PROTOCOLUL DE CERCETARE: STUDIUL DE CAZ-MARTOR

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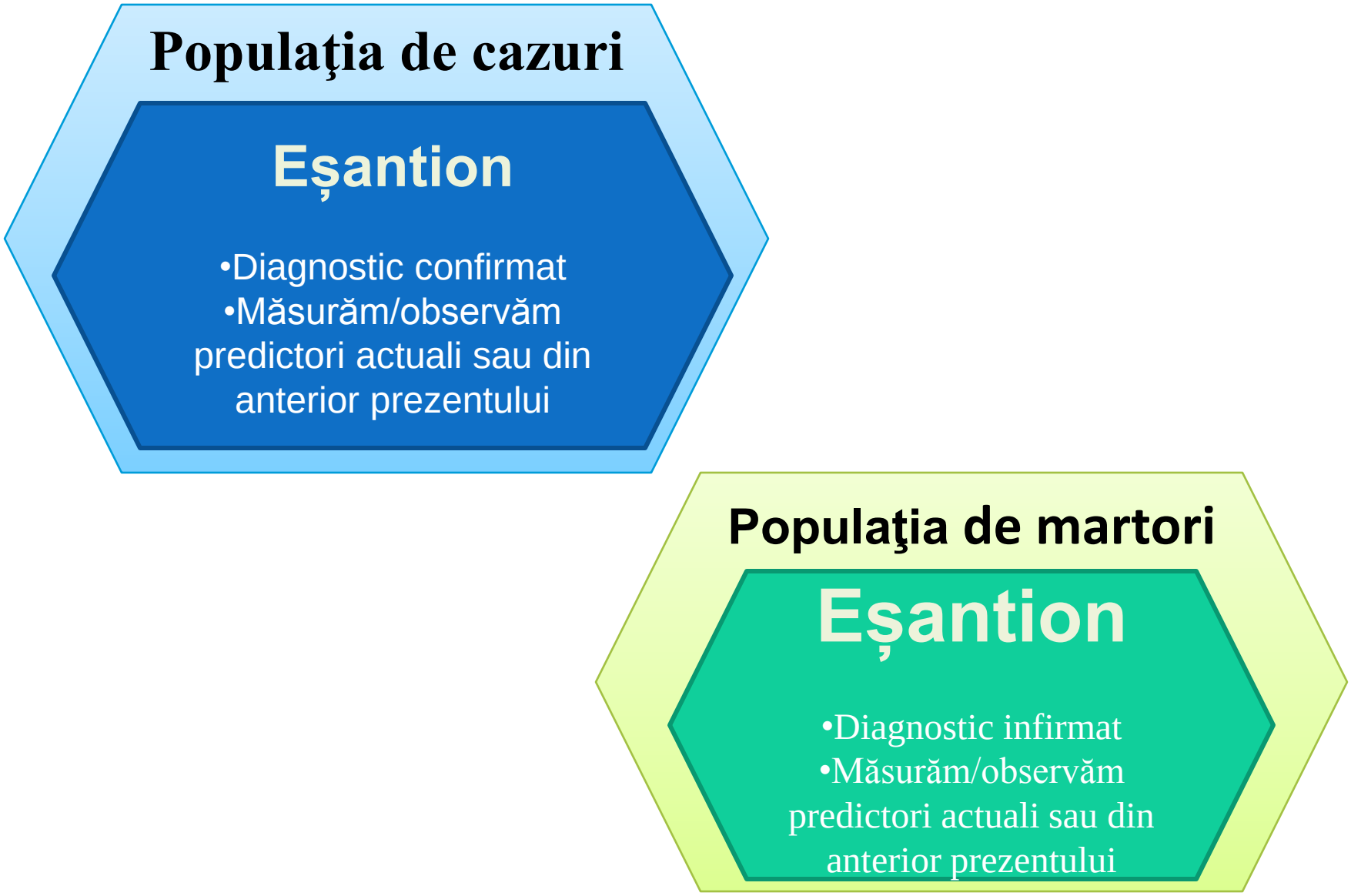
OUTILINE

- Studiul caz-martor
- Studiul caz-martor de tip cuib (*nested case-control study*)
- Studiul caz-martor de tip incidenţă-densitate

"Well, if I recall correctly, on April 17 , 1991, at 6:37 p.m. Eastern Time, I ate 6 ounces of grilled salmon steak, farm raised, 2/3 cup of rice, 1/2 cup steamed broccoli, 1 cup of mixed salad greens with 2 tablespoons of French dressing, a 12 ounce glass of unsweetened iced tea and 3 scoops of Tin Roof ice cream for dessert."

STUDIUL CAZ-MARTOR


Populaţia de cazuri
Eșantion
•Diagnostic confirmat
•Măsurăm/observăm predictori actuali sau din anterior prezentului
Populaţia de martori
Eșantion
•Diagnostic infirmat
•Măsurăm/observăm predictori actuali sau din anterior prezentului

Design-ul de tip caz-martor

+

- Eficacitate pentru patologiile rare
- Utile pentru identificarea/generarea ipotezelor

-

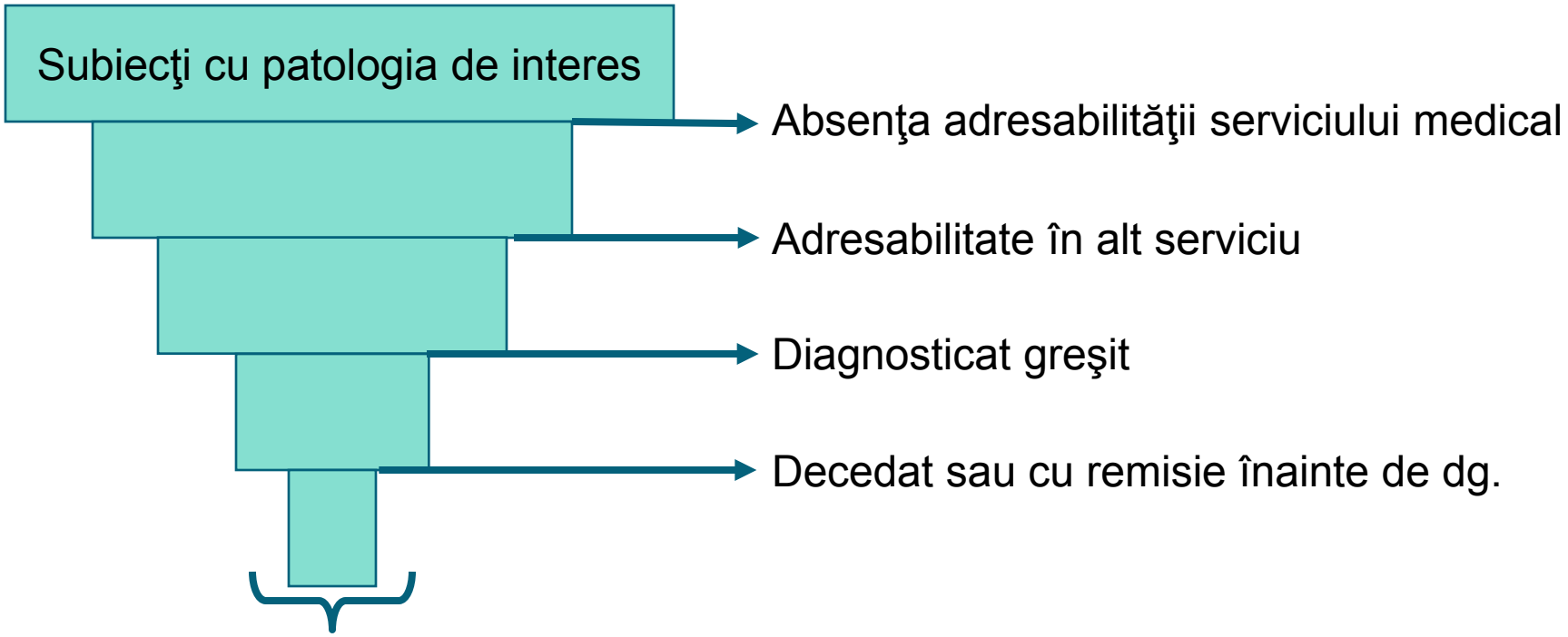
- permite studierea unei singure variabile de tip răspuns
- susceptibile la erori:
  - Eşantionare separată pentru cazuri şi martori
  - Evaluarea retrospectivă a predictorilor

Design-ul de tip caz-martor

Eroarea de eşantionare şi controlul acesteia

- Eşantionul caz: subiecţii cu patologia de interes
  - Eşantionul poate să nu fie reprezentativ deoarece subiecţii care nu au fost diagnosticaţi, cei care au fost incorect diagnosticaţi şi respectiv cei care nu sunt disponibili pentru studiu nu vor fi incluşi în eşantion
- Eşantionul martor: convenabil (aceeaşi clinică sau spital)
  - Frecvent au patologii care se asociază cu factorii de risc de interes → rezultate care nu sunt adevărate

Eşantionul caz



Eroarea de eşantionare şi controlul acesteia

Alegerea eşantionului caz şi martor din populaţie:

- Posibil dacă există registru de raportare a patologiei
  - Eşantionul caz este reprezentativ pentru populaţie
- Utilizarea a mai mult de un eşantion martor (diferite metode de selecţie a eşantioanelor)
- Potrivirea (*matching*): cele două grupuri sunt comparabile
  - Multe patologii sunt apar frecvent la un anumit gen sau la o anumită vârstă

Eroarea de măsurare şi controlul acesteia

• Colectarea retrospectivă a datelor necesită uneori întrebări cu privire la expuneri care au avut loc cu ani în urmă ← memoria subiecţilor este imperfectă

- Subiecţii din grupul caz îşi amintesc sau raportează expunerea diferit de subiecţii din grupul martor (differential misclassification) = eroare de rechemare (recall bias)
  - Standardizarea variabilelor
  - Utilizarea metodelor obiective (ex.!)
  - Suplimentarea variabilelor de interes cu măsurători din surse diferite
  - Utilizarea datelor înregistrate anterior apariţiei rezultatului de interes
  - Utilizarea orbirii

Orbirea în studiul caz-martor

	Statusul caz-martor	Factori de risc
Subiect	Posibil dacă şi subiecţii din grupul caz şi cei din grupul martor au patologia (de interes) care poate fi relaţionată cu factorul de risc	Include factori de risc fictivi şi verifică dacă există diferenţe semnificative între cazuri şi martori în ceea ce priveşte aceşti factori
Cercetător	Posibil dacă nu există caracteristici care să permită vizuală a cazurilor faţă de martori	Posibil dacă cel care ia interviul subiectului este diferit de cercetător

Dublu-orb cu privire la status

Design-ul de tip caz-martor

- Nu permite estimarea incidenţei sau prevalenţei ← proporţia subiecţilor care prezintă patologia de interes este determinată de numărul de subiecţi pe care cercetătorul decide să-i includă în studiu şi nu de proporţia acestora în populaţie

→ informaţii descriptive a caracteristicilor subiecţilor cu patologia de interes

→ estimare a puterii de asociere între fiecare din variabilele de tip predictor şi de tip rezultat (de tip rata şansei - OR)

RATA ŞANSEI

	Caz	Martor
FR+	**A**	**B**
FR-	**C**	**D**

OR = (A/C)/(B/D)

Potrivire (matched)

OR = F/G

F = o pereche formată dintr-un martor cu FR- şi un caz cu FR+

G = o pereche formată dintr-un martor cu FR+ şi un caz cu FR-

RATA ŞANSEI (OR): INTERPRETARE

OR=1 Exposure does not affect odds of outcome

OR>1 Exposure associated with higher odds of outcome

OR<1 Exposure associated with lower odds of outcome

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938757/

RATA ŞANSEI (OR): INTERPRETARE

Eur Heart J Cardiovasc Imaging. 2014 Nov 2. pii: jeu217. [Epub ahead of print]

Relationship of left ventricular mass to coronary atherosclerosis and myocardial ischaemia: the CORE320 multicenter study.

Kishi S[1], Magalhaes TA[1], George RT[1], Dewey M[2], Laham RJ[3], Niinuma H[4], Friedman LA[5], Cox C[5], Tanami Y[6], Schuijf JD[7], Vavere AL[1], Kitagawa K[8], Chen MY[9], Nomura CH[10], Brinker JA[1], Rybicki FJ[11], Di Carli MF[11], Arbab-Zadeh A[1], Lima JA[12].

Author information

Abstract

AIMS: The aim of this study was to investigate the association of left ventricular mass (LVM) with coronary atherosclerosis and myocardial infarction (MI).

METHODS AND RESULTS: Patients (n = 338) underwent 320 × 0.5 mm detector row coronary computed tomography (CT) angiography, invasive coronary angiography (ICA), and single-photon emission CT (SPECT) myocardial perfusion imaging. Quantitative coronary atheroma volume was obtained from the CT images for the entire coronary tree (19-segment model) with an arterial contour detection algorithm. Normalized total atheroma volume (NormTAV) was analysed to reflect quantitative total atheroma volume. LVM was measured on myocardial CT images and indexed to height to the power of 2.7 (LVMi). Patients with obstructive coronary artery disease (CAD) were defined as those with ≥50% diameter stenosis by quantitative ICA. Abnormal perfusion defect was defined as ≥1 abnormal myocardial segment by SPECT. The association of LVMi with coronary atherosclerosis and myocardial perfusion defect on SPECT at the patient level was determined with uni- and multivariable linear and logistic regression analyses. Obstructive CAD was present in 60.0% of enrolled patients. LVMi was independently associated with abnormal summed rest score [SRS; odds ratio (OR), 1.07; 95% confidence interval (CI), 1.03-1.09] and summed stress score (OR, 1.04; 95% CI, 1.01-1.07). An increase in LVMi was also independently associated with that in NormTAV (coefficient, 10.44; 95% CI, 1.50-19.39) and SRS ≥1 (OR, 1.05; 95% CI, 1.01-1.10), even after adjusting for cardiovascular risk factors in patients without previous MI.

CONCLUSIONS: LVM was independently associated with the presence of coronary artery atherosclerosis and MI.

KEYWORDS: Atheroma volume; Coronary atherosclerosis; Left ventricular mass; Myocardial ischaemia

Protocol 00PRT/3 INTER-HEART: a global case-control study of risk factors for acute myocardial infarction

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Background

Although cardiovascular disease mortality has declined in most developed countries, increases are occurring in developing countries. Our knowledge of risk factors for acute myocardial infarction is largely derived from studies in the developed countries. Applicability of these results to other populations is unknown. Therefore we are conducting INTER-HEART, a case-control study in 52 countries, to determine the association between risk factors and acute myocardial infarction within populations defined by ethnicity and/or geographic region, and to assess the relative importance of risk factors across these populations.

Hypothesis

We hypothesise that the relative impact of conventional risk factors (smoking, hypertension, elevated cholesterol, diabetes) and emerging risk factors (glucose abnormalities, abdominal obesity, homocysteine, other nutritional, psychosocial) for cardiovascular disease differs between people of varying ethnic and geographic origin.

Methods

INTER-HEART will study approximately 14 000 incident cases of acute myocardial infarction and 16 000 controls matched by age (+/- 5 years) and sex, with no history of heart disease. Recruitment will take place in 241 centres from 52 countries in Asia, Europe, Middle East Crescent, Africa, Australia, and North and South America.

All patients admitted to the coronary care unit or equivalent cardiology ward of participating centres are screened to identify incident cases of acute myocardial infarction. Cases are identified with standardised definitions and enrolled within 24 hours of symptom onset. At least one control per case is recruited with specific criteria.

The study questionnaire was translated into 11 languages and collects data on demographic factors (country of origin, first language), socioeconomic status (education, occupation, income), lifestyle (tobacco use, physical activity, dietary patterns), and personal and family history of cardiovascular disease and risk factors. Trained staff administer the questionnaire before the patient leaves the hospital. The components of the questionnaire were compiled with previously validated questions included in studies of risk factors for cardiovascular disease. Data on medications (prehospital, inhospital, and discharge) and interventions are abstracted from charts. Standard physical measurements are done in duplicate by the same examiner on each participant: height, weight, waist, and hip circumference, and heart rate. 20 mL non-fasting blood is drawn to be stored frozen for biochemical analyses (total cholesterol, high-density lipoprotein; apolipoprotein B, immunoglobulin G and immunoglobulin A antibodies indicating infection with Chlamydia pneumoniae, glycated haemoglobin, homocysteine, serum folate, serum albumin, serum creatinine, white cell count). Genetic materials (buffy coat) will also be collected to assess the relevance of candidate genes for acute myocardial infarction within each ethnic group. Conditional logistic regression will be used to assess the relation between acute myocardial infarction and risk factors within countries or regions, and the relation between risk factors and disease across countries or regions. Overall effect estimates will be derived from the region-specific estimates with mixed-effects model.

Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

Prof Salim Yusuf DPhil [a], Steven Hawken MSc [a], Stephanie Ôunpuu PhD [a], Tony Dans MD [a], Alvaro Avezum MD [a], Fernando Lanas MD [a], Matthew McQueen FRCP [a], Andrzej Budaj MD [a], Prem Pais MD [a], John Varigos BSc [a], Liu Lisheng MD [a], on behalf of the INTERHEART Study Investigators

Listed at end of paper

Summary

Background

Although more than 80% of the global burden of cardiovascular disease occurs in low-income and middle-income countries, knowledge of the importance of risk factors is largely derived from developed countries. Therefore, the effect of such factors on risk of coronary heart disease in most regions of the world is unknown.

Methods

We established a standardised case-control study of acute myocardial infarction in 52 countries, representing every inhabited continent. 15152 cases and 14820 controls were enrolled. The relation of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins (Apo), and psychosocial factors to myocardial infarction are reported here. Odds ratios and their 99% CIs for the association of risk factors to myocardial infarction and their population attributable risks (PAR) were calculated.

Findings

Smoking (odds ratio 2·87 for current *vs* never, PAR 35·7% for current and former *vs* never), raised ApoB/ApoA1 ratio (3·25 for top *vs* lowest quintile, PAR 49·2% for top four quintiles *vs* lowest quintile), history of hypertension (1·91, PAR 17·9%), diabetes (2·37, PAR 9·9%), abdominal obesity (1·12 for top *vs* lowest tertile and 1·62 for middle *vs* lowest tertile, PAR 20·1% for top two tertiles *vs* lowest tertile), psychosocial factors (2·67, PAR 32·5%), daily consumption of fruits and vegetables (0·70, PAR 13·7% for lack of daily consumption), regular alcohol consumption (0·91, PAR 6·7%), and regular physical activity (0·86, PAR 12·2%), were all significantly related to acute myocardial infarction ($p<0·0001$ for all risk factors and $p=0·03$ for alcohol). These associations were noted in men and women, old and young, and in all regions of the world. Collectively, these nine risk factors accounted for 90% of the PAR in men and 94% in women.

Interpretation

Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.

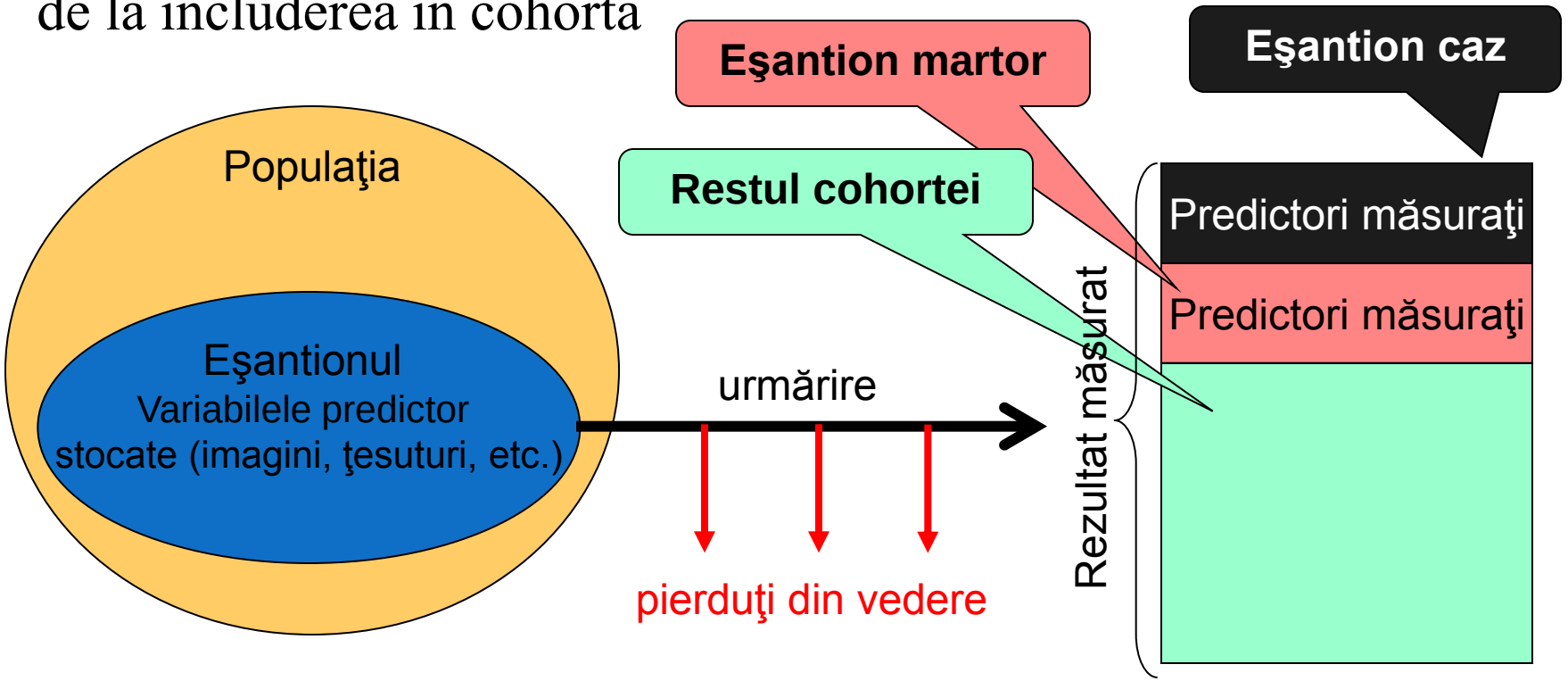
Published online September 3, 2004 http://image.thelancet.com/extras/04art8001web.pdf

STUDIUL CAZ-MARTOR DE TIP CUIB

caz-martor într-o cohortă

CAZ-MARTOR DE TIP CUIB

Există o cohortă definită pentru care datele cu privire la expunere şi respectiv caracteristicile populaţiei sunt disponibile de la includerea în cohortă



Elevated Serum Estradiol and Testosterone Concentrations Are Associated with a High Risk for Breast Cancer

Jane A. Cauley, DrPH; Frances L. Lucas, PhD; Lewis H. Kuller, MD, DrPH; Katie Stone, PhD; Warren Browner, MD, MPH; and Steven R. Cummings, MD, for the Study of Osteoporotic Fractures Research Group

- Cohorta: SOP (Study of Osteoporotic Fractures)
  - Eşantioane de sânge congelate
- Identificarea cazurilor la sfârşitul perioadei de urmărire (3,2 ani): chestionar & certificate de deces → 97 subiecţi cu cancer de sân
- Selectarea martorilor: eşantion randomizat de 244 femei care nu au dezvoltat cancer de sân
- Măsurarea predictorilor: estradiol şi testosteron în sângele congelat. Personal de laborator orb (nu cunoştea statutul de caz sau martor).

→ femeile cu nivel crescut de estradiol sau testosteron a avut un risc de 3 ori mai mare de a dezvolta cancer de sân comparativ cu cele care au avut nivele scăzute ale hormonilor sexuali investigaţi

BMJ Open 2014;**4**:e004499 doi:10.1136/bmjopen-2013-004499

Epidemiology

Exposure to combined oral contraceptives and risk of venous thromboembolism: a protocol for nested case–control studies using the QResearch and the CPRD databases

Yana Vinogradova, Carol Coupland, Julia Hippisley-Cox

Abstract

Introduction Many studies have found an increased risk of venous thromboembolism (VTE) associated with the use of combined hormonal contraceptives, but various methodologies have been used in the study design relating to definition of VTE event and the selection of appropriate cases for analysis. This study will focus on common oral hormonal contraceptives, including compositions with cyproterone because of their contraceptive effect and will perform a number of sensitivity analyses to compare findings with previous studies.

Methods and analysis 2 nested case–control studies will be based on the general population using records from UK general practices within the QResearch and Clinical Practice Research Datalink databases. Cases will be female patients aged 15–49 with primary VTE diagnosed between 2001 and 2013. Each case will be matched by age, year of birth and practice to five female controls, who are alive and registered with the practice at the time of diagnosis of the case (index date). Exposure to different hormonal contraceptives will be defined as at least one prescription for that contraceptive in the year before the index date. The effects of duration and the length of any gap since last use will also be investigated. Conditional logistic regression will be applied to calculate ORs adjusted for smoking, ethnicity, comorbidities and use of other medications. Possible indications for prescribing hormonal contraceptives, such as menstrual disorders, acne or hirsutism will be included in the analyses as confounding factors. A number of sensitivity analyses will be carried out.

Ethics and dissemination The initial protocol has been reviewed and approved by ISAC (Independent Scientific Advisory Committee) for Medicine and Healthcare Products Regulatory Agency Database Research. The project has also been reviewed by QResearch and meets the requirements of the Trent Research Ethics Committee. The results will be published in a peer-reviewed journal.

ORIGINAL RESEARCH | Annals of Internal Medicine

Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction

Cohort and Nested Case–Control Studies

Aaron S. Kesselheim, MD, JD, MPH; Katsiaryna Bykov, PharmD, MS; Jerry Avorn, MD; Angela Tong, MS; Michael Doherty, MS; and Niteesh K. Choudhry, MD, PhD

Background: Generic prescription drugs made by different manufacturers may vary in color or shape, and switching among these drug products may interrupt medication use.

Objective: To determine whether nonpersistent use of generic drugs among patients with cardiovascular disease after myocardial infarction (MI) is associated with inconsistent appearance of their medications.

Design: Cohort and nested case–control studies.

Setting: Claims from a commercial health insurance database in the United States.

Patients: Patients discharged after hospitalization for MI between 2006 and 2011 who initiated treatment with a generic β-blocker, angiotensin-converting enzyme inhibitor, angiotensin II–receptor blocker, or statin. Case patients discontinued their index medication for at least 1 month; control patients continued treatment. Control patients were matched to case patients on therapeutic class, number of dispensings before nonpersistence, sex, and age.

Measurements: Rates of changes in pill color and shape during the year after MI were calculated. Next, 2 refills preceding nonpersistence were evaluated to determine whether pill color or shape had changed. Odds of discordance among case and control patients were compared using conditional logistic regression.

Results: A total of 29% of patients (3286 of 11 513) had a change in pill shape or color during the study. Statins had the most changes in appearance, whereas β-blockers had the fewest. A total of 4573 episodes of nonpersistence was matched to 19 881 control episodes. The odds of nonpersistence in case patients increased by 34% after a change in pill color (adjusted odds ratio, 1.34 [95% CI, 1.12 to 1.59]) and 66% after a change in pill shape (adjusted odds ratio, 1.66 [CI, 1.43 to 1.94]).

Limitation: Only 3 categories of drugs indicated after MI were evaluated, and clinical outcomes were not addressed.

Conclusion: Variation in the appearance of generic pills is associated with nonpersistent use of these essential drugs after MI among patients with cardiovascular disease.

Primary Funding Source: Agency for Healthcare Research and Quality and the Harvard Program in Therapeutic Science.

Ann Intern Med. 2014;161:96-103. doi:10.7326/M13-2381 www.annals.org

For author affiliations, see end of text.

STUDIUL CAZ-MARTOR CUIB INCIDENŢĂ-DENSITATE

incidence-density nested case-control study

CÂND?

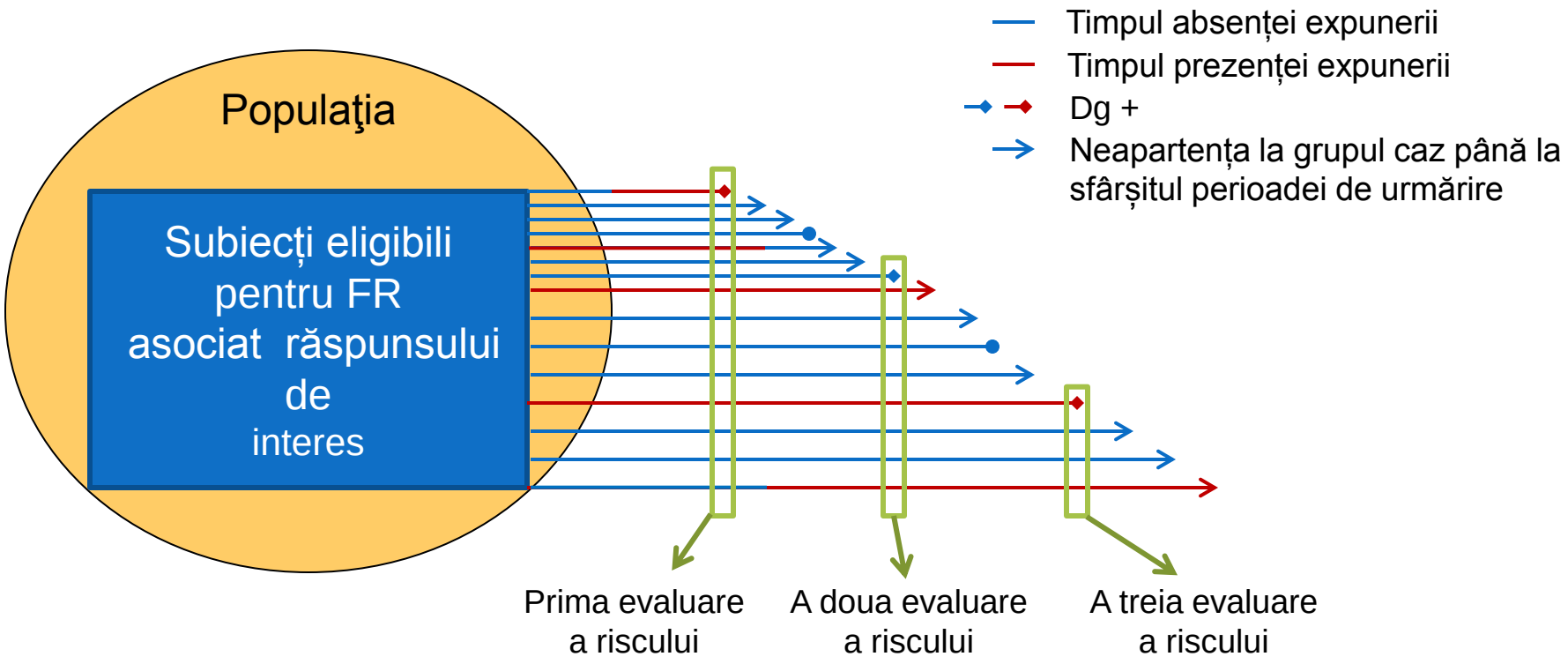
- Urmărirea este variabilă sau incompletă
- Expunerea de interes variază în timp

CUM?

- Definește criteriile de includere și recrutează cohorta.
- Definește data de intrare a fiecărui subiect și omogenizează timpul de urmărire
- Culege și stochează specimene, imagini, etc. pentru a fi ulterior analizate
- Urmărește cohorta și identifică cazurile și data diagnosticului
- Include în eșantionul martor unul sau mai mulți pacienți cu aceeași factori de risc (sunt urmăriți aceeași perioadă de timp ca și cazurile)
- Măsoară variabila predictor în specimene, imagini, etc. atât la cazuri cât și la martori

CÂND?

- Urmărirea este variabilă sau incompletă
- Expunerea de interes variază în timp



VOLUMUL EȘANTIONULUI

Asumpții								
OR	2	2	2	2	2	2	2	2
% expunere martori	5	5	5	5	5	5	10	10
Risc alfa	5	5	5	5	5	5	5	5
Puterea studiului (%)	90	80	90	80	90	80	90	80
Raport caz:martor	1	1	2	2	3	3	1	1
Estimarea volumului eșantionului								
n (caz)	690	516	506	371	444	322	378	283
n (martor)	690	516	1012	742	1332	966	378	283
Total	1380	1032	1518	1113	1776	1288	756	566

Asumpții								
OR	2	2	2	2	3	3	2	2
% expunere martori	5	5	10	10	5	5	15	15
Risc alfa	5	5	5	5	5	5	5	5
Puterea (%)	90	80	90	80	90	80	90	80
Matched	da	da	da	da	da	da	da	da
Estimarea volumului eșantionului								
n perechi discordante expuși	91	69	91	69	38	29	91	69
n perechi	666	503	369	278	219	168	272	206
Total	1332	1006	738	556	438	336	544	412

Design	+	-
Cross-secțional		
	○ Durată relativ scurtă ○ Prim pas pentru un studiu de cohortă sau un trial clinic ○ Prevalența pentru *x* predictori și *y* rezultate	○ Nu permite stabilirea sencvenței de apariție a evenimentelor ○ Nu se pot utiliza pentru predictori si/sau rezultate rare
Cohortă		
Toate	○ Stabilește secvența evenimnetelor ○ *x* predictori și *y* rezultate ○ Numărul evenimentelor rezultat cresc cu timpul ○ → incidența, RR, excesul de risc	○ Necesită eșantioane mari ○ Nu se aplică în cazul patologiilor rare
Prospectiv	○ Control adecvat asupra subiecților selectați ○ Evită eroarea în măsurarea predictorilor	○ Perioada de urmărire poate fi lungă ○ Costurile frecvent sunt mari
Retrospectiv	○ Urmărirea se face în trecut ○ Costuri ↓↓↓	○ Control mic asupra selecției și a măsurătorilor
Cohorte multiple	○ Cohorte diferite au expuneri diferite	○ Erori și factori de confuzie ← populații diferite

Design	+	-
Caz-martor		
	○ Util în bolile rare ○ Durată scurtă ○ Volum de eșantion mic ○ Costuri ↓↓↓	○ Erori și factori de confuzie ← 2 populații diferite
Design-uri hibrid		
Caz-martor cuib	○ Avantajele studiului de cohortă retrospectiv ○ Costuri ↓ (determinari costisitoare ale predictorilor)	○ Se bazează pe o cohortă definită anterior
Incidență-densitate	○ FR sunt analizați luând în considerare modificările în timp ale nivelelor acestora și pierderea subiecților din vedere	○ Nivelele FR și incidența cazurilor se măsoară de mai multe ori în timpul urmăririi ○ Frecvent necesită o cohortă definită anterior
Cuib caz-cohortă	○ Utilizarea unui singur grup martor pentru mai multe studii caz-martor cu rezultate de interes diferite	○ Identic cu caz-martor cuib
Caz-crossover	○ Cayurile sunt proprii martori →↓↓↓ erorile de eșantionare și factorii de confuzie	○ Expunerea are doar rezultate imediate, efecte pe termen scurt

"Excellent health statistics - smokers are less likely to die of age related illness"