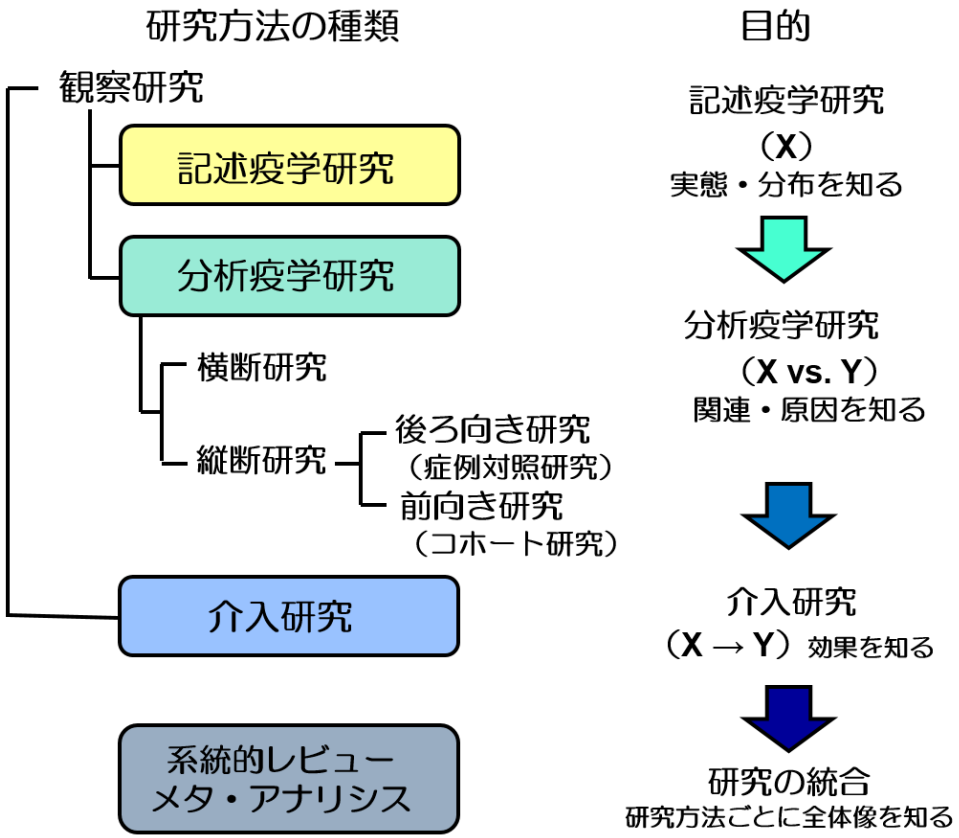
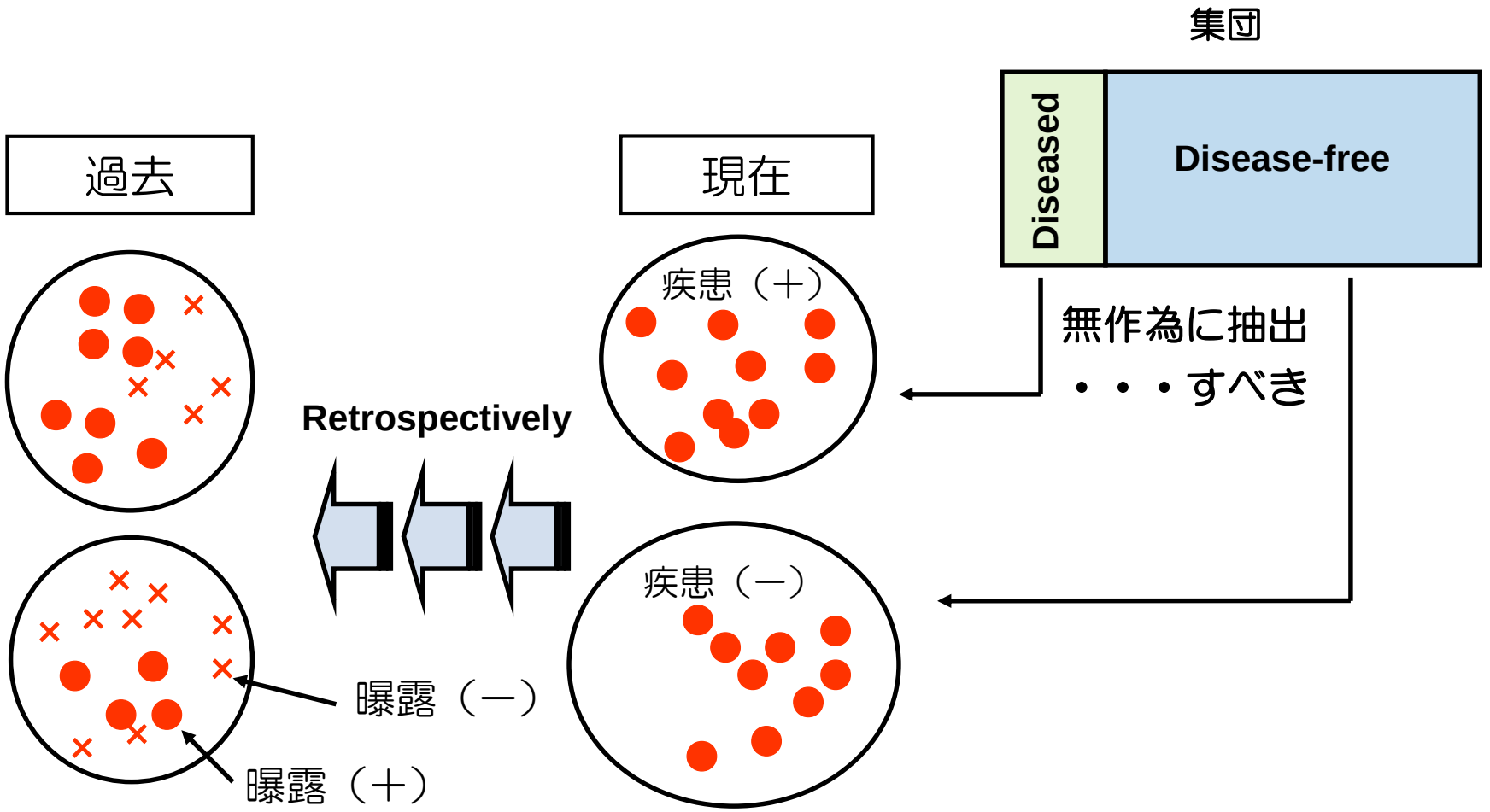
症例対照研究（case-control study）

原因を知りたい問題（疾病）をもつ集団と問題を持たない集団の特性を比較検討する疫学研究

結果（疾病）から見て群を分けている点に注意
（結果を先につかまえて、後からその原因を見つけに行くという方法）



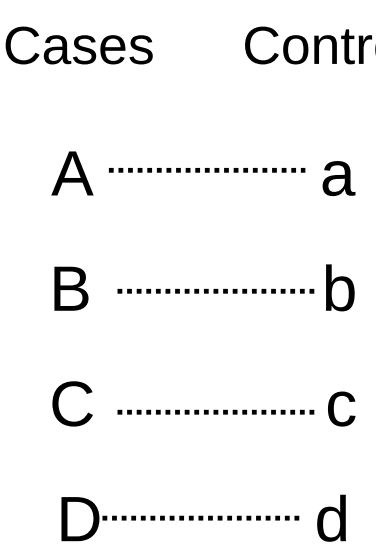
Case-control study: research in inverse



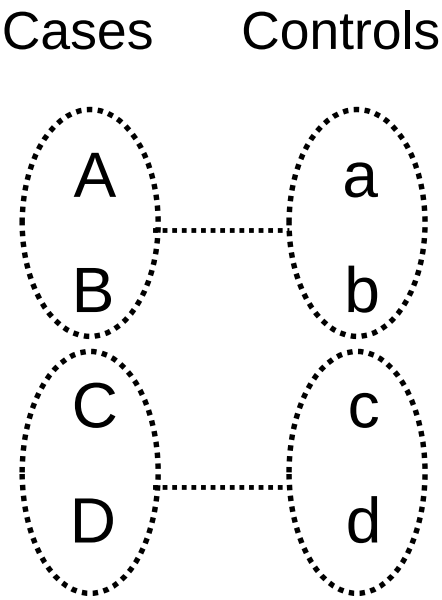
対照群には集団代表性が保証されるべきである…が。

Controlling confounding factors

No difference between case and control groups for all the possibly-related factors (confounding factors) except for the factor of interest.



Subject (individual) matching



Group matching

症例対照研究の例

#9215. Miyake, et al. Int J Tuberc Lung Dis 2006; 10: 333-9.

Dietary fat and meat intake and idiopathic pulmonary fibrosis: a case-control study in Japan.

Mortality of IPF = 3.3 (M) and 2.5 (W) per 100,000 persons in Japan.

The median survival time is 4.2 yrs

Case = idiopathic pulmonary fibrosis (IPF) diagnosed within 2 years

Control = acute bacterial pneumonia or common cold

Age > 40yrs.
21 collaborating hospitals and 29 affiliated hospitals.

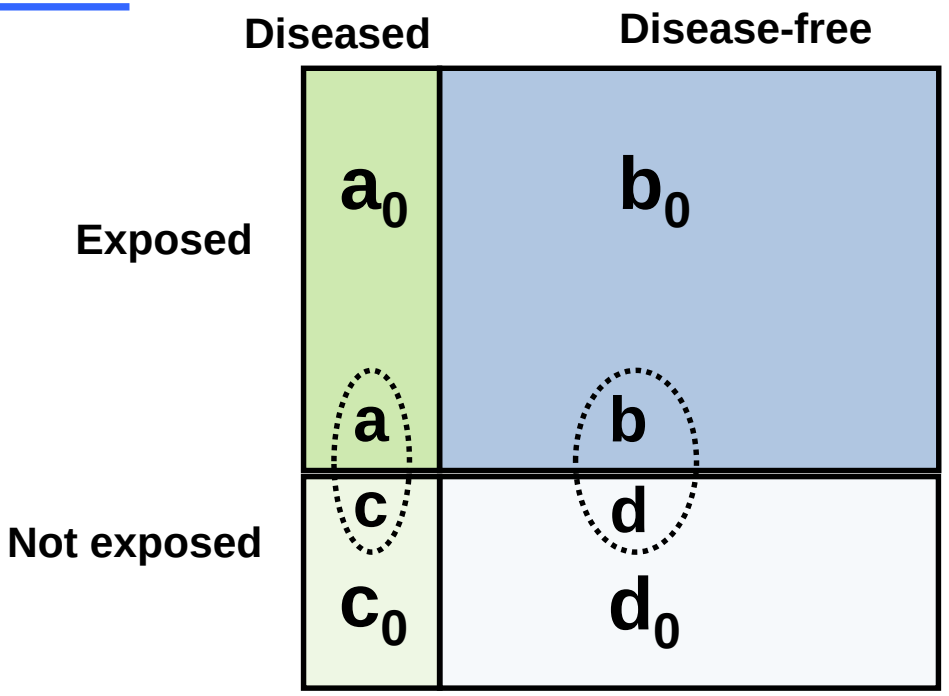
Dietary habits = at present

結果の前に、対象者の特性（**characteristics**）をしっかりと示すことが重要（表１の役目）

Table 1 Characteristics of study population

Variable	*n* (%) or mean (SD) Cases (*n* = 104)	Controls (*n* = 60)
Sex male (%)	94 (90.4)	55 (91.7)
Age, years (%)		
40–49	3 (2.9)	2 (3.3)
50–59	16 (15.4)	19 (31.7)
60–69	56 (53.9)	25 (41.7)
⩾70	29 (27.9)	14 (23.3)
Region (%)		
Kanto-Koshinetsu	57 (54.8)	27 (45.0)
Tokai	12 (11.5)	10 (16.7)
Kinki	14 (13.5)	5 (8.3)
Chugoku-Shikoku	4 (3.9)	7 (11.7)
Kyushu	17 (16.4)	11 (18.3)
Pack-years of smoking (%)		
Never	20 (19.2)	15 (25.0)
>0–19.9	10 (9.6)	11 (18.3)
20.0–39.9	30 (28.9)	10 (16.7)
40.0–59.9	29 (27.9)	15 (25.0)
⩾60.0	15 (14.4)	9 (15.0)
High employment status (%)*	18 (17.3)	8 (13.3)
Occupational exposure (%)†	33 (31.7)	5 (8.3)

		結果（疾病）	
		+	-
原因（暴露）	+	a	b
	-	c	d



Odds ratio = ad / bc

= (a/c)/(b/d) } When sampling is appropriate

≒ $(a_0/c_0)/(b_0/d_0)$

≒ $(a_0/c_0)/[(a_0+b_0)/(c_0+d_0)]$ } When prevalence is low: $a_0 \ll b_0$, $c_0 \ll d_0$

= $([a_0/(a_0+b_0)]/[c_0/(c_0+d_0)]$ = relative risk

サンプリングが適切で、かつ、罹患率が非常に低い場合は、
オッズ比は、相対危険に近似できる（症例対照研究とコホート研究の結果を比較できる）。

・・・多くの研究で問題になるのは「サンプリングが適切か」のほう。さらに、 (a_0/c_0)よりも、(b_0/d_0)を保証するほうが現実的には難しい場合が多いと思われる。

結果の示し方の例

#9215. Miyake, et al. Int J Tuberc Lung Dis 2006; 10: 333-9.

Odds ratios [OR] for idiopathic pulmonary fibrosis by quartiles of intake of selected foods high in fat (a part of the table)

Variable (meat)*	Cases (n)	Controls (n)	Sex and age adjusted OR (95% CI)	Multivariate[1] adjusted OR (95% CI)
Q1 (15.4)	21	20	1.00	1.00
Q2 (32.7)	31	10	2.89 (1.16-8.06)	5.90 (1.76-21.70)
Q3 (44.7)	22	19	1.25 (0.51-3.08)	2.11 (0.71-6.56)
Q4 (79.9)	30	11	3.65 (1.38-10.35)	7.19 (2.15-27.07)

* Quatile medians in g per day adjusted for energy intake using residual methods are given in parentheses.

[1] Adjusted for age, sex, region, pack-years of smoking, employment status, occupational exposure, fruit intake, and body mass index.

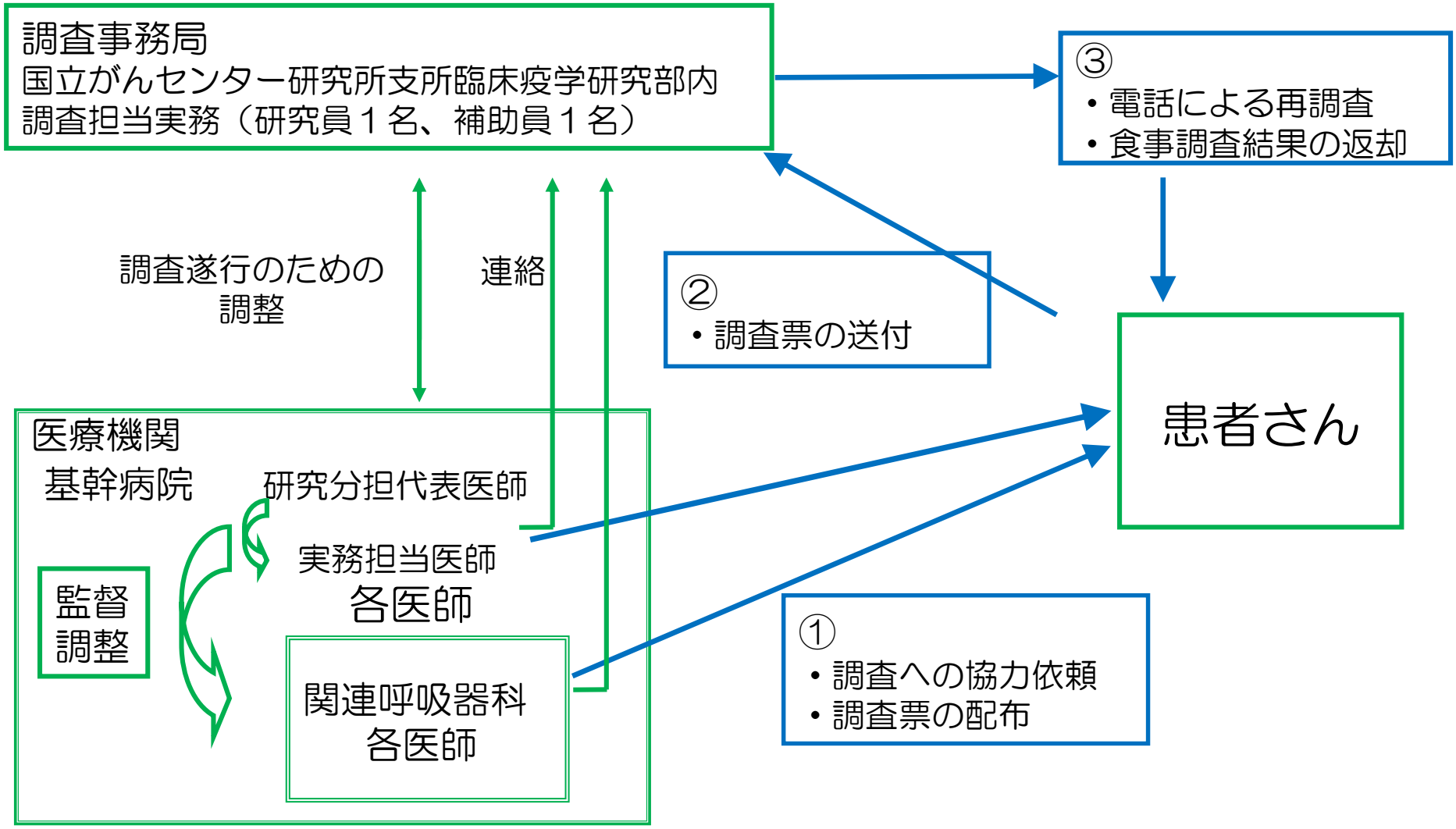
* OR = odds ratio; CI = confidence interval; Q = quartile.

あらかじめ決められた分け方がない場合は、人数が均等になるように分ける。
３分位（tertile）、
４分位（quartile）、
５分位（quintile）など。

対照群が症例群より少ないのは問題。１：１か、それ以上であるべき。
（対照群に比べて…と表現するから）

何が交絡因子になりうるかを知っていて統計学的に調整しているのは偉いが、こんなにたくさんの交絡因子が入らないようにデザインできなかったのか？！

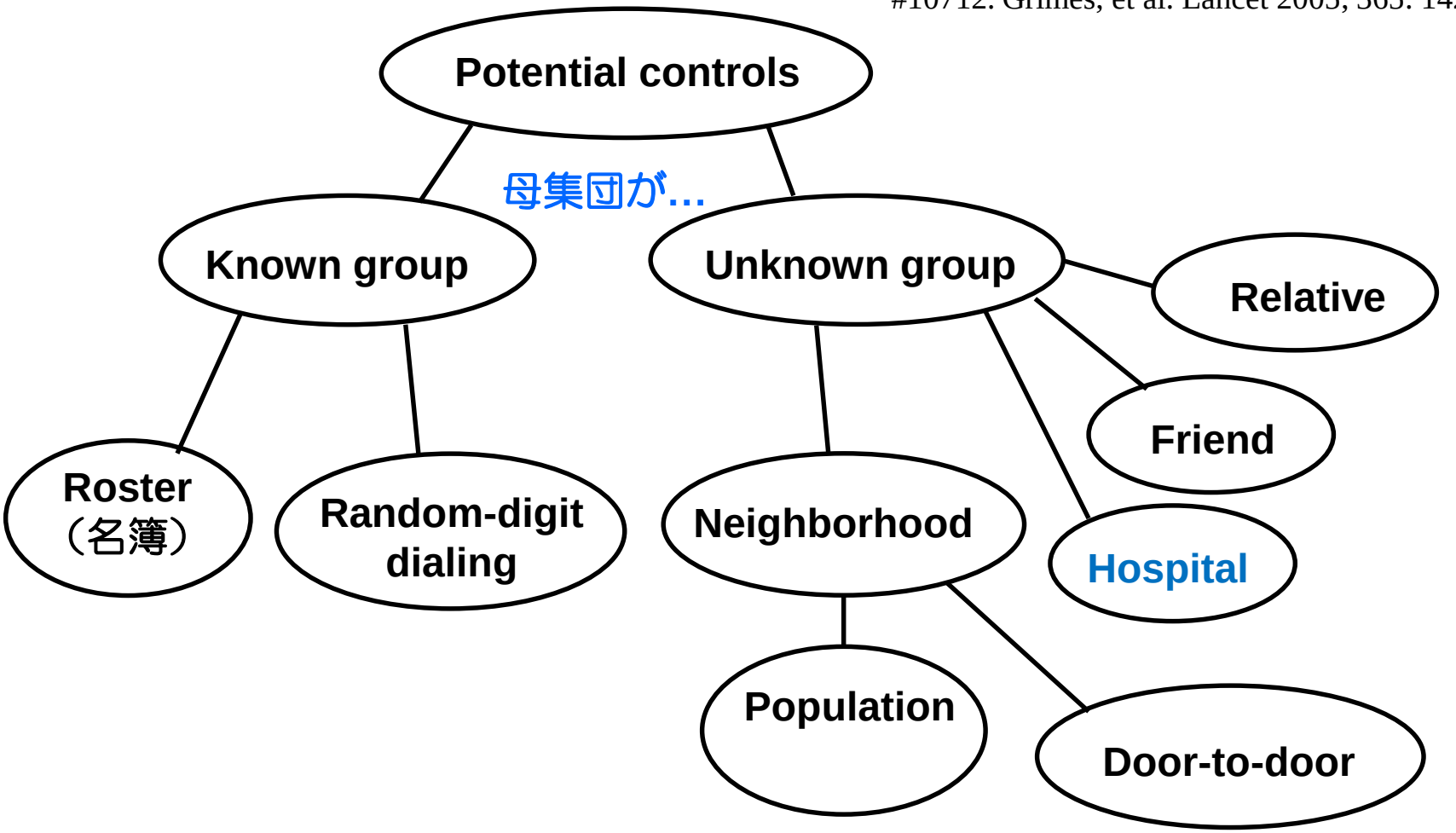
複数の病院で症例対照研究を行なうときの調査作業分担の例



対象者と現場関係者の作業負担を可能な限り軽減させる方法を考えること。

対照群をどこから得るか？

#10712. Grimes, et al. Lancet 2005; 365: 1429-33.



「必要数が得られない。」という問題も大きいが、
「協力的な人を得にくい」という問題のほうが現実的には大きいかもしれない。
（対照群のほうがデータの質が悪くなりがち。）

選択バイアス（selection bias）

対象者の選択に生じるバイアス

Admission rate bias (Berkson’s bias)

病院に来るまでに死亡すると症例になれない。

Incidence-prevalence bias (Neyman’s bias) … Prevalence or incidence

潜在期間が長い疾患は対照群に入ってしまう。

Non-respondent bias

喫煙に関する質問票調査への協力率は非喫煙者よりも喫煙者で低い。

Many others…

いろいろ考えてみてください。

情報バイアス（information bias）
(observation, classification, or measurement bias)

得られる情報に生じるバイアス

もしも、聞き取り者が対象者がどちらの群かを知っていたら…

もしも、症例群の対象者と対照群の対象者が異なって回答したら…

防げることと、防げないことがある。

せめて、防げることは防ぐ努力をしよう。

その前に、何がバイアスになりうるかを予見する力が必要である。

Further readings:

#10713. Schulz KF, Grimes DA. Case-control studies: research in reverse. Lancet 2002; 359: 431-4.

#10712. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. Lancet 2005; 365: 1429-33.

バイアス一覧表 （その１）

#15984. Delgado-Rodriguez M, Llorca J. Bias. J Epidemiol Community Health 2004; 58: 635-41.

No.	Specific name of bias	Group of bias	Subgroup of bias (next level to specific name)	Type of design affected
1	Incidence-prevalence bias (synonym of Neyman bias)			
2	Apprehension bias	Information bias	Observer bias	All studies
3	Competing risks	Selection bias	Ascertainment bias	All studies
4	Differential misclassification bias	Information bias	Misclassification bias	All studies
5	Misclassification bias	Information bias		All studies
6	Mode for mean bias	Information bias	Reporting bias	All studies
7	Non-differential misclassification bias	Information bias	Misclassification bias	All studies
8	Obsequiousness bias	Information bias	Reporting bias	All studies
9	Observer expectation bias	Information bias	Observer bias	All studies
10	Observer/interviewer bias	Information bias	Misclassification bias	All studies
11	Recall bias	Information bias	Misclassification bias	All studies
12	Reporting bias	Information bias	Misclassification bias	All studies
13	Missing information in multivariable analysis	Selection bias	During study implementation	All studies (mainly retrospective)
14	Detection bias	Selection bias	Uneven diagnostic procedures in the target popula	CC study
15	Diagnostic suspicion bias	Selection bias	Detection bias	CC study
16	Exclusion bias	Selection bias	Inappropriate definition of the eligible population	CC study
17	Exposure suspicion bias	Information bias	Recall bias	CC study
18	Friend control bias	Selection bias	Inappropriate definition of the eligible population	CC study
19	Mimicry bias	Selection bias	Detection bias	CC study
20	Overmatching	Selection bias	Inappropriate definition of the eligible population	CC study
21	Relative control bias	Selection bias	Inappropriate definition of the eligible population	CC study
22	Confounding by indication	Confounding		CC study, CH study
23	Rumination bias	Information bias	Recall bias	CC study, retrospective CH study
24	Detection bias	Information bias	Misclassification bias	CH study
25	Diagnostic suspicion bias	Information bias	Detection bias	CH study
26	Mimicry bias	Information bias	Detection bias	CH study
27	Healthy worker effect	Selection bias	Inappropriate definition of the eligible population	CH study (mainly retrospective)
28	Losses/withdrawals to follow up	Selection bias	During study implementation	CH study, trial
29	Regression dilution bias	Information bias	Regression to the mean	CH study, trial
30	Regression to the mean	Information bias		CH study, trial

バイアス一覧表 （その2）

No.	Specific name of bias	Group of bias	Subgroup of bias (next level to specific name)	Type of design affected
31	Neyman bias	Selection bias	Ascertainment bias	CS study, CC study with prevalent cases
32	Length biased sampling	Selection bias	Ascertainment bias	CS study, screening
33	Confounding by group	Confounding		Ecological study
34	Ecological fallacy	Information bias		Ecological study
35	Berkson's bias	Selection bias	Inappropriate definition of the eligible population	Hospital based CC study
36	Inclusion bias	Selection bias	Inappropriate definition of the eligible population	Hospital based CC study
37	Ascertainment bias	Selection bias	Inappropriate definition of the eligible population	Observational study
38	Centripetal bias	Selection bias	Healthcare access bias	Observational study
39	Diagnostic/treatment access bias	Selection bias	Healthcare access bias	Observational study
40	Family aggregation bias	Information bias	Reporting bias	Observational study
41	Healthcare access bias	Selection bias	Ascertainment bias	Observational study
42	Healthy volunteer bias	Selection bias	Non-response bias	Observational study
43	Non-random sampling bias	Selection bias	Lack of accuracy of sampling frame	Observational study
44	Non-response bias	Selection bias	During study implementation	Observational study
45	Popularity bias	Selection bias	Healthcare access bias	Observational study
46	Protopathic bias	Information bias		Observational study
47	Referral filter bias	Selection bias	Healthcare access bias	Observational study
48	Lack of intention to treat analysis			Randomised trial
49	Lead-time bias	Information bias		Screening study
50	Citation bias	Selection bias	Lack of accuracy of sampling frame	Systematic review/meta-analysis
51	Dissemination bias	Selection bias	Lack of accuracy of sampling frame	Systematic review/meta-analysis
52	Language bias	Selection bias	Inappropriate definition of the eligible population	Systematic review/meta-analysis
53	Post hoc analysis	Selection bias	Publication bias	Systematic review/meta-analysis
54	Publication bias	Selection bias	Lack of accuracy of sampling frame	Systematic review/meta-analysis
55	Allocation of intervention bias	Execution of an intervention		Trial
56	Compliance bias	Execution of an intervention		Trial
57	Differential maturing			Trial
58	Hawthorne effect	Information bias		Trial
59	Participant expectation bias	Information bias	Recall bias	Trial
60	Contamination bias	Execution of an intervention		Trial, mainly community trials
61	Purity diagnostic bias	Selection bias	Spectrum bias	Validity of diagnostic tests

バイアス一覧表

#15984. Delgado-Rodriguez M, Llorca J. Bias. J Epidemiol Community Health 2004; 58: 635-41.

研究の種類別にみたバイアスの数

	疫学研究の種類	バイアスの数（種類）
1	All studies	12
2	Observational study	11
3	Ecological study	2
4	Cross sectional study	2
5	Case-control study	13
6	Cohort study	9
7	Trial	10
8	Systematic review/meta-analysis	5
9	Others	3
10	合計 (バイアスの数[種類]＝61)	67

症例対照研究に特有のバイアス

No.	Specific name of bias	Group of bias	Subgroup of bias (next level to specific name)	Type of design affected
22	Confounding by indication	Confounding		CC study, CH study
17	Exposure suspicion bias	Information bias	Recall bias	CC study
23	Rumination bias	Information bias	Recall bias	CC study, retrospective CH study
14	Detection bias	Selection bias	Uneven diagnostic procedures in the target popula	CC study
15	Diagnostic suspicion bias	Selection bias	Detection bias	CC study
16	Exclusion bias	Selection bias	Inappropriate definition of the eligible population	CC study
18	Friend control bias	Selection bias	Inappropriate definition of the eligible population	CC study
19	Mimicry bias	Selection bias	Detection bias	CC study
20	Overmatching	Selection bias	Inappropriate definition of the eligible population	CC study
21	Relative control bias	Selection bias	Inappropriate definition of the eligible population	CC study
31	Neyman bias	Selection bias	Ascertainment bias	CS study, CC study with prevalent cases
35	Berkson's bias	Selection bias	Inappropriate definition of the eligible population	Hospital based CC study
36	Inclusion bias	Selection bias	Inappropriate definition of the eligible population	Hospital based CC study

症例対照研究の特長をうまく使った例

Does resent alcohol consumption reduce the risk of acute myocardial infarction and coronary death in regular drinkers (Auckland, New Zealand)?

飲酒習慣をもつ人では、飲酒はその直後の心筋梗塞の危険を下げるか？

Non-fatal myocardial infarction in men

No. of drinks in the 24 hours*	Controls (n=458) (%)	Cases (n=278) (%)	Odds ratio (95% confidence interval)	
			Crude	Adjusted**
None	43	51	1.0	1.0
1-2	17	12	0.77	0.73 (0.59-0.91)
3-4	16	11	0.78	0.67 (0.51-0.87)
>4	24	26	0.95	0.76 (0.61-0.95)

Coronary death in men

	(n=294)	(n=172)		
None	46	60	1.0	1.0
1-2	19	11	0.67	0.61 (0.44-0.84)
3-4	18	13	0.75	0.57 (0.41-0.79)
>4	17	16	0.85	0.60 (0.43-0.82)

Controls were a group-matched, age- and sex-stratified random sampling selected from the study population using the electoral rolls as the sampling frame.

* One drink = 8g alcohol.
** Adjusted for age, smoking, and usual alcohol consumption

#1363. Jackson, et al. Am J Epidemiol 1992; 136: 819-24

Does recent alcohol consumption reduce the risk of acute myocardial infarction and coronary death in regular drinkers (Auckland, New Zealand)?

飲酒習慣をもつ人では、飲酒はその直後の心筋梗塞の危険を下げるか？

質問方法

面談方法

非致死性心筋梗塞では、心筋梗塞イベント（発症）のおよそ3～4週後に面談を行った。 対照群は、同じインタビュアーによって同じ研究センターで面談を行った。 死亡例とその対照群では、近親者への面談を面談者の自宅で行った。死亡例の場合は死亡の6～8週間後に行われた。

最近の飲酒

最近の飲酒の影響を調べるために、症例群では発症前24時間以内の飲酒状況を質問票で収集した。 死亡例では症状発現前24時間以内について調べた。対照群では、面接実施1週間以内から無作為に選んだ24時間中の飲酒状況を調べた。

（事前調査）質問票の事前調査では、本人でも家族でも、症例群では、発症前24時間以内の飲酒状況を、たとえ、4～8週間後であっても即座に思い出した。一方、対照群では、7日以上前になると思い出しが困難であった。

#1363. Jackson, et al. Am J Epidemiol 1992; 136: 819-24.

後日談…というか、同じ研究グループによって再び研究が行われた。すると…

Is the apparent cardioprotective effect of recent alcohol consumption due to confounding by prodromal symptoms?

#11635. Wouters, et al. Am J Epidemiol 2000; 151: 1189-93.

Odds ratios (95% confidence intervals) adjusted for age, regular drinking pattern, smoking, and previous coronary heart disease

	Drinking in the past 24 hrs	Myocardial infarction	Coronary death
Jackson, et al.	No	1.0	1.0
	Yes	0.75 (062-0.90)	0.64 (0.50-0.82)
Current study (using the Jackson's criteria)	Yes	0.70 (0.49-1.00)	0.89 (0.53-1.51)
Current study (excluding 24-h nondrinkers who felt unwell)	Yes	0.89 (0.62-1.28)	0.79 (0.48-1.31)

Adjusted odds ratios (95% CI) of MI and coronary disease death (cases=443, controls=763) (adjusted for all other variables)

Variable	Odds ratio
Alcohol drinking during the past 24 hours	1.07 (0.78-1.48)
Prodromal symptoms	**9.21 (3.90-21.77)**
Previous coronary heart disease	9.19 (6.72-12.58)
Gender	4.11 (3.01-5.61)
Age (per year)	1.05 (1.04-1.06)
Regular moderate-heavy drinking	0.65 (0.41-1.02)
Regular light drinking	0.78 (0.53-1.14)
Current smoking	5.12 (3.64-7.20)
Former smoking	1.20 (0.88-1.63)

「前駆症状があったために飲酒を控えた」がバイアスとなって、有意な結果になっていた！

症例対照研究 (case-control study)

本日の結論

まれな疾患に対しては強力な研究方法

一見簡単にみえる。

しかし、バイアスがいっぱい。

期待される答えはあくまでも対照群に対する相対的な値。

対照群が結果（研究の質）を決める（対照群が命）。

使うとき・結果を理解するときの注意：
対照群は適切か、交絡因子は考慮され、正しく排除されているか？
生じうるバイアスは何か？　思い出しバイアスには特に注意。

今週の宿題：　**case-control study**