrijwilligheid betekent dat de toestemming zonder dwang of beïnvloeding gegeven wordt. Beïnvloeding is echter zeer snel mogelijk. Door de manier van informatie verstrekken of het achterwege laten van informatie beïnvloeden artsen, wellicht vaak onbewust, de keuzen van patiënt en ouders. In de emotionele omstandigheden bij een ernstige ziekte wordt al snel op de arts vertrouwd die de behandeling en het onderzoek aankaart.[9] Patiënten geven ook aan dat zij het moeilijk vinden om tegen het voorstel van de arts in te gaan, omdat zij bang zijn dat dit gevolgen heeft voor de behandeling.[10] Bovendien kan er dan nog de druk zijn van het binnen enkele uren of dagen moeten beslissen over de onderzoeksdeelname.

THERAPEUTISCHE MISCONCEPTIE

Aparte vermelding bij de procedure voor informed consent verdient de zogenaamde 'therapeutische misconceptie': de tendens om de wetenschappelijke oriëntatie van het onderzoek te verwarren met de therapeutische oriëntatie van een behandeling. De therapeutische misconceptie werd voor het eerst beschreven in 1982 als de misvatting dat deelname

aan een wetenschappelijk onderzoek hetzelfde is als het krijgen van een door een arts op de persoon afgestemde behandeling.[11 12] Proefpersonen kunnen moeite hebben om in te zien dat het doel van het onderzoek is om wetenschappelijke kennis te verkrijgen (ook al draagt dat in de toekomst bij om betere zorg te kunnen leveren); zij kunnen soms moeilijk inzien dat eventueel voordeel voor de proefpersoon zelf formeel slechts een 'bijproduct' van die kennis is.

Uit onderzoek blijkt dat 40-80% van de proefpersonen deze denkfout maakt.[13] In de huidige medische praktijk, waar onderzoek en behandeling sterk met elkaar verweven kunnen zijn, is de kans op deze misconceptie vrij groot. Patiënten kunnen bijvoorbeeld denken dat zij bij een randomisatie zelf mogen kiezen aan welke arm zij deelnemen of dat artsen dit bepalen op grond van wat het beste voor hen is. Het is dan niet altijd duidelijk dat er willekeurig wordt geloot.

Ook artsen kunnen last hebben van de therapeutische misconceptie. Zij kunnen bijvoorbeeld spanning ervaren tussen hun rol als clinicus en onderzoeker. Zo laten 2 studies zien dat oncologen, zelfs degenen met veel onderzoekservaring, meestal het perspectief van de clinicus aannemen in plaats van dat van de onderzoeker, wanneer zij onderzoeksdeelname bespreken.[14 15] Vaak is er een oprecht geloof dat door middel van klinische studies er een perfecte harmonie is tussen de doelen van patiëntenzorg enerzijds en wetenschappelijke vooruitgang anderzijds. De best mogelijke zorg lijkt dan te worden geboden in de strenge opzet van een onderzoeksprotocol (Vries MC de, Wit JM, Engberts DP, Leeuwen E van. Norms versus practice: justifying poor informed consent from children in pediatric oncology research. Schriftelijke mededeling).

Behandelrelatie en onderzoeksrelatie. Een fundamenteel uitgangspunt van de ethiek van wetenschappelijk onderzoek is echter dat er een groot verschil is tussen de behandelrelatie tussen arts en patiënt en de onderzoeksrelatie tussen onderzoeker en proefpersoon (http://ohsr.od.nih.gov/guidelines/belmont.html).[16]

In de behandelrelatie overheerst het individuele belang van de patiënt. De ethische principes van goeddoen en niet schaden zijn hier belangrijk. Incidenteel verkregen nieuwe kennis is secundair aan het uiteindelijke doel van de activiteit, namelijk het geven van een behandeling. Vaak worden behandelingen uitgevoerd zonder de expliciete toestemming van de patiënt. Men spreekt dan van impliciete of veronderstelde toestemming, zoals bij het doen van een venapunctie wanneer de patiënt zijn arm uitsteekt. Patiënten laten behandelbeslissingen vaak over aan hun arts. Onderzoeken laten zien dat veel patiënten (tot 63%) vinden dat hun arts het voortouw moet nemen in het besluitvormingstraject. Slechts 10% van de patiënten vindt dat zij zelf een grote betrokkenheid moeten hebben.[17 18]

Daarentegen is het doel van de onderzoeker in de onderzoeksrelatie om vooruitgang van kennis te bereiken om zo toekomstige behandelingen te kunnen verbeteren. Het therapeutische voordeel is secundair aan het overheersende doel van het verkrijgen van deze kennis. Daarom is voor elke onderzoekshandeling expliciet toestemming vereist. Soms wordt beweerd dat gerandomiseerde studies kunnen voldoen aan de basale plicht van 'therapeutisch' goeddoen vanwege de zogenaamde 'klinische equipoise', de oprechte onzekerheid van de onderzoeker over welke van de trial-armen voor de patiëntengroep als geheel uiteindelijk, na afronden van het onderzoek, het beste zal blijken te zijn.

Het fundamentele verschil tussen deze 2 relaties is dat de ervaren clinicus zijn behandeling selecteert en volgt – rekening houdend met individuele, patiëntspecifieke redenen –, terwijl de onderzoeker afziet van de patiëntgerichte overwegingen en kiest voor loting en randomisatie om een gegeneraliseerd resultaat te verkrijgen voor de hele patiëntengroep, waarbij individuele eigenschappen en voorkeuren dus niet meetellen. En ofschoon in de afweging de voordelen en de risico's van deelname aan onderzoek vaak minstens zo gunstig kunnen zijn als die van een standaardbehandeling, is juist een kenmerk van gerandomiseerde studies dat wij nooit vooraf zeker kunnen weten wat de voordelen en de risico's werkelijk zullen zijn, zoals ook de Utrechtse studie liet zien. Met het desondanks communiceren naar proefpersonen van de absolute gelijkheid van de verschillende onderzoeksarmen wordt de kans op de therapeutische misconceptie vergroot.[19]

BESCHOUWING

Het verkrijgen van valide toestemming is geen eenvoudige taak. De informed-consentprocedure zou moeten beginnen met het verhelderen van de situatie: een proefpersoon die denkt dat hij een op de persoon afgestemde therapie zal krijgen, terwijl hij wordt behandeld volgens een onderzoeksprotocol, kan geen valide toestemming geven. Proefpersonen hebben recht op een redelijke mogelijkheid om tot een goede beslissing te komen over onderzoeksdeelname. Daarvoor is het noodzakelijk dat artsen en onderzoekers helder het verschil uitleggen tussen de behandeling in het betreffende onderzoek en de standaardbehandeling.[20] Dit kan een tijdrovende taak blijken, vooral in een setting waarin onderzoek en behandeling sterk met elkaar verweven zijn. Wanneer het onderzoek een acute aandoening betreft en het bij de experimentele conditie om toediening van een voedingssupplement gaat, zoals bij de Utrechtse studie, lijkt een terugval op klinische equipoise voor de hand te liggen. Goedkeuring door een METC en de redelijke verwachting van klinische equipoise kunnen de toestemmingsprocedure echter nooit vervangen.

Goed geformuleerde informatiebrieven kunnen onder-

zoekers helpen om uit te leggen welke elementen van een protocol behoren tot het wetenschappelijk onderzoek en dientengevolge optioneel zijn.[21]

In een recent onderzoek binnen de kinderoncologie gaven ouders zelf adviezen over hoe men de kwaliteit van de informatievoorziening zou kunnen verbeteren.[22] De informatie moet afgestemd worden op de situatie van de proefpersonen en niet op de juridische eisen – door die laatste worden de patiënt-informatieformulieren vaak erg lang en moeilijk. Ouders wilden ook een duidelijker onderscheid, in tijd en/of gesprekspartner, tussen behandelgesprekken enerzijds en onderzoeksgesprekken anderzijds. Tenslotte wilden zij meer tijd voor hun beslissing.

Juist dit laatste punt is moeilijk te realiseren wanneer het onderzoek direct gestart moet worden na het stellen van de diagnose en de patiënten ernstig ziek zijn, zoals bij de probioticastudie. Een oplossing voor deze situaties zou kunnen zijn om allereerst altijd een naaste van de patiënt bij de informatieverstrekking te betrekken, die meeluistert tijdens de informed-consentprocedure. Daarnaast zou deze procedure meer als proces gezien moeten worden en niet als een momentopname. Wanneer men vaker tijdens de studie (en wanneer de patiënt minder ziek is) uit zou leggen wat de studie inhoudt, wat de risico's zijn en wat het verschil is met een standaardbehandeling, kan men voorkómen dat patiënten achteraf het idee hebben dat zij niet goed zijn voorgelicht.

Opvallend is dat de meeste artsen aangeven weinig onderricht gekregen te hebben in het voeren van toestemmingsgesprekken en de eisen die aan dergelijke gesprekken gesteld moeten worden. Die bekwaamheid onttrekt zich ook aan het oordeel van de toetsingscommissies, die zich beperken tot het beoordelen van de schriftelijke informatie over het onderzoek.

CONCLUSIE

Uit bovenstaande kunnen wij concluderen dat de informed-consentprocedure veel valkuilen kent en dat een echt valide toestemming moeilijk te realiseren is, vooral bij onderzoek naar acute aandoeningen. Bij het optreden van problemen, zoals in het UMC Utrecht, kan daarom achteraf gemakkelijk gewezen worden op gebreken in de toestemmingsprocedure. Het lijkt dan ook noodzakelijk artsen die hierbij betrokken zijn verder te scholen op dit gebied. Daarbij zou de nadruk vooral moeten liggen op de informed-consentprocedure als proces, waarbij de patiënt gedurende de studie meer inzicht krijgt in wat het onderzoek werkelijk inhoudt.

Belangenconflict: geen gemeld. Financiële ondersteuning: geen gemeld.

Aanvaard op 18 februari 2008

Literatuur

1 Besselink MGH, Santvoort HC van, Buskens E, Boermeester MA, Goor H van, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371:651-9.
2 Besselink MGH, Santvoort HC van, Buskens E, Boermeester MA, Goor H van, Timmerman HM, et al. Probioticaprofylaxe bij voorspeld ernstige acute pancreatitis: een gerandomiseerde, dubbelblinde, placebogecontroleerde trial. Ned Tijdschr Geneeskd. 2008;152:685-96.
3 Santen H van. Patiënten probiotica waren al zieker. NRC Handelsblad januari 25 2008.
4 Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. N Engl J Med. 2003;348:721-6.
5 Grossman SA, Piantadosi S, Covahey C. Are informed consent forms that describe clinical oncology research protocols readable by most patients and their families? J Clin Oncol. 1994;12:2211-5.
6 Tarnowski KJ, Allen DM, Mayhall C, Kelly PA. Readability of pediatric biomedical research informed consent forms. Pediatrics. 1990;85: 58-62.
7 Wendler D. Can we ensure that all research subjects give valid consent? Arch Intern Med. 2004;164:2201-4.
8 Greenley RN, Drotar D, Zyzanski SJ, Kodish E. Stability of parental understanding of random assignment in childhood leukemia trials: an empirical examination of informed consent. J Clin Oncol. 2006;24: 891-7.
9 Ong LML, Haes JCJM de, Hoos AM, Lammes FB. Doctor-patient communication: a review of the literature. Soc Sci Med. 1995;40:903-18.
10 Heneghan AM, Mercer M, DeLeone NL. Will mothers discuss parenting stress and depressive symptoms with their child's pediatrician? Pediatrics. 2004;113(3 Pt 1):460-7.
11 Appelbaum PS, Roth LH, Lidz CW. The therapeutic misconception: informed consent in psychiatric research. Int J Law Psychiatry. 1982;5: 319-29.
12 Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and the therapeutic misconception. Hastings Cent Rep. 1987;17:20-4.
13 Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. IRB. 2004;26:1-8.
14 Joffe S, Weeks JC. Views of American oncologists about the purposes of clinical trials. J Natl Cancer Inst. 2002;94:1847-53.
15 Taylor KM. Integrating conflicting professional roles: physician participation in randomized clinical trials. Soc Sci Med. 1992;35: 217-24.
16 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. Washington: Department of Health, Education, and Welfare; 1979.
17 Blanchard CG, Labrecque MS, Ruckdeschel JC, Blanchard EB. Information and decision-making preferences of hospitalized adult cancer patients. Soc Sci Med. 1988;27:1139-45.
18 Sutherland HJ, Llewellyn-Thomas HA, Lockwood GA, Tritchler DL, Till JE. Cancer patients: their desire for information and participation in treatment decisions. J R Soc Med. 1989;82:260-3.
19 Miller FG, Brody H. A critique of clinical equipoise. Therapeutic misconception in the ethics of clinical trials. Hastings Cent Rep. 2003; 33:19-28.
20 Appelbaum PS. Clarifying the ethics of clinical research: a path toward avoiding the therapeutic misconception. Am J Bioeth. 2002;2: 22-3.
21 Ungar D, Joffe S, Kodish E. Children are not small adults: documentation of assent for research involving children. J Pediatr. 2006;149 (1 Suppl):S31-3.
22 Eder ML, Yamokoski AD, Wittmann PW, Kodish ED. Improving informed consent: suggestions from parents of children with leukemia. Pediatrics. 2007;119:e849-59.

Abstract

Ethics of medical scientific research: informed consent and the therapeutic misconception

– Ethical approval of research involving human beings is based on two pillars: supervision of the scientific merit of the research and the risks and burdens for participants by an institutional review board (IRB) or the Dutch Central Committee on Research Involving Human Subjects (CCMO), and obtaining informed consent from the participant or his or her legal guardian.
– Discussions on the ethical acceptability of a study generally focus on the first pillar, assessment by an IRB. The second pillar, obtaining informed consent, is often neglected.
– Some ethical concepts play a role in obtaining informed consent, especially the concept of the 'therapeutic misconception', i.e. that participating in a study is the same as receiving individualised treatment from a physician.
– Of importantance in this matter is the fundamental difference between the research relationship (between investigator and participant) and treatment relationship (between physician and patient).
– Understanding the concept of therapeutic misconception is essential to explaining why it is often difficult to obtain valid informed consent from patients for medical research.

Ned Tijdschr Geneeskd. 2008;152:679-83