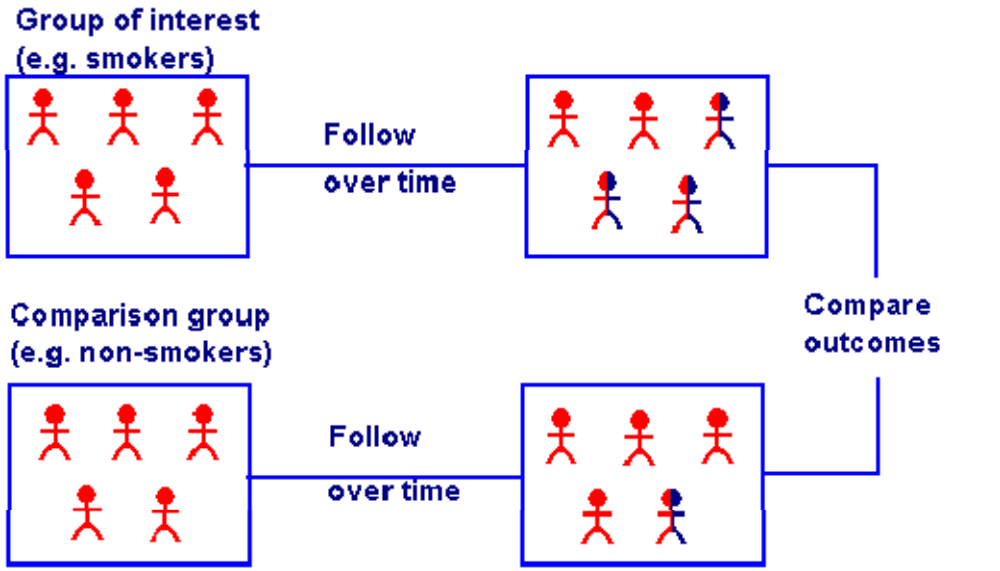

Studio di coorte

Disegno

(schema essenziale semplificato)



- Lo studio inizia con l'identificazione di un **gruppo di individui che non presentano la malattia**/evento in studio
- Si divide il gruppo iniziale in (almeno) una **coorte degli esposti ad un fattore** di rischio o protettivo e una **coorte dei non esposti**
- Si seguono le coorti nel **tempo** mediante un sistema di misurazione della comparsa di malattia (o un altro evento definito)
- Si confronta la frequenza di malattia negli esposti e nei non esposti

Classificazione

- Lo studio di coorte è uno studio epidemiologico
  - Osservazionale
  - Analitico
- Possiamo distinguere: studi di coorte
  - Prospettici
  - Storici

Definizione delle variabili

- Negli studi descrittivi è necessario definire l'evento (malattia, decesso) e come viene registrato
- Nello studio di coorte è necessario definire operativamente come si misura la/e esposizione/i
- Oltre a malattia ed esposizione sono definite e registrate altre variabili che possono essere responsabili di una diversa frequenza di malattia negli esposti e nel gruppo di controllo

Natura dell'esposizione

- The term *exposure is used here to* include not only exposures to exogenous agents that may be causally related to disease, but also socioeconomic factors, health habits, endogenous factors, and factors that may confound or modify the primary exposure-disease relation.

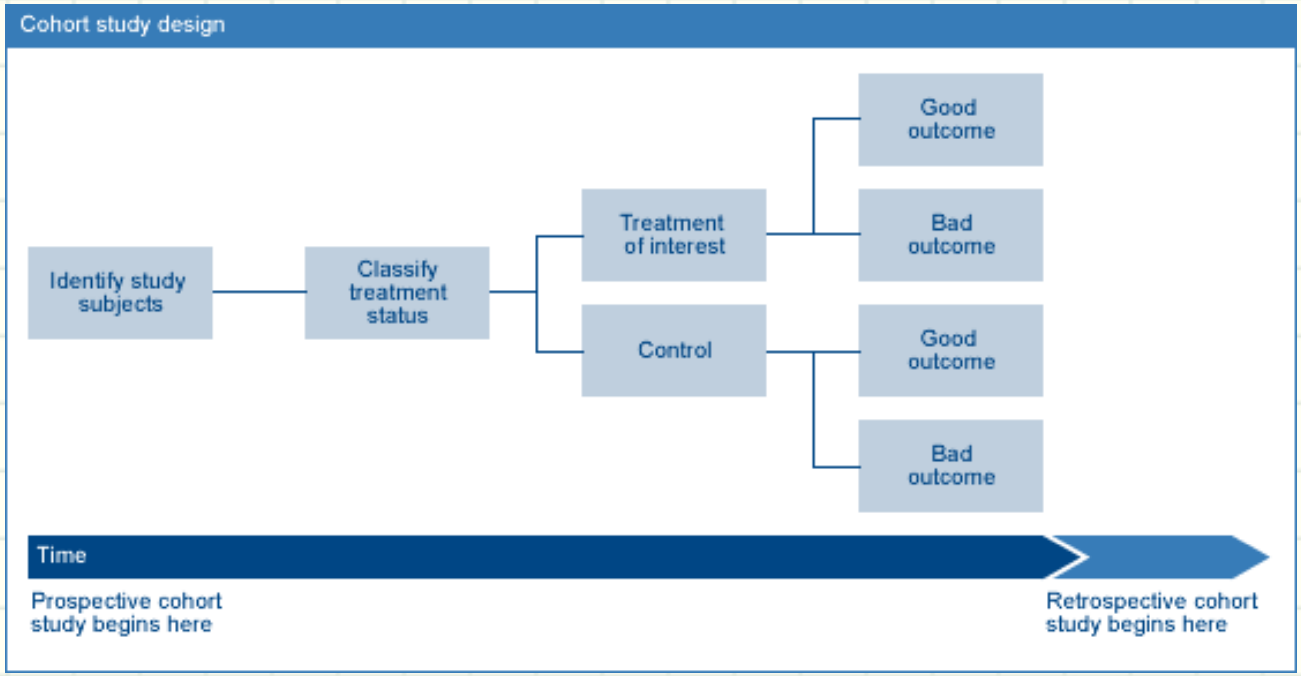
White E, Hunt JR, Casso D. Exposure Measurement in Cohort Studies: The Challenges of Prospective Data Collection. *Epidemiologic Reviews* 1998; 20: 43-56

- Dal punto di vista della natura delle variabili possiamo avere fattori continui (BMI, pressione arteriosa) o discreti (n. sigarette fumate) o classificati in categorie (dicotomici o politomici, ordinali o nominali)

Studio di coorte prospettico

- E’ un disegno in genere molto costoso
- E’ un disegno longitudinale che spesso richiede molti anni nel caso di malattie cronico degenerative
- Viene utilizzato se
  - Vi sono già evidenze sul sospetto fattore
  - La frequenza della malattia è elevata in una popolazione identificabile
  - La sorveglianza della coorte nel tempo è sostenibile (stabilità della popolazione, validità della rilevazione degli eventi)

Coorte storica e retrospettiva

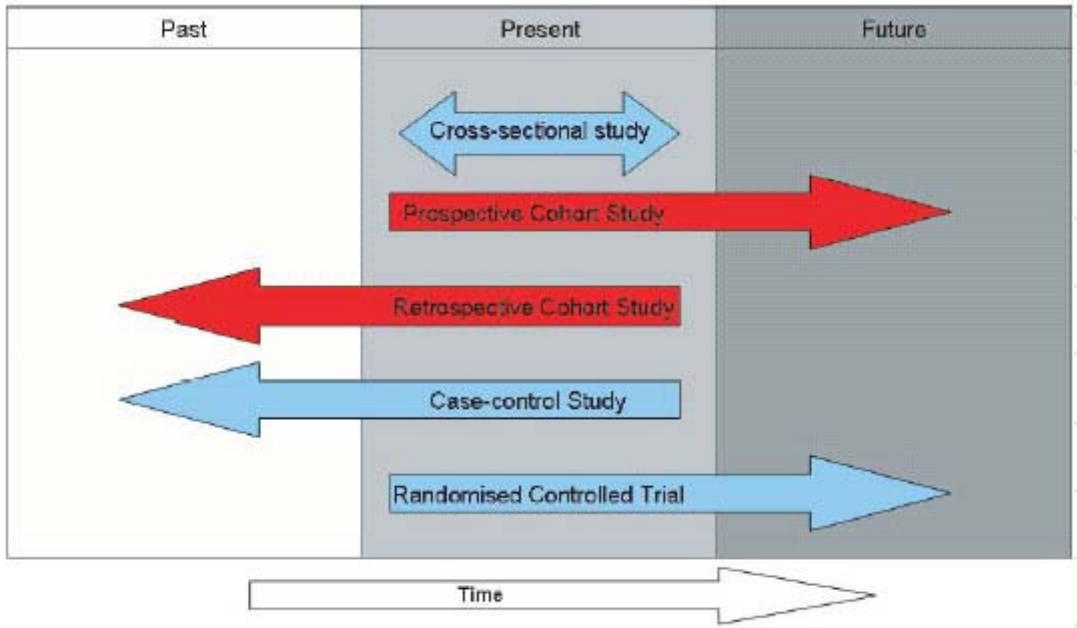


Quando esiste un sistema di registrazione che contiene informazioni su: esposizione ed evento è possibile eseguire uno studio che ricostruisce l'esperienza della coorte nel passato tale disegno si dice di coorte storica o retrospettivo

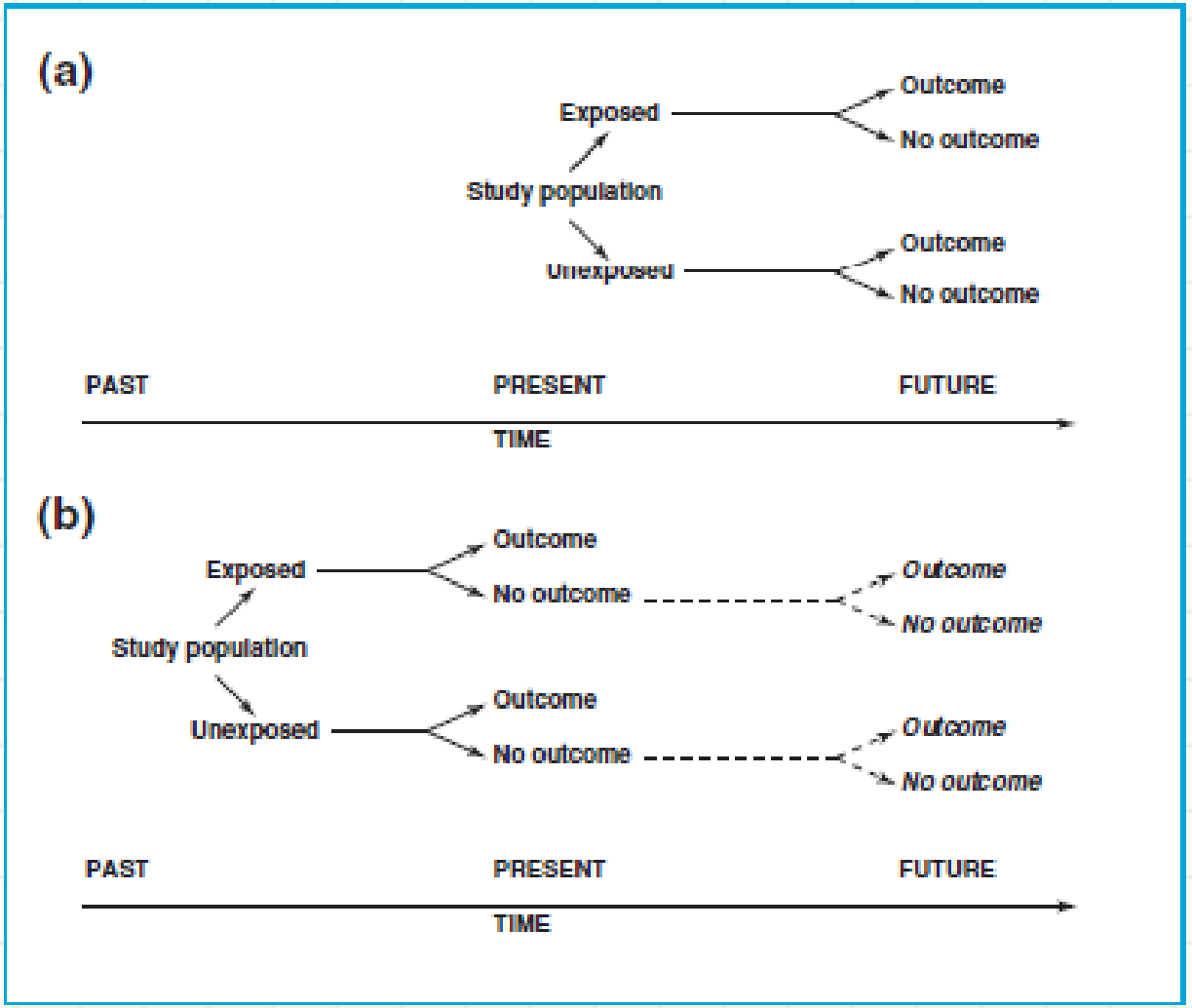
Coorte storica

- Ridotto tempo di realizzazione
- Ridotti costi
- Dimensione dello studio, variabili in studio e qualità dei dati non possono essere modificati ma sono intrinseci agli archivi storici disponibili

Retrospettivo, trasversale, prospettico



Levin A. **Study design IV: Cohort studies**
Evidence-Based Dentistry 2003; **7:** 51–52.



La direzione dello studio esposizione>malattia è la stessa nel disegno prospettico e storico

Disegni ibridi

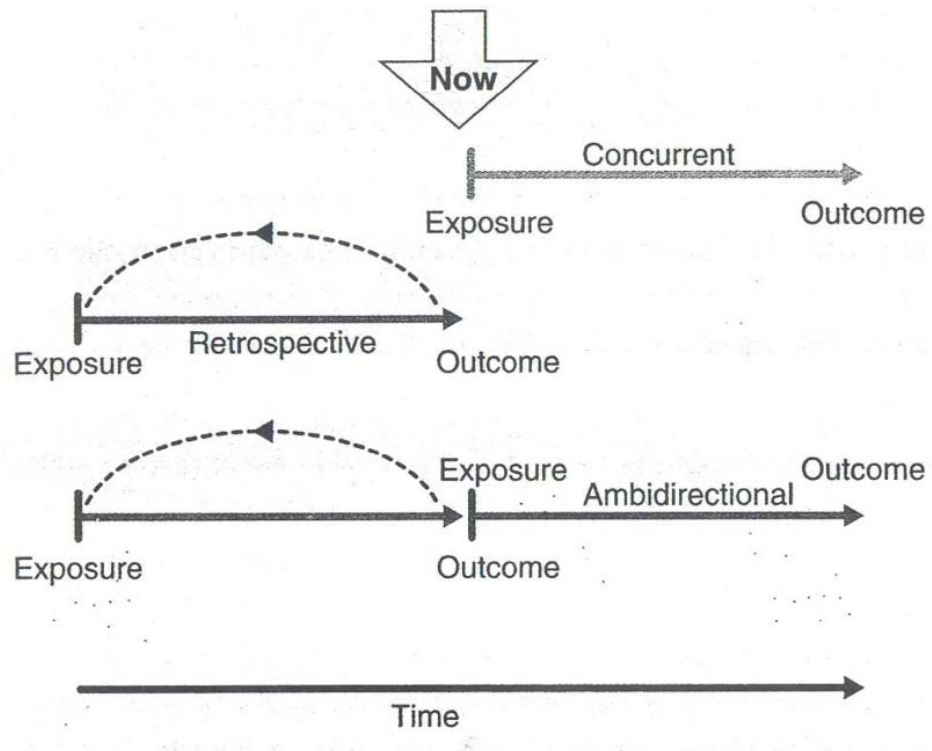


Fig. 4.2 Schematic diagram of concurrent, retrospective and ambidirectional cohort studies.

Da Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet* 2002

- La misura / ricostruzione dell'esposizione può avvenire al momento dell'arruolamento o ricostruire la storia di esposizione
- La individuazione dell'evento può essere prospettica in uno studio con valutazione storica dell'esposizione

Coorti: selezione della popolazione in studio

- Popolazione generale (residenti in un'area)
- Sottogruppi della popolazione (medici, infermiere: studio esposizioni non specifiche)
- Coorti occupazionali (studio di esposizioni professionali)

- L'individuazione delle condizioni di un esperimento naturale in cui esposti e non esposti hanno simile disposizione a sviluppare la malattia (le popolazioni esposta e non esposta differiscono per la sola esposizione) rappresenta la condizione di maggiore validità dello studio

Criteri di selezione

La scelta della popolazione da studiare (esposti e non esposti) dipende da vari elementi come

- la difficoltà di definire gli appartenenti (identificabilità),
- la possibilità di seguire nel tempo la coorte,
- l'interesse dello studio alla indagine di uno o più fattori,
- la diffusione dell'esposizione

"A *general population cohort may be drawn from a geographically well* defined area

, which is initially surveyed to establish baseline exposure status with respect to a number of factors and then examined periodically to ascertain disease outcomes. One of the great **advantages of this type of cohort study is that it allows a large number of common exposures to be considered in relation to a large number of outcomes**. The Framingham Study is a classical example of this.

Chapter 8 – Cohort studies in Cancer Epidemiology: Principles and Methods IARC Non serial Publication Edited by I. Dos Santos Silva

The Framingham Study

- Approximately 5000 residents of the town of Framingham, in Massachusetts (USA), have been followed up since 1948 (Dawber *et al.*, 1951). There were several reasons for selecting this location for the study, mainly determined by logistic and other practical considerations to ensure that it would be feasible to identify and follow participants for many years.

The Framingham Study

- At the time the study was set up, Framingham was a relatively **stable community including both industrial and rural areas**, with a number of occupations and industries represented. The town was small enough to allow residents to come to **one central examining facility and there was only one major hospital**.
- Follow-up of this cohort has permitted assessment of the effects of **a wide variety of factors (e.g., blood pressure, serum cholesterol, alcohol intake, physical exercise, smoking) on the risk of numerous diseases**, ranging from cardiovascular diseases and cancer to gout, gallbladder disease and eye conditions.

The Nurses'Health Study

Design and population

A longitudinal study of **a cohort of 121,700 registered nurses** to examine the **relation between contraception and breast cancer; later expanded to include diet and other exposures and outcomes**

Length of follow-up

Women enrolled in 1976; **20 year** follow-up conducted in 1996

Enrollment, consent, and baseline activities

- Participants were registered nurses recruited by mail via an introductory letter, two-page questionnaire, and prepaid return envelope
- Information collected at baseline to assist in tracking included the participant's name, Social Security number, birthdate, and the name, address, and phone number of a personal contact

The Nurses'Health Study

- Registered nurses were selected to be followed prospectively.
- We anticipated **because of their nursing education, they would be able to respond with a high degree of accuracy** to brief, technically-worded questionnaires and would be motivated to participate in a long term study

Identificazione del gruppo di controllo

- Interno: la popolazione selezionata viene suddivisa in base alla esposizione in due o più coorti
- Esterno: la coorte esposta è confrontata con una coorte ritenuta confrontabile o con la incidenza di malattia nella popolazione generale

Gruppi di controllo per uno studio di coorte occupazionale

- Gruppo di controllo **interno**: occupati nella stessa coorte ma in mansione non esposta
- Gruppo di controllo **esterno**
  - A: lavoratori con una occupazione simile ma priva di esposizione
  - B: popolazione generale residenti nell'area

Confronto con la popolazione generale

- "In this case, the disease experience observed in the cohort is compared with the disease experience of the general population at the time the cohort is being followed.

+ Comparison with rates in the general population has several disadvantages.

– First, it can be done only for outcomes for which such information exists for the general population.
– Second, it assumes that only a very small proportion of the general population is exposed to the risk factor of interest, otherwise the presence of the exposure in the comparison group will lead to a gross underestimation of its true effect.
– Third, even if the general population is chosen to be as similar as possible to the exposed cohort in relation to basic demographic and geographic characteristics, it may well differ with respect to other risk factors for the disease, such as diet, smoking, etc…"

Chapter 8 – Cohort studies in Cancer Epidemiology: Principles and Methods IARC Non serial Publication Edited by I. Dos Santos Silva

Dimensione dello studio

- In base alla natura della coorte possiamo distinguere studi di coorte condotti su:
- soggetti sani (eziologici)
- persone affette da condizioni di pre-malattia o a rischio elevato di malattia
- soggetti malati
- La dimensione dello studio dipende dalla frequenza degli eventi
- Negli studi eziologici la numerosità necessaria è di solito elevata condizionando elevati costi e l'impossibilità di realizzare studi di coorte per patologie rare

Misura dell'esposizione

Prospective cohort studies have used :

- mailed self-administered questionnaires,
- interviewer-administered questionnaires,
- measures of blood or other tissues,
- physical measures,
- medical tests (such as electrocardiography),
- use of medical or other exposure records, and/or
- measures of the environment (e.g., air or water sampling)
- many studies use multiple methods.

White E, Hunt JR, Casso D. Exposure Measurement in Cohort Studies: The Challenges of Prospective Data Collection. Epidemiologic Reviews 1998; 20: 43-56

- Lo studio di coorte può tener conto della natura dinamica dell'esposizione
- La rilevazione periodica comporta la possibilità di avere dati mancanti per la sola esposizione o per esposizione ed evento

Valutazione dell'esposizione in vari studi di coorte

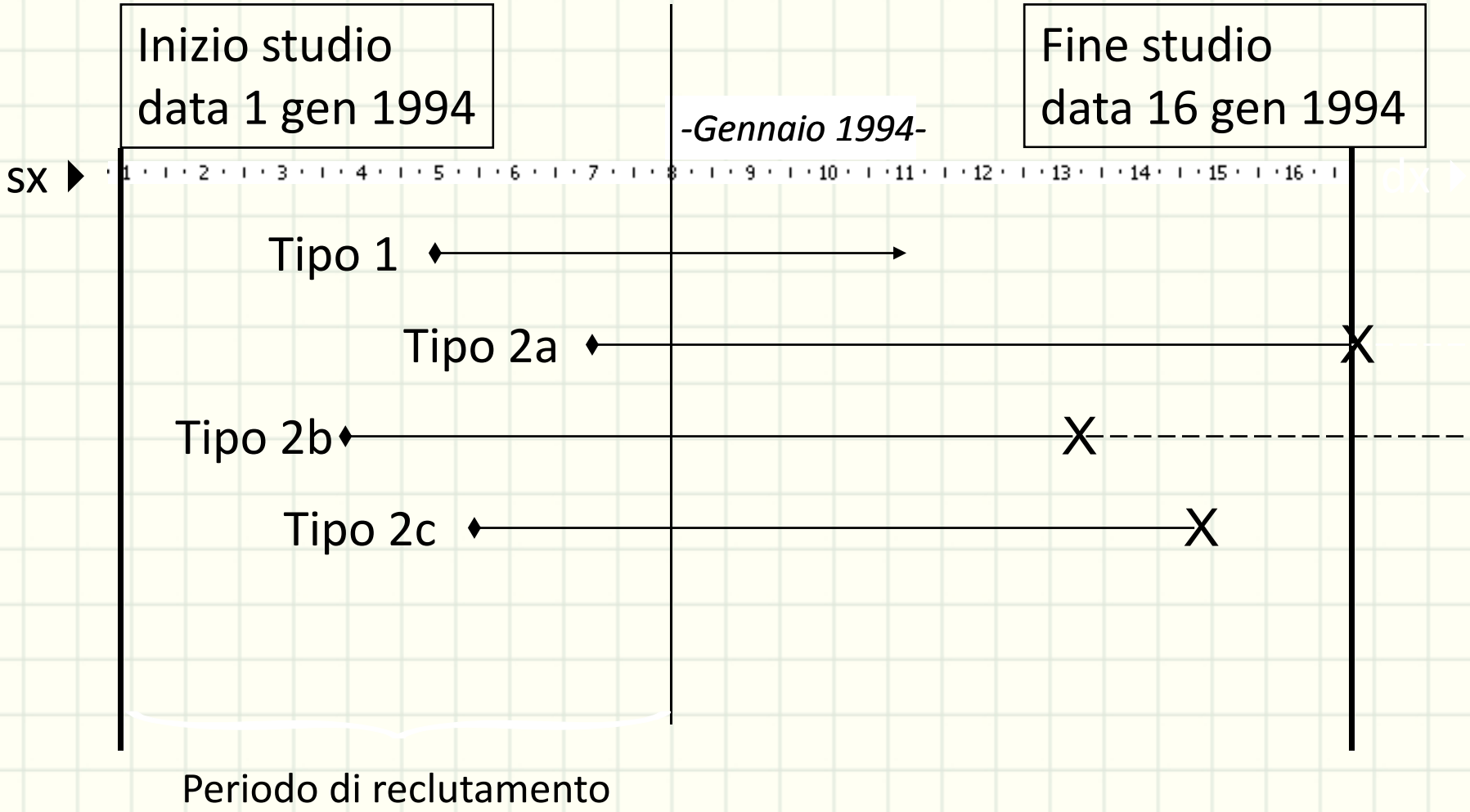
TABLE 1. *Examples of exposure assessment methods in selected prospective cohort studies*

Study (reference(s))	Year begun	Main focus	Study population	Size	Baseline exposure instruments*	Follow-up exposure instruments*	Frequer exposure
The Framingham Heart Study (6–8)	1948	Risk factors for cardiovascular disease	Residents of Framingham, MA, ages 28–62 years	5,209	Interview, clinic examination (PE, lab, tests)	Interview, clinic examination (PE, lab tests)	Every 2 years
Colorado Plateau Uranium Miners Study (9)	1950	Occupational risk factors for cancer	White, male underground uranium miners, Colorado Plateau	3,415	Clinic examination (PE), questionnaire, environmental measures (airborne radiation)	Questionnaire (in-person or mailed), environmental measures (airborne radiation)	Triennial
American Cancer Society: Cancer Prevention Study I (10)	1959	Cigarette smoking and cancer mortality	US men and women aged 30 years and older	1,045,087	Self-administered questionnaire delivered by volunteers	Self-administered questionnaire	Every 2 years
The Alameda County Study (11)	1965	Factors associated with health and mortality	Residents of Alameda County, CA, ages 16–94 years	6,928	Mailed questionnaire; telephone interview or home interview of nonrespondents	Mailed questionnaire; telephone interview or home interview of nonrespondents	At years 9, 18,
Honolulu Heart Program (12)	1965	Coronary heart disease and stroke in men of Japanese ancestry	Men of Japanese ancestry living on Oahu, HI, ages 45–65 years	8,006	Mailed questionnaire, interview, clinic examination (PE, lab, tests)		
The Oral Contraception Study of the Royal College of General Practitioners (13, 14)	1968	Oral contraceptive use and cancer	Married premenopausal British women	47,000	Medical form completed by physician based on patient interview or medical record	Same	Every 6 months
Nurses' Health Study (15, 16)	1976	Originally oral contraceptive use and cancer, expanded to women's health	Married female US registered nurses ages 30-55 years	121,700	Mailed questionnaire	Mailed questionnaire Lab (toenail sample) Lab (home blood draw)	Every 2 years At year 6 At year 13

Follow-up

- La stabilità della coorte è un elemento essenziale degli studi longitudinali
- Lo studio deve disporre di un sistema in grado di rilevare la comparsa dell'evento/malattia
- Il sistema deve essere eguale per esposti e non esposti
- Oltre all'evento in alcuni studi di coorte si valuta periodicamente lo stato e il livello di esposizione

Problemi di osservazione



Tipi di osservazioni

Un'osservazione 'tipo 1' si dice '**osservazione completa'** in quanto sono noti data di ingresso nello studio, data di uscita dallo studio e modalità (cioè l'evento si è verificato durante l'osservazione)

Le osservazioni 'tipo 2' sono accomunate dalla mancata osservazione dell'evento in studio e costituiscono il principale tipo di '**osservazioni incomplete**'.
L'incompletezza delle singole osservazioni riguarda l'estremo destro del tempo in studio *(right censoring)*

Tipi di osservazioni II

Nel 'tipo 2a' la conclusione dello studio interrompe l'osservazione prima che l'evento si sia verificato e si ha una cosiddetta ***censura amministrativa***

Il 'tipo 2b' viene definito '**perso al *follow-up***' : mentre lo studio è in corso, l'individuo non è più osservabile

E' il caso, ad esempio, di un individuo che si trasferisce in una zona sconosciuta da dove non è possibile avere ulteriori informazioni o di uno che interrompe la partecipazione.

Il 'tipo 2c' è caratterizzato dal verificarsi di un **evento competitivo** che preclude la possibilità che l'evento in studio si realizzi

Come un deceduto per infarto in uno studio sulla durata di una fistola artero-venosa

Retaining and tracking cohort participants is crucial for "longitudinal" cohort studies

Hunt JR and White E. Retaining and Tracking Cohort Study Members: *Epidemiologic Reviews* 1998; 20:57-70

- Effetto della perdita i. non differenziale: tende a ridurre la dimensione dello studio e quindi la capacità di evidenziare differenze di rischio tra i gruppi; ii. differenziale: la perdita selettiva tende ad alterare il risultato del confronto tra le coorti

Remedia

- Selezione di coorti stabili ed identificabili
- Inclusione soggetti con speranza di vita adeguata rispeto alla durata prevista dello studio (esclusione anziani, gravi patologie)
- Utilizzo di procedure per limitare gli abbandoni e recuperare comunque informazioni sui persi al follow-up

The Nurses'Health Study: Follow-up procedures

Follow-up procedures and intervals

- Follow-up questionnaires are mailed to all cohort members every 2 years
- Questionnaires are mailed with a cover and a newsletter updating participants on study progress
- Personal contacts are identified by study members every 4 years
- First questionnaire is mailed in June; second mailing is sent to nonresponders in September
- Third and fourth mailings with full questionnaire are sent to nonresponders
- Fifth mailing of short version questionnaire with key exposure variables and outcomes is sent to nonresponders
- Newsletter with study updates is included in fifth mailing

Extra efforts to minimize nonresponse

- A telephone follow-up to nonresponders (to the five mailings) was added in 1982
- Additional approaches were added in 1986, including sending questionnaires by United Parcel Service and certified mail
- In 1990, used both telephone and certified mail to reach nonresponders from earlier years

Framingham Heart Study

Da Wikipedia

- Over 1000 medical papers have been published related to the Framingham Heart Study. It is generally accepted that the work is outstanding in its scope and duration, and overall is considered very useful.
- It was rightly assumed from the start of the Framingham Heart Study that cardiac health can be influenced by lifestyle and environmental factors, and by inheritance.
- The Framingham Heart Study is the origin of the term **risk factor**. **Before the Framingham Heart Study, doctors had little sense of prevention. In the 1950s, it was believed that clogging of arteries and narrowing of arteries (atherosclerosis, arteriosclerosis) was a normal part of aging and occurred universally as people became older.** High blood pressure (hypertension) and elevated serum cholesterol (hypercholesterolemia) were also seen as normal consequences of aging in the 1950s, and no treatment was initiated. These and further risk factors, e.g., homocysteine, were gradually discovered over the years.[3][4][5][6][7]

Framingham Heart Study

Da Wikipedia

- The Framingham Heart Study, along with other important large studies, e.g., the Seven Countries Study, Nurses' Health Study, Women's Health Initiative, also showed the importance of healthy diet, not being overweight or obese, and regular exercise in maintaining good health, and that there are differences in cardiovascular risk between men and women.[8][9] It also confirmed that cigarette smoking is a highly significant factor in the development of heart disease, leading to angina pectoris, myocardial infarction (MI), and coronary death, along with other important studies about smoking, e.g., the British Doctors Study.[10][11]

Major findings from the Framingham Heart Study

1960s Cigarette smoking increases risk of heart disease. Increased cholesterol and elevated blood pressure increase risk of heart disease. Exercise decreases risk of heart disease, and obesity increases it.

1970s Elevated blood pressure increases risk of stroke. In women who are postmenopausal, risk of heart disease is increased, compared with women who are premenopausal. Psychosocial factors affect risk of heart disease.

1980s High levels of HDL cholesterol reduce risk of heart disease.

1990s Having an enlarged left ventricle of the heart (left ventricular hypertrophy) increases risk of stroke. Elevated blood pressure can progress to heart failure.

Framingham Risk Score is published, and correctly predicts 10-year risk of future coronary heart disease (CHD) events. At 40 years of age, the lifetime risk for CHD is 50% for men and 33% for women.

Major findings from the Framingham Heart Study

2000s

- So called "high normal blood pressure" increases risk of cardiovascular disease (high normal blood pressure is called prehypertension in medicine; it is defined as a systolic pressure of 120–139 mm Hg and/or a diastolic pressure of 80–89 mm Hg). Lifetime risk of developing elevated blood pressure is 90%.
- Obesity is a risk factor for heart failure. Serum aldosterone levels predict risk of elevated blood pressure. Lifetime risk for obesity is approximately 50%.
- Social contacts of individuals are relevant to whether a person is obese, and whether cigarette smokers decide to quit smoking. Four risk factors for a precursor of heart failure are discovered. 30-year risk for serious cardiac events can be calculated.

2000s segue

- Inheritance patterns in families,[17] heritability and genetic correlations,[18] molecular markers,[19] and associations have been studied. The **association studies** include traditional genetic association studies, i.e., looking for associations of cardiovascular risk with gene polymorphisms (single-nucleotide polymorphisms, SNPs) in candidate genes, and **genome wide association studies (GWAS)**.[7] For example, one genome wide study, called the 100 K Study, included almost 1400 participants of the Framingham Heart Study (from the original cohort, and the offspring cohort), and revealed a genetic variant associated with obesity. The researchers were able to replicate this particular result in four other populations.[20] Further, the SHARe Study (SNP Health Association Resource Study) uncovered new candidate genes, and confirmed already known candidate genes (for homocysteine and vitamin B12 levels) in participants of the Framingham Heart Study.[21]Some genes increase risk of atrial fibrillation. ..

Nurses' Health Study (original cohort)

- The Nurses' Health Study was established by Dr. Frank Speizer in 1976 with funding from the National Institutes of Health. The primary motivation in starting the NHS was to investigate the potential long term consequences of the use of oral contraceptives, a potent drug that was being prescribed to hundreds of millions of normal women.
- Registered nurses were selected to be followed prospectively. We anticipated because of their nursing education, they would be able to respond with a high degree of accuracy to brief, technically-worded questionnaires and would be motivated to participate in a long term study.
- Married registered nurses who were aged 30 to 55 in 1976, who lived in the 11 most populous states and whose nursing boards agreed to supply the study with their members' names and addresses were enrolled in the cohort if they responded to our baseline questionnaire. The original states were California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania and Texas.
- Approximately 122,000 nurses out of the 170,000 mailed responded. Every two years cohort members receive a follow-up questionnaire with questions about diseases and health-related topics including smoking, hormone use and menopausal status.

Nurses' Health Study (original cohort) 2

- Because we recognized that diet and nutrition would play important roles in the development chronic diseases, in 1980, the first food frequency questionnaire was collected. Subsequent diet questionnaires were collected in 1984, 1986 and every four years since.
- At the request of some of the nurses and with the addition of investigators to the research team interested in quality of life issues, question related to quality-of-life were added in 1992 and repeated every four years.
- Because certain aspects of diet cannot be measured by questionnaire, particularly minerals that become incorporated in food from the soil in which it is grown, the nurses submitted 68,000 sets of toenail samples between the 1982 and 1984 questionnaires.
- Similarly, to identify potential biomarkers, such as hormone levels and genetic markers, 33,000 blood samples were collected in 1989-90 followed by second samples from 18,700 of these participants in 2000-01. These samples are stored and used in case/control analyses.
- As of this writing, response rates to our questionnaires are at 90% for each two-year cycle.

Nurses' Health Study II

- The Nurses' Health Study II was established by Dr. Walter Willett and colleagues in 1989 with funding from the National Institutes of Health. The primary motivation for developing the Nurses' Health Study II was to study oral contraceptives, diet and lifestyle risk factors in a population younger than the original Nurses' Health Study cohort.
- This younger generation included women who started using oral contraceptives during adolescence and were thus maximally exposed during their early reproductive life. Several case-control studies suggesting such exposures might be associated with substantial increases in risk of breast cancer provided a particularly strong justification for investment in this large cohort. Further, we planned to collect detailed information on type of oral contraceptive used, which was not obtained in the Nurses' Health Study.
- The initial target population was women between the ages of 25 and 42 years in 1989; the upper age was to correspond with the lowest age group in the Nurses' Health Study. The original goal was to enroll 125,000 women. Our strategy was to do a single mailing inviting women to enroll and then only enroll the most enthusiastic potential participants who would complete a single questionnaire after one request, thus identifying those who would be most likely to continue participation during the follow-up period.

Nurses' Health Study II

- We anticipated that follow-up in this population might be complicated and difficult because it represented the time of life where names might change because of marriage, professional changes would be frequent, and women would have complicated, busy lives because of child-bearing.
- We contacted state nursing boards in states with large populations and in states whose nursing boards were able to provide information on gender and date of birth or age. The following states were included in the initial mailing: California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina and Texas. The overall response rate to the baseline mailing was approximately 24% (123,000 of 517,000.) After exclusions for incomplete forms and women who did not meet study criteria, a total of 116,686 women remained in Nurses' Health Study II.
- Developing the baseline questionnaire, we relied heavily on our experience from the Nurses' Health Study. We conducted a number of small pilot studies to optimize the wording for the complex questions on lifetime oral contraceptive use, particularly to make them suitable for an optically scannable format. We also sent draft versions of the questionnaire to leading colleagues in the field of breast cancer research and incorporated their feedback into the final version. A color booklet containing pictures of all oral contraceptive preparations ever sold in the United States was developed and mailed to participants with the baseline questionnaire.
- Every two years, cohort members receive a follow-up questionnaire with questions about diseases and health-related topics including smoking, hormone use, pregnancy history, menopausal status. In 1991, the first food-frequency questionnaire was collected and subsequent food-frequency questionnaires are administered at four-year intervals. A two-page quality-of-life supplement was included in the first mailing of the 1993 and 1997 questionnaires.
- Blood and urine samples from approximately 30,000 nurses were collected in the late 1990's.
- As of this writing, response rates to NHS II questionnaires are at 90% for each two-year cycle.

Nurses' Health Study III

- In 2010, Drs. Walter Willett, Janet Rich-Edwards, Stacey Missmer, and Jorge Chavarro started Nurses' Health Study 3 in collaboration with investigators at the Channing Laboratory and the Harvard School of Public Health. For the first time ever, the study is entirely web-based. Participants include female LPN/LVNs and RNs, and it's also open to nurses in Canada. NHS3 aims to be more representative of nurses' diverse backgrounds. It will closely look at health issues related to lifestyle, fertility/pregnancy, environment, and nursing exposures.

The most striking finding, according to one of the lead investigators

- "The overall message is that heredity isn't destiny," she said. "We largely control our risk of these major diseases through our lifestyle practices. The findings are really striking to us."

Jo Ann E. Manson, M.D., Dr.P.H., professor of medicine at Harvard Medical School and chief of preventive medicine at Brigham and Women's Hospital

The most striking finding

- NHS found that the vast majority of heart attacks in women are preventable through relatively simple lifestyle modifications—
- exercising regularly,
- maintaining healthy weight, and
- making dietary changes such as reducing saturated fats (found in meat and high-fat dairy products like butter) and *trans* fatty acids (found in baked goods containing partially hydrogenated vegetable oils, such as pastries), increasing fiber and fruits and vegetables, and not smoking.
- Lifestyle factors may prevent at least 80% of adult-onset diabetes and 70% to 80% of heart disease and stroke.

THE NEW ENGLAND JOURNAL OF MEDICINE Sept. 12, 1991

POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

Ten-Year Follow-up from the Nurses' Health Study

MEIR J. STAMPFER, M.D., GRAHAM A. COLDITZ, M.B., B.S., WALTER C. WILLETT, M.D., JOANN E. MANSON, M.D., BERNARD ROSNER, PH.D., FRANK E. SPEIZER, M.D., AND CHARLES H. HENNEKENS, M.D.

Abstract *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal,* based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

Methods. We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976, when 121,700 female registered nurses in the United States completed questionnaires sent to them by mail about their medical history, including previous cardiovascular disease, menopause, diabetes, hypertension, high serum cholesterol levels, and parental myocardial infarction. We included questions on height, weight, smoking, the use of postmenopausal hormones, and the use of oral contraceptives.[5] Every two years, follow-up questionnaires were mailed to obtain updated information and identify newly diagnosed major illnesses. A dietary questionnaire was added in 1980.[6]

Questionario

Ascertainment of Estrogen Use

In 1976 the women were asked whether they had taken hormone supplements after menopause, and if so, for how long. Information on hormone use, including the type taken, was updated in the subsequent questionnaires sent every two years through 1986, with explicit questions about current use and duration of use in the intervening period. Because no information on current use was explicitly

Evento: questionario + accerrtamento

Identification and Confirmation of Cardiovascular End Points

The study end points included nonfatal myocardial infarction, fatal coronary heart disease, coronary-artery bypass grafting or angioplasty, fatal and nonfatal stroke, total cardiovascular mortality, and deaths from all causes after the return of the 1976 questionnaire but before June 1, 1986. Nurses who reported having a nonfatal myocardial infarction or stroke on a follow-up questionnaire were asked for permission for a study investigator to review their medical records. Nonfatal myocardial infarctions were considered confirmed by hospital records if they met the World Health Organization criteria[7] (i.e., symptoms plus either cardiac-enzyme elevations or diagnostic electrocardiographic changes). Myocardial infarctions that required hospitalization and for which confirmatory information was obtained by interview or letter, but for which no medical records were obtainable, were designated as probable. Thus, infarc-

Table 1. Distribution of Characteristics and Coronary Risk Factors Reported by the Women in the Cohort, According to Postmenopausal Hormone Use, with Standardization for Age.*

VARIABLE	HORMONE USE		
	CURRENT	FORMER	NONE
	percent of subjects		
Parental MI before the age of 60	10.6	10.0	9.3
Hypertension	23.2	25.0	21.8
Diabetes mellitus	2.7	3.8	3.5
High serum cholesterol	9.9	11.2	7.6
Current smoker (15–24 cigarettes/day)	11.2	14.7	14.5
Quetelet index ≥29†	9.8	13.3	15.0
Bilateral oophorectomy	50.3	39.3	9.3
Past use of oral contraceptives	34.0	27.6	23.9
Vigorous physical activity ≥1 time/week‡	48.2	43.1	42.4
	grams per day		
Mean dietary intake‡§			
Saturated fat	27.6	26.2	26.7
Cholesterol	0.32	0.32	0.32
Polyunsaturated fat	8.9	8.7	8.7
Dietary fiber	17.3	17.2	16.8
Alcohol	7.9	7.5	7.3

*Data are standardized to the age distribution of the person-years of follow-up for the cohort, from 1976 through 1986. MI denotes myocardial infarction.

†The Quetelet index was calculated by dividing the weight in kilograms by the square of the height in meters.

Conclusions. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.

Come è andata a finire?

- Aveva ragione lo studio Framingham o il Nurse's?
- La controversia è stata risolta?

- La conoscenza si forma mediante
  - ripetizione degli studi e ri-formulazione dei quesiti in base alle evidenze
  - Ricorso a studi che forniscono evidenze più solide

Studio di coorte < Studio sperimentale randomizzato controllato

Table 1 Comparison of cohort studies and randomised controlled trials

Item	Cohort studies	Randomised controlled trials
Populations studied	Diverse populations of patients who are observed in a range of settings	Highly selected populations recruited on the basis of detailed criteria and treated at selected sites
Allocation to the intervention	Based on decisions made by providers or patients	Based on chance and controlled by investigators
Outcomes	Can be defined after the intervention and can include rare or unexpected events	Primary outcomes are determined before patients are entered into study and are focused on predicted benefits and risks
Follow-up	Many cohort studies rely on existing experience (retrospective studies) and can provide an opportunity for long follow-up	Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence
Analysis	Sophisticated multivariate techniques may be required to deal with confounding	Analysis is straightforward

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer Ann Intern Med. 2013;158:47-54.

- The USPSTF recommends **against** the use of **combined estrogen and progestin** for the prevention of chronic conditions **in postmenopausal women**. (Grade D* recommendation).

* The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

Population	Postmenopausal women	Postmenopausal women who have had a hysterectomy
Recommendation	Do not prescribe combined estrogen and progestin for the prevention of chronic conditions. Grade: D	Do not prescribe estrogen for the prevention of chronic conditions. Grade: D

Risk Assessment	This recommendation applies to the average-risk population. Risk factors for a specific chronic disease or individual characteristics that affect the likelihood of a specific therapy-associated adverse event may cause a woman's net balance of benefits and harms to differ from that of the average population.	
Preventive Medications	Although combined estrogen and progestin therapy (specifically, oral conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d) decreases the risk for fractures in postmenopausal women, there is an accompanying increased risk for serious adverse events, such as stroke, invasive breast cancer, dementia, gallbladder disease, deep venous thrombosis, and pulmonary embolism. Estrogen therapy (specifically, oral conjugated equine estrogen, 0.625 mg/d) decreases the risk for fractures and has a small effect on the risk for invasive breast cancer, but it is also associated with important harms, such as an increased likelihood of stroke, deep venous thrombosis, and gallbladder disease. Neither combined estrogen and progestin therapy nor estrogen alone reduces the risk for coronary heart disease in postmenopausal women.	
Balance of Benefits and Harms	The chronic disease prevention benefits of combined estrogen and progestin do not outweigh the harms in most postmenopausal women.	The chronic disease prevention benefits of estrogen are unlikely to outweigh the harms in most postmenopausal women who have had a hysterectomy.

CHD

- **Cardiovascular Events**
- The primary outcome of interest in WHI* was the rate of CHD (defined as CHD death plus total myocardial infarction rate). Although **observational evidence previously suggested a protective effect of hormone therapy on CHD, these findings were not replicated in WHI**.
- Combined estrogen and progestin therapy *showed a trend toward an increased risk* for CHD after 5 years of follow-up, which persisted through 8.6 years (HR, 1.22 [CI, 0.99 to 1.50]).
- For the overall enrolled population, there was no reduction in the risk for CHD with estrogen alone after nearly 8 years of follow-up (HR, 0.95 [CI, 0.78 to 1.15]) (6, 7).
- *Subgroup analysis* did reveal a potential reduction in CHD in women aged 50 to 59 years (HR, 0.59 [CI, 0.38 to 0.90]) but not in women aged 60 to 69 or 70 to 79 years (15); this finding warrants confirmation in future studies.

**WHI : Women's Health Initiative (randomized, controlled trial)*

Ictus

- Women's risk for stroke is statistically significantly increased with the use of postmenopausal hormone therapy.
- The estrogen-only group in WHI was stopped early because of the observed increased stroke rate (HR, 1.36 [CI, 1.08 to 1.71]); the estrogen and progestin group reported similar findings (6, 7).