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Sample-size Formula for Case-cohort Studies

To the Editor:

The case-cohort design is an efficient alternative to the full cohort design. When compared with the case-control study nested within the cohort, the case-cohort design has flexibility for a series of exploratory analyses because a single subcohort is employed to analyze multiple outcomes.[1,2] This design feature is of particular importance in some specific types of research, including pharmacoepidemiology studies. For example, it can be used to evaluate the association between a single specific drug and multiple adverse events, of which the association with some of the events is often unknown or little understood at the beginning of the study. Nevertheless, the case-cohort design has not often been employed. One of the reasons hindering the wide use of the design may be the scarcity of the information essential for planning individual studies, including sample size calculation. Recently, Cai and Zeng[3,4] have presented a method for power/sample size calculation as a natural generalization of the log-rank test in the full cohort design. We show a simple sample size formula for the case-cohort design interpretable as the straightforward expansion of the conventional sample-size formula for the cohort study.

N_{full} denotes the sample size needed for the cohort study and $N_{1\ \text{full}}$ ($N_{0\ \text{full}}$) is the size of the exposed (unexposed) population in the full cohort, that is, $N_{\text{full}} = (1 + K)N_{1\ \text{full}}$ where $K = N_{0\ \text{full}}/N_{1\ \text{full}}$. When RR is the relative risk, or the ratio of the risk (incidence proportion) in the exposed (P_1) to that in the unexposed (P_0) (ie, $RR = P_1/P_0$) and P_D is the common estimate of the incidence proportion under the null hypothesis defined as $P_D = (N_{1\ \text{full}} P_1 + N_{0\ \text{full}}P_0)/N_{\text{full}} = P_0(RR + K)/(1 + K)$, based on the conventional sample size formula for the cohort study, $N_{1\,full} = [(Z_{\alpha/2}\sqrt{A} + Z_{\beta}\sqrt{B})/C]^2$ where z_c is $(1 - c)$ th standard normal quantile, $A = (1 + 1/K)P_D(1 - P_D)$, $B = RR \cdot P_0 (1 - RR \cdot P_0) + P_0(1 - P_0)/K$ and $C = P_0 (RR - 1)$. Using m, the ratio of the subcohort to cases in the entire cohort, the entire size of the case-cohort study, N, is simply formulated as

$$N = \left(1 + \frac{1}{m}\right) N_{full}$$

Of note, m should be assigned by a researcher who is planning the study.

A simulation study using a model subject to time-to-event analysis[5] revealed that the proposed sample size yielded a satisfactory empirical power and type I empirical error rate. For a single event, the number of subjects where the detailed information on covariates is collected (ie, subcohort members and/or cases) defined as n_{detail} is the smallest when $m = 1$; however, for multiple events, n_{detail} is the smallest when m is larger than 1. In general, with a larger m, the size of the entire cohort N is closer to N_{full} but n_{detail} is larger. To achieve a good balance between N and n_{detail}, $m = 3$–5 may be adopted in many occasions. For example, $(N, n_{\text{detail}}) = (19, 972, 70)$ and $(11, 984, 126)$ for $m = 1$ and 5, respectively, when $(P_0, RR, K, \alpha, \beta) = (0.001, 4, 3, 0.05, 0.2)$. In actual situations, if the estimation for all or some of covariates is quite costly, the value of n_{detail} may be minimized by adjusting m within available resources. Details on derivation of the formula and simulation are available in the eAppendix (http://links.lww.com/EDE/A449).

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Increasing Study Participation

To the Editor:

Factors such as age, sex, race, socioeconomic status, and education are associated with participation in epidemiologic studies, but there is limited literature concerning reasons for participation or nonparticipation. The literature has tended to focus on determinants of participation rates in clinical trials and physician surveys, rather than in population-based epidemiologic studies.[1] We conducted a series of focus groups to examine the reasons behind participants' decision to take part (or not take part) in a population-based case-control study of colorectal cancer (the Western Australian Bowel Health Study). We also asked what they believed would encourage people to take part in research.

Four focus groups were conducted: consenting cases (n = 11); consenting controls (n = 12); nonresponding controls (ie, controls who did not respond to the invitation letter, n = 7); and nonconsenting controls (ie, controls who did not consent to participate in the case-con-

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trol study, n = 5). The focus-group participants were between 40 and 80 years of age. Participation in the case-control study required completing 2 self-administered questionnaires and voluntarily supplying a DNA sample. Approval for the focus-group study was obtained from The University of Western Australia Human Research Ethics Committee and the Confidentiality of Health Information Committee of the Western Australian Department of Health. Written informed consent was obtained from all participants.

The majority of people in the focus groups of consenting participants cited altruistic reasons, such as civic duty and a desire to benefit the future health of family members, friends, and the wider community, as the main reason for taking part in the case-control study. Cases, in particular, were strongly motivated by altruism. Altruism has been commonly reported as a motive for participation in population-based[2] and clinical research.[3–5] Focus-group participants also identified the promise of a summary of the research findings and the provision of a reply paid envelope as good incentives to participate.

In the focus group of nonresponders, lack of relevance was the main reason given for not participating in the case-control study. Most of the focus group of nonresponders had not consciously decided to decline participation, but rather had not particularly taken notice of the invitation. A personal appeal to altruism may be an effective method to increase participation among participants for whom the study topic is not relevant.[2] Three of the 5 participants in the nonconsenting group expressed concerns about the privacy and retention of the DNA sample, suggesting that this may also have had an effect on their decision to not participate.

The focus group participants suggested several methods to increase participation in research:

- Researchers need to approach potential participants with a more positive message about the disease being studied and the research study, rather than worrying messages about the number of deaths being caused by the disease;
- The initial invitation should be concise and have a message that captures the reader's imagination; and
- A journalist or professional writer, rather than the researchers, should design the letter and information sheets.

Participants also noted that they had greatly valued personalized initial contact in a study, and suggested that immediate follow-up is best done by phone as soon as possible. There was a consensus that public education and raising awareness of health research (an idea that has been raised previously[6]) would also be beneficial in encouraging participation in population-based studies.

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Maternal Epilepsy and Cognitive/Psychiatric Status of Sons

To the Editor:

Developmental impairments have been reported among children and adolescents exposed in utero to antiepileptic drugs, particularly valproic acid.[1,2] We examined whether mother's history of epilepsy was associated with IQ and psychiatric status in early adulthood in a cross-sectional analysis of prospectively collected data (described in detail elsewhere[3]). The study population included 21,051 men born as singletons in 1977–1983 in northern Denmark, presenting for the mandatory medical examination and intelligence testing to determine army fitness. Evidence of a mental illness was considered present among men with diagnoses F.XX per 10th Revision of the International Classification of Diseases. Low IQ was defined as a score below 85 on the conventional IQ scale. Draft evaluation data were linked, via birth registration, to mother's hospitalization records in the Danish National Patient Registry.[4] We identified maternal diagnoses of epilepsy recorded since the Registry's inception, in

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TABLE. Association of Prenatal Exposure to Maternal Epilepsy With Mental Illness and IQ at Age 19 Among 21,051 Danish Men

	Observed Data			Adjusted Estimate of Association (95% CI)[a]		
Maternal Epilepsy Hospitalization	**Mental Illness No. Cases/ Total (%)**	**Low IQ No. Cases/ Total (%)**	**IQ Mean (SD)**	**Prevalence Ratio for Mental Illness**	**Prevalence Ratio for Low IQ**	**Mean Difference in IQ**
No[b]	1451/20,979 (6.9)	2841/18,484 (15.4)	100.0 (15.0)	1.0	1.0	0.0
Yes						
Anytime before delivery	8/72 (11.1)	12/62 (19.3)	95.3 (16.0)	1.6 (0.8 to 3.0)	1.2 (0.7 to 2.0)	−4.2 (−8.0 to −0.4)
Before pregnancy	4/38 (10.5)	5/34 (14.7)	98.0 (17.0)	1.5 (0.6 to 3.8)	1.0 (0.4 to 2.2)	−2.5 (−7.6 to 2.5)
During pregnancy	4/34 (11.8)	7/28 (25.0)	92.5 (15.0)	1.7 (0.7 to 4.2)	1.4 (0.7 to 2.8)	−6.3 (−12.0 to −0.6)

[a]Adjusted prevalence ratios were estimated by pooled Mantel-Haenszel analysis, and adjusted mean differences by multiple linear regression, controlling for maternal married status (yes/no); maternal age at delivery (≤20; 21–35; >35 years), and birth order (first/subsequent).
[b]Reference category.

1977, until each draftee's date of birth. Analyses were adjusted for mother's age at delivery, mother's marital status, and birth order.

The median age at conscription was 19.0 years (range, 18.0–25.0 years). Of the 21,051 men, 2505 (12%) were exempt from full evaluation on the basis of medical history, and did not have IQ measurements. Of the 21,051 men, 72 (0.3%) had been born to mothers with a prior hospitalization for epilepsy.

A mental-illness diagnosis was recorded among 1451 men (6.9%), including 8 of 72 men (11.1%) whose mothers had been hospitalized for epilepsy. The adjusted prevalence ratio (PR) was 1.6 (95% confidence interval [CI] = 0.8 to 3.0) compared with unexposed men. Of the 18,546 men, 62 with IQ measurements (0.3%) had a record of maternal epilepsy hospitalization, and 2853 of them (15.4%) had a low IQ, producing an adjusted PR of 1.2 (95% CI = 0.7 to 2.0). Mean IQ scores were 95.3 and 100.0 for men with and without a prenatal record of maternal epilepsy, respectively. The adjusted mean difference associated with prenatal history of maternal epilepsy was −4.2 points (95% CI = −8.0 to −0.4). The associations tended to be stronger for maternal epilepsy diagnosed during the pregnancy (Table).

We found greater prevalence of mental illness and mild cognitive impairment among men with prenatal exposure to maternal epilepsy. Men undergoing intelligence testing during army conscription represent a relatively healthy subgroup of the underlying birth cohort; therefore, the observed associations are not likely to be mediated by severe disability or congenital malformations. The 0.3% prevalence of maternal epilepsy in our data is low relative to the reported 0.6% for women of reproductive age in Denmark.[5] Epileptic mothers identified here had exacerbation of disease requiring hospitalization. The stronger association seen for epilepsy hospitalization recorded during gestation could represent the effect of disease exacerbation, or of pharmacotherapy in women who were required to start or resume medication while pregnant. Both seizure type and medication type may affect offspring IQ.[6] Earlier studies in children and adolescents showed 6–9-point lower mean IQ scores at age 3 for prenatal exposure to valproic acid as compared with other antiepileptic drugs.[2] Confounding by indication is pervasive in studies of these medications, because therapy depends on the type and severity of the disease.[1,7] Although we had no data on maternal pharmacotherapy, valproic acid has been on the market for more than 40 years, and some mothers in our study probably received that drug.[8]

Despite the low power of this analysis, our results are unlikely due to chance in the context of existing evidence. Barring potential confounding by maternal IQ, our results suggest that mild developmental deficits after maternal epilepsy—or its treatment—persist into adulthood even in relatively healthy men.

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Sensitivity Analysis When Data Are Missing Not-at-random

To the Editor:

The impact of missing data on the validity of results has often been overlooked in the medical literature.[1] Missing data are usually classified as ignorable (including missing completely at random [MCAR] and missing at random [MAR]), and nonignorable (missing not-at-random [MNAR]).[2] It is not possible to distinguish between ignorable and nonignorable missing data using observed data.

For analysis of ignorable missing data, multiple imputation—a relatively flexible and general purpose approach—is available in standard statistical software,[2] and is increasingly used. In contrast, the MNAR hypothesis is rarely explored, although it has been recommended to perform sensitivity analyses through various models for the nonresponse mechanism.[2] The mixture modeling principle, which assumes that the variables of interest have different distributions according to the status missing or nonmissing, is an attractive tool.[3] The impact of variations in the imputation model on the overall results helps to assess their robustness.

One reason for not systematically performing sensitivity analysis could be the lack of simple tools for implementation. We propose a package with an adaptation of the "mice" function from R® software to easily perform sensitivity analysis under various scenarios of nonresponse mechanisms.[4,5]

The algorithm MICE allows multiple imputation for data sets with mixed types of variables (continuous, binary, categorical). We propose a strategy in 3 steps:

1. Fit an imputation model under the ignorable-missing-data hypothesis by calling the function "mice."
2. Modify the imputation model by specifying supplementary parameters θ as arguments for the "sens.mice" function. For binary or categorical variables, this parameter is the odds ratio comparing the odds of the modality of interest among subjects with missing value with the odds among subjects without missing value. For continuous variables, this is the difference in expected values. For standardized variables, this difference can be expressed as a coefficient of variation.
3. Impute the missing data using the function sens.mice, resulting in a "mids" object which contains the newly imputed data sets.

In the absence of historical data on the missing-data mechanism, we

TABLE. Example of Sensitivity Analysis on the Odds Ratio Estimating the Association Between Viral Load and Poor Mental Health Using the R Data Set "CHAIN"

	No.	% of Viral Load[a]	aOR (95% CI)[b]
Viral load as a binary variable			
Complete cases	353		
<400 c/mL	188		1.00
≥400 c/mL	165	46.7	1.66 (0.94 – 2.93)
Multiple imputation			
MAR	508		
≥400 c/mL		50.0	2.01 (1.21 – 3.35)
MNAR (θ = 1.2)	508		
≥400 c/mL		50.8	1.73 (1.04 – 2.85)
MNAR (θ = 1.5)	508		
≥400 c/mL		52.1	1.73 (1.05 – 2.83)
MNAR (θ = 2.0)	508		
≥400 c/mL		53.9	1.75 (1.03 – 2.97)
Viral load as a trinary variable			
Complete cases	353		
<400 c/mL	188		1.00
400–9999 c/mL	78	22.1	1.40 (0.71 – 2.75)
≥10,000 c/mL	87	24.7	1.99 (1.01 – 3.94)
Multiple imputation			
MAR	508		
400–9999 c/mL		22.6	1.45 (0.81 – 2.60)
≥10,000 c/mL		28.1	2.23 (1.26 – 3.95)
MNAR (θ = [1.2; 1.2])	508		
400–9999 c/mL		22.4	1.71 (0.91 – 3.21)
≥10,000 c/mL		29.1	2.39 (1.29 – 4.42)
MNAR (θ = ([1.2; 1.5])	508		
400–9999 c/mL		22.0	1.64 (0.87 – 3.09)
≥10,000 c/mL		30.4	2.30 (1.26 – 4.19)

θ: Supplementary parameter in "sens.mice," corresponding to the odds ratio comparing the modality of interest (category of viral load) among subjects with missing value with the subjects without missing value. It then takes 1 and 2 values with the binary and the trinary variable, respectively.
[a]"% of viral load" expresses the percentage of patients with a given modality of viral load.
[b]aOR: odds ratio adjusted on all other covariates, that is, age, family income, physical health, CD4 count, HAART. MAR indicates missing at random; MNAR, missing not at random.

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suggest looking for parameter values that modify the overall conclusions, ie, the test results or a point estimate outside of the original confidence interval. These values should be consistent with the targeted exposure effect and should correspond to reasonable hypotheses supported by epidemiologic evidences.

As an illustrative example, we apply a sensitivity analysis supposing MNAR data on the data set "CHAIN"[6] included in the package "mi."[7] We present results from 4 imputation models that relate poor mental health (as measured by a binary variable) to the self-reported viral load (taken as either a binary or a trinary variable) adjusted on 5 covariates. We assumed that nonresponders were more likely to have high viral load than responders. The magnitude of the variations was in the range of the observed odds ratio between viral load and mental health among complete cases. We compared the results with the complete cases analysis and with the multiple imputation analysis assuming MAR data (Table). The resulting odds ratio was decreased but still substantial. Estimates were robust to the explored MNAR scenarios as conclusions were not modified as compared with multiple imputation; magnitude of the effects was smaller than the assumed variations.

The "SensMice" package is provided as an eAppendix (http://links.lww.com/EDE/A455).

Both the package and the reference manual are freely available at: http://lertim.fr/Members/rgiorgi/DossierPublic/fonctions-r-s/.

A sensitivity analysis under different scenarios of nonresponse mechanism could be easily performed using the proposed package. It is of particular interest when the mechanism is highly suspected to be nonignorable, eg, for self-reported characteristics as psychologic disorders, quality of life, or income.[8]

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Aircraft Noise and Myocardial Infarction Mortality

To the Editor:

Huss et al[1] present the first large-scale epidemiologic study investigating a link between residential exposure to aircraft noise and mortality from myocardial infarction (MI) in Switzerland. The study was carried out carefully, and the reported results are compatible with the existing literature. However, the paper is somewhat vague as regards the origin and reliability of the air-traffic data underlying exposure assessments, the computational-noise models that were used for the exposure calculations, and, most importantly, the time period for which aircraft noise exposure was assessed and upon which the analysis is based. Because cardiovascular disease is usually the result of accumulated exposure over long time spans, individual integrated-exposure histories dating back as far as possible would be the predictor of choice. The paper does not sufficiently clarify the time period of noise exposure that underlies the analysis of mortality. This could be the average exposure of a reference year (eg, 2005), or an average over several years. Depending on operational parameters, the short-term exposure in a reference year at a particular location is just a proxy for the relevant long-term exposure at that location. The average noise exposure around most airports has steadily decreased in recent decades, owing to the replacement of old and noisy aircraft with newer types. A peculiarity of the Zurich Airport (which accounts for much of the noise exposure in this study) may additionally shift the reported exposure-effect relationship: the years 2001 to 2005 (the time span for which exposure data were apparently available) were characterized by a decrease of aircraft movements at Zurich Airport due to the demise of Swissair in 2001. Because of this, people who have lived 10–15 years or longer at the same place (eg, those from the Model III subpopulation, reported in the original Table 3) may have an increased risk due not only to their longer exposure time, but also because they may enter the model with an underestimated exposure dose. If this is true, hazard ratios would begin to increase at slightly higher exposure values. To reduce such sources of bias, it seems advisable to consider

the actual noise exposure history of each person as closely as possible, however, troublesome this may be.

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The authors respond:

We thank Mark Brink[1] for his interest in our work. Zurich aircraft noise levels as applied in our study were calculated on the basis of actual flight movements on an annual basis, and all calculations were carried out by the Swiss Federal Laboratories for Materials Testing and Research.[2] For Zurich airport, we used the energetic average from the years 2001 to 2005, the time period covering the mortality data in our analysis. Reports on the computational noise modeling for all other airports can be accessed online.[3] For these airports, we used available exposure data that usually referred to 1 year (eg, Basel year 2004, Geneva year 2000). Between 2001 and 2005, there was indeed a slight decrease of noise exposure (1–2 dB) around Zurich airport, but the exposure levels between these years are highly correlated, as the same areas are affected by aircraft noise.

We agree that it would be interesting to know whether persons with a long duration of residence entered our calculations with an underestimation of the noise levels, and to take long-term exposure history into account. However, there is uncertainty about the latency time of noise exposure and a resulting myocardial infarction (MI) event. It is well known that chronic as well as acute stress can trigger an MI.[4] If myocardial infarction mortality is the consequence of acute exposure applying past exposure levels could introduce an error into the calculation. It is thus unclear how best to evaluate noise-exposure history. In addition, the high temporal correlation of the exposure levels means that firm conclusions about the relevant exposure time window cannot be drawn. The increasing risk observed with duration of residency may also reflect the fact that long-term residents were less likely to live in new or renovated buildings with better sound insulation; while 30% of the highly exposed persons lived in an old or not-renovated building at the time of the census, this percentage increased to 36% in long-term residents.

In summary, the results of our study (as well as others)[5] do not suggest a well-defined threshold below which no harmful effects occur. Instead our study indicates a continuous risk increase with increasing exposure levels. Noise abatement policy should therefore focus on the health benefit that any noise reduction might bring.

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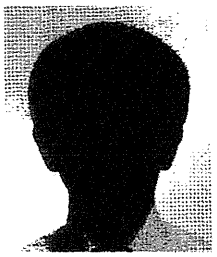
糖尿病患者における転倒

——糖尿病合併症，身体能力低下，血糖コントロールとの関連

Falling in patients with diabetes mellitus

——Association with complications, low physical performance, and glycemic control



荒木　厚(写真)　千葉優子

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◎高齢糖尿病患者は糖尿病でない人と比較して転倒しやすく，転倒のリスク要因を多くもっている．糖尿病患者は非糖尿病者と比べて下肢の筋量，筋力，筋肉の質が低下しやすく，サルコペニアになりやすい．糖尿病患者，とくに末梢神経障害合併患者では身体能力，とくに歩行，歩行速度の低下やバランス障害をきたしやすく，それらが転倒につながりやすい．Up and Go時間，開眼片足立ち時間，椅子からの立ち上り時間などは，転倒を予測する身体能力の検査として有用である．手段的日常生活動作(IADL)低下，うつ状態，認知機能低下も転倒の要因である．血糖コントロールの指標のHbA1cが高すぎても低くなりすぎても転倒しやすい．また，低血糖頻度の増加は転倒と関連する．バランストレーニング，下肢のレジスタンストレーニングを含めた運動療法は，糖尿病患者のバランス能力，歩行速度，下肢筋力の改善につながり，転倒の防止に有効である可能性がある．

Key word　転倒，高齢者糖尿病，神経障害，バランス能力，運動療法

高齢糖尿病患者は糖尿病でない人と比較して，認知症，うつ，サルコペニアなどの老年症候群に罹患する頻度が2〜3倍高い[1]．転倒も老年症候群のひとつで，糖尿病患者で多いことが知られている．この糖尿病患者に転倒が多い原因として，①糖尿病合併症，②身体能力(パフォーマンス)の低下，③うつ症状，認知機能の低下，④血糖コントロールの影響，などが考えられる．

本稿では，糖尿病患者における転倒の要因とその予防について概説したい．

糖尿病における転倒の頻度

高齢糖尿病患者は年間に18〜78%転倒し，糖尿病がない人と比較すると1.5〜3倍転倒しやすい[2-4]．とくにインスリン治療の糖尿病患者でこの傾向は顕著である．The Study of Osteroporotic Fracturesでは，9,247名の高齢女性(平均年齢74歳)を7.2年間追跡し，1年間に18%が転倒し，インスリン治療者は2.78倍(95%CI：1.84-4.24)，非インスリン治療者は1.68倍(95%CI：1.37-2.07)転倒しやすいと報告した[2]．また，最初の2年間は糖尿病患者の転倒回数が非糖尿病者と比べて多いと報告している．The Women's Health and Aging Studyでは，65歳以上の1,002名の住民を対象とした3年間の追跡調査を行い，64.9%が追跡期間にすくなくとも1回転倒を起こした．糖尿病女性は糖尿病がない人と比較してすくなくとも1回の転倒は1.38倍，2回以上の転倒は1.69倍多く，インスリン治療者ではさらに転倒が多かった[3]．介護施設に入所している高齢糖尿病患者(平均年齢88歳)139名の平均299日の追跡調査では，糖尿病患者の転倒頻度は78%と対照の30%と比べて多く，糖尿病は転倒の独立した危険因子であった[4]．

著者らは，60歳以上の糖尿病患者169例(平均年齢76歳)，糖尿病がない対照32例(平均年齢76歳)を対象として断面調査を行い，過去1年間の転倒歴・転倒回数を調べて比較した[5](図1)．その結

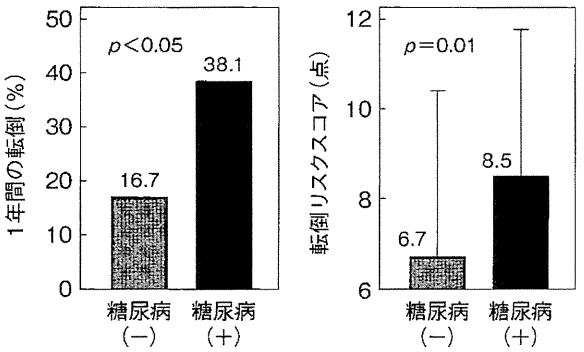

図 1　糖尿病患者は転倒が多く，転倒リスクスコアが高い

果，1年間の転倒は糖尿病患者が38.1%，対照患者が16.7%であり，糖尿病患者は対照と比べて転倒する頻度が有意に高く，約2.3倍であった．糖尿病患者の転倒回数は1.0±4.7回，対照は0.5±1.3回であり，多い傾向が認められた．

また，糖尿病患者は転倒のリスクを多く有している．鳥羽らが開発した転倒リスクスコア[6]を糖尿病患者と非糖尿病者と比較すると，糖尿病患者の転倒リスクスコアは対照と比較して高値を示した(10.2±3.1 vs. 8.5±3.7, $p<0.05$, 図1)．転倒リスクスコアの質問のなかでは，糖尿病患者では“つまずくことがある”“てすりにつかまらないと階段の昇り降りが不可能”“歩行速度が遅い”“1 kmくらいを続けて歩くことが不可能”“めまい・ふらつきがある”“目が見えにくい”“毎日お薬を5種類以上飲んでいる”の頻度が多いという結果が得られた．これは糖尿病患者が歩行機能の障害，視力障害，前庭機能障害またはバランス障害，多剤服用などの転倒のリスク因子を多くもっており，これが転倒の高頻度につながっていることを示唆する．

糖尿病患者の合併症と転倒

合併症のなかでも，神経障害は転倒と関連する重要な因子である[7,8]．50〜85歳の82名の糖尿病患者の断面調査では，ミシガン糖尿病神経障害スコアで評価した多発性神経障害が重症であることは，BMI高値とともに2年間の2回以上の転倒や外傷を伴う転倒と関連していた[7]．Health Aging and Body Composition Study(Health ABC Study)における446人(年齢73.6歳)の4.9年間の追跡調査では，腓骨神経の神経伝導速度の振幅低下，シスタチンC高値，コントラスト視力の低下が転倒の独立した予測因子であった[9]．55歳以上の糖尿病患者60名を対象としたイギリスの研究では，1年間での転倒歴がある患者は転倒がない患者と比較して末梢神経障害の頻度が多く(86% vs. 56%, $p<0.001$)，振動覚閾値が高かった[10]．London District General Hospitalの65歳以上の糖尿病患者77名を対象とした転倒調査では，脳卒中の既往があると1年間の転倒の頻度は1.9倍増えると報告されている[11]．また，冠動脈疾患の既往も転倒と関連するという報告もある[3]．したがって，重症の神経障害，腎症，脳卒中，視力低下を有する糖尿病患者は転倒に注意し，転倒予防などの介入を行う必要がある．

糖尿病患者の身体能力低下と転倒

糖尿病患者は非糖尿病者と比べて筋肉量が低下しやすいだけでなく下肢の筋力や筋肉の質が低下しやすく，したがってサルコペニアになりやすい[12,13]．The Health ABC Studyでは，70〜79歳で糖尿病がない2,047名，登録時に糖尿病が診断されていなかった未診断の糖尿病患者226名，すでに診断されている糖尿病患者402名を5年間追跡し，DXA法で測定した四肢の除脂肪量は2つの糖尿病群で糖尿病がない群と比べて年間の減少率が大きく，未診断の糖尿病患者でより減りやすかった[12]．CTで評価した大腿の筋断面積も女性では同様に2つの糖尿病群で減少をきたした．また，同じThe Health ABC Studyの断面調査では，糖尿病患者は非糖尿病者と比べて腕や下肢の筋肉量がみかけ上多いが，それらの筋力は女性では有意に低下し，男性では同様であった[13]．筋肉の質を「同じ領域における単位筋肉量当り筋力」と定義すると，糖尿病患者の筋肉の質は男女とも有意に低下していた．

糖尿病患者はバランス能力も低下している．とくに，減弱した光のなかでの立位のバランス能力が低下し，歩行時の揺れが大きいことが報告されている[14]．75歳以上の糖尿病患者を9年間追跡した調査では，糖尿病患者はパーキンソン病に似た症状のために歩行障害のリスクが大きかった[15]．

表 1　糖尿病の有無と身体能力テストの結果

変数	糖尿病(−)(n=32)	糖尿病(+)(n=169)	p 値
年齢	76.3±6.3	76.2±6.8	n. s.
性(男性%)	30.3	35.3	n. s.
開眼片足立ち時間(sec)	21.8±22.5	10.8±17.5	<0.05
閉眼片足立ち時間(sec)	2.7±1.9	2.0±1.5	0.067
握力(kg)	14.9±9.0	13.3±7.9	n. s.
functional reach(cm)	30.4±7.3	28.9±7.2	n. s.
Up and Go 時間(sec)	9.7±2.6	12.0±4.9	<0.001

上記の著者らの調査でも，糖尿病患者は糖尿病がない人と比べて開眼片足立ち時間が短く，Up and Go 時間が長いという結果が得られている(表 1)．糖尿病患者が末梢神経障害を合併すると，立ったときや平らでない床では体を安定させることが困難となり，歩行速度が遅くなり，歩幅が小さくなる[16]．したがって，糖尿病患者のバランス障害，歩行障害は神経障害が一部関与していると考えられる．

この糖尿病患者における筋力の低下，歩行速度の遅さ，およびバランス能力の低下は転倒の予測因子となっている．Health ABC Study では，椅子からの起立時間の増加，立位バランス時間の増加，歩行速度の遅さが糖尿病患者の転倒のリスクであった[17]．多変量解析で糖尿病の末梢神経障害を加えると，これらの因子は有意でなくなることから，やはり糖尿病の身体能力低下の一部は末梢神経障害で説明できるという．上記のイギリスの研究でも，転倒者は歩行速度の低下，足の背屈，足底屈，内半・外反の筋力低下，および高頻度の骨性隆起物や中足骨骨頭隆起がみられた[10]．また，ロジスティック回帰分析の結果，歩行速度低下，足の背屈筋力低下，神経障害の症候スコアが転倒の 75% を予測すると報告した．Women's Health and Aging Study では，筋・骨の広範な痛み，インスリン治療，過体重以外に下肢機能の悪化，およびバランス能力の低下が転倒と関連した[3]．著者らの研究でも，糖尿病患者の転倒回数は開眼片足立ち時間，Up and Go 時間と有意の相関がみられた[5](表 2)．Up and Go 時間は，多変量解析でも転倒の有無と有意に関連する因子であり，筋力とバランス能力の両者を反映し，転倒を予測する身体能力の検査として有用であると思われる．

表 2　糖尿病患者の転倒回数と臨床所見

変数	Spearman の相関係数	p 値
年齢(歳)	0.086	n. s.
性	−0.060	n. s.
低血糖の有無	0.179	<0.05
低血糖の回数	0.204	<0.01
開眼片足立ち時間(sec)	−0.163	<0.05
閉眼片足立ち時間(sec)	−0.087	n. s.
Up and Go 時間(sec)	0.216	<0.01
老研式活動能力指標(点)	−0.216	<0.01
老年期うつ病評価尺度(GDS-15)(点)	0.217	<0.01
認知機能検査(MMSE)(点)	−0.166	<0.05

血糖コントロールと転倒

糖尿病患者における高血糖は転倒に影響を及ぼす．上記の London District General Hospital の研究では，75 歳以上，女性，脳卒中のほかに HbA1c が 7.0% 以上の高血糖があると，7.0% 未満の群と比較して 7.8 倍転倒が多くなった[11]．一方，血糖値が低すぎることも転倒と関連する．Health ABC Study では，HbA1c 6.0% 以下の患者では転倒のリスクが 4.4 倍と高いことが報告されている[9]．この HbA1c 低値による転倒のリスク増加は，インスリン治療の患者でのみ有意であり，経口薬使用の患者では当てはまらないという．Nelson らは，75 歳以上の糖尿病患者 111 名を対象に調査し，HbA1c 7.0% 以下，または虚弱の患者で転倒しやすく，HbA1c 7.0% 以下では 2.71 倍の転倒のリスクを有していた[18]．こうした研究では低血糖の評価は行っていないが，低血糖が転倒の誘因となる可能性もある．

上記の著者らの調査では，低血糖の頻度を，①低血糖まったくなし，②年 1〜2 回，③年 3 回以上，の 3 群で比較すると，転倒の頻度は 34%，

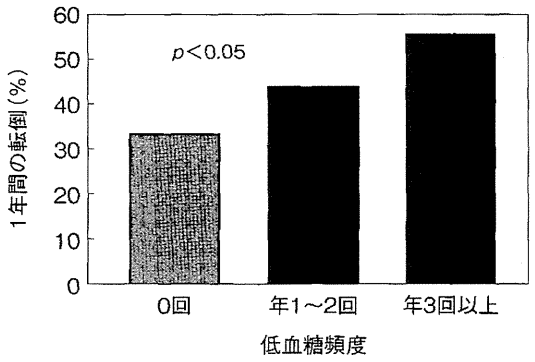

図 2　糖尿病患者における低血糖の頻度と1年間の転倒

44%，56%と有意に増加した[5]（図2）．また，低血糖の有無や頻度は転倒回数と関連していた（表2）．さらに年齢，性，糖尿病の有無，老年期うつ病評価尺度（geriatric depression scale：GDS）-15，Up and Go時間，低血糖の有無の6因子を用いてロジスティック回帰解析を行うと，低血糖とUp and Go時間が転倒と関連する独立した因子であることが明らかとなった．

これらの結果から，糖尿病患者の転倒防止の観点からは，血糖コントロールは高血糖も低血糖もないHbA1c（JDS値）6.5%前後が理想である．しかし，低血糖のリスクが高い虚弱な高齢者では転倒しやすいので，安全域を考え，HbA1c 6.5～7.9%（SU薬使用者），HbA1c 7.0～7.9%（インスリン治療者）でよいと思われる．

その他の転倒要因

杖を使用する患者や装具を使用する患者も，転倒が約2倍になることが報告されている[11]．関節症，筋骨格系疼痛，過体重，虚弱，転倒リスクの高い薬剤の服用が多いことも転倒と関連する因子であった[2-4,18]．著者らの調査ではGDS-15で評価されるうつ症状が多いこと，認知機能の低下，手段的日常生活動作（instrumental activity of daily living：IADL）の低下が転倒と有意の相関関係を示した[5]（表2）．また最近，National Health and Nutrition Examination Survey（NHANES）研究において，糖尿病患者では前庭機能が低下していることが報告された[19]．糖尿病罹病期間が長いほど，また高血糖であるほど前庭機能が低下しており，この前庭機能の低下も転倒の要因になりうると考えられる．

糖尿病患者の転倒予防

上記のことから，図3に示すように糖尿病患者の転倒要因は糖尿病合併症，身体能力の低下，血糖コントロール不良，機能低下などである．したがって，糖尿病患者の転倒を防ぐためには，運動療法（バランストレーニング，レジスタンストレーニング），栄養サポート，心理サポート，環境整備，適切な血糖コントロール，ビタミンDの投与など多くの手段が考えられる．このなかでもっとも重要なことは，バランストレーニング，下肢

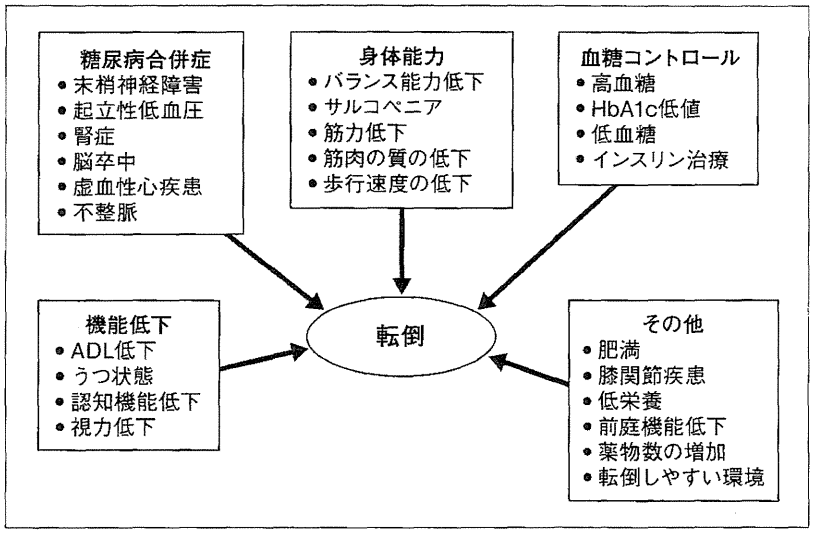

図 3　糖尿病患者における転倒要因

の筋力トレーニングを含めた運動療法であろう．

最近，平均年齢62歳の2型糖尿病患者16名と対照21名で，6週間のバランストレーニングとレジスタンス(筋力)トレーニングを組み合わせて運動介入を行った研究が報告された[20]．糖尿病患者は対照と比べてバランスが悪く，反応時間が遅く，姿勢の動揺が大きかったが，運動によってそれらのすべてが改善を示した．また，別のRCT研究においても糖尿病患者の歩行・バランストレーニングは歩行速度を速くし，バランス能力，転倒恐怖の軽減，股関節可動域の拡大，足関節の足底屈筋力の改善をもたらした[21]．これらの結果は，バランストレーニングとレジスタンストレーニングが糖尿病患者の転倒のリスクを減らすことを示唆する．

一般にビタミンDの投与は骨だけでなく筋肉にも作用し，転倒予防効果があるといわれている[22]．最近，ビタミンD投与はインスリン感受性や分泌にも好影響を及ぼすことがわかってきており，その意味でも糖尿病患者にも試す価値があるであろう[23]．しかし，投与にあたっては高Ca血症に注意して使用すべきである．

今後，高齢糖尿病患者を対象に，こうしたバランストレーニング，筋力トレーニングや適切な血糖コントロールが実際に転倒を減らすかをみる研究が必要であると思われる．

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prescribed an additional treatment of 5 mg of imidapril daily. Her swallowing reflex latency time normalized after ACE inhibitor treatment. She had been hospitalized three times because of COPD exacerbations in the previous year and experienced two exacerbations during the 6.1 years of follow-up.

In addition to the regular treatment of COPD, ACE inhibitor treatment improved the swallowing reflexes of these individuals and reduced the frequency of COPD exacerbations (from 3 to 0.46 per year in case 1, and from 3 to 0.33 per year in case 2). The patients had not recognized their impaired swallowing reflexes, because they were on entirely oral diets without complaints of dysphagia and had no prior history of symptomatic stroke or oropharyngeal or esophageal abnormalities.

Aspiration is associated with impairment of swallowing and cough reflex, which is mediated through substance P.[2] ACE inhibitors decrease the catabolism of substance P, resulting in prevention of aspiration[5,6] and protection against pneumonia in older adults.[6–8] The findings of the current study suggest that ACE inhibitors protect against aspiration tracheobronchitis and exacerbations of COPD.

ACE inhibitors have also been demonstrated to have beneficial effects on the heart,[9] although the follow-up examination of these individuals, including electrocardiogram and echocardiogram, did not indicate a significant change. The blood pressure of these individual did not decrease significantly during the follow-up period. Although symptomatic hypotension has been reported to be rare,[10] one should be careful about adverse effects of ACE inhibitor treatment in older adults.

ACE inhibitor therapy is a potential option for preventing COPD exacerbations in selected individuals with impaired swallowing reflexes. Large randomized controlled clinical trials will be useful.

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RESEARCH STUDIES

SHELTER-ACQUIRED PNEUMONIA AFTER A CATASTROPHIC EARTHQUAKE IN JAPAN

To the Editor: At 2:46 p.m. on March 11, 2011, a magnitude 9.0 earthquake hit the northeast part of Japan followed by enormous tsunamis, which destroyed many of the coastal cities. The tsunamis, which reached as high as 10 to 38 meters, completely destroyed more than 90% of dwellings. A large number of hospitals and nursing homes were also destroyed. Although more than 1 month had passed after the worst disaster in Japan's history, uncountable aftershocks continued as of April 18.

According to a report from the National Police Agency, more than 13,000 deaths were confirmed, and more than 14,000 people were still missing. Furthermore, 150,000 people were still forced to live in 2,400 shelters, such as gymnasiums and school halls, 40% of whom were aged 65 and older. These refugees were exposed to cold, unhygienic conditions and malnutrition because of power failures, insufficient food supply, and lack of running water. Under unfavorable circumstances, the refugees faced the threat of disease. As time went by, the number of individuals with respiratory diseases increased. Many older people were transferred to backup hospitals because of pneumonia from shelters located in severely damaged areas. Tohoku University Hospital was one of the backup hospitals.

To clarify clinical features of the new-onset pneumonia in refugees, called shelter-acquired pneumonia (SAP), the medical records of 17 individuals transferred to Tohoku University Hospital were examined. The mean duration of time living at a shelter until the onset of pneumonia was 15.2 ± 5.1 days. The mean age of the individuals was 81.6 ± 4.2 (male:female ratio 14:3). All of the individuals had a history of cerebrovascular accident or

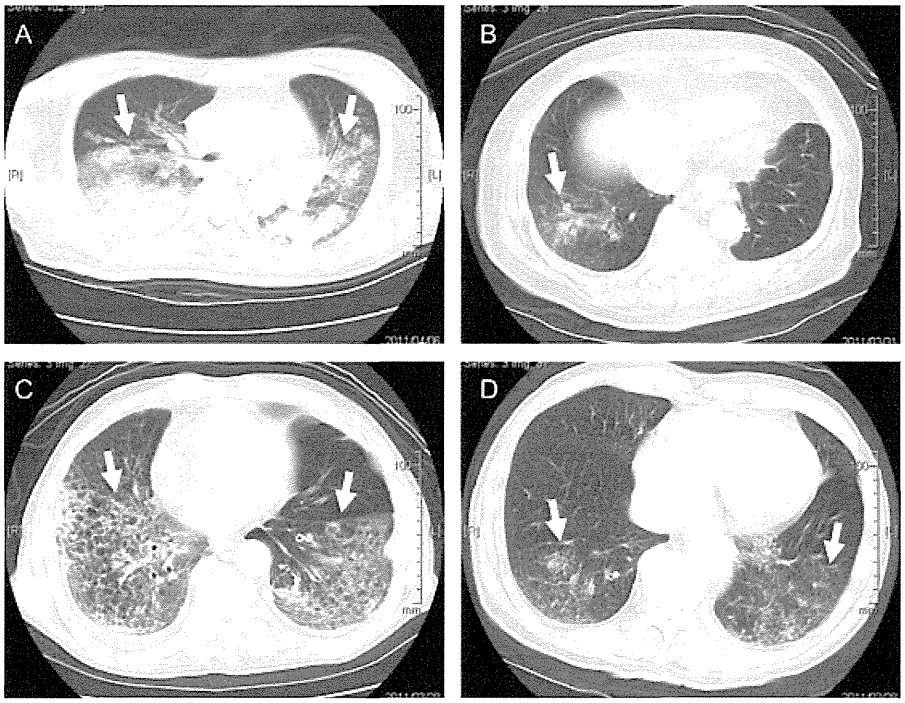

Figure 1. Chest computed tomography scans of four randomly selected individuals showed that the consolidation was distributed prominently in the lower part or back of both lungs (A, C, D) or in one lung (B).

neurodegenerative disorder with frailty. Laboratory examination on admission revealed low serum albumin (2.6 ± 0.8 g/dL) and cholesterol (110 ± 24 mg/dL) levels, low peripheral blood lymphocyte count (1,032 ± 527/μL), and high serum C-reactive protein levels (21.1 ± 14.6 mg/dL). Urine pneumococcal antigen was positive in three of these individuals. The individuals had prolonged swallowing reflexes (4.1 ± 0.6 seconds (normal < 2.0 seconds)) and low sensitivities of cough reflex (2.1 ± 0.5 log mg/mL (normal < 0.5 log mg/mL)), indicating higher risk for silent aspiration.[1] The chest computed tomography scans of the individuals showed that the consolidation was distributed prominently in the lower part or the back of the lung (Figure 1). These results suggest that silent aspiration might have triggered the pneumonia. The shelters were so crowded that people were forced to sleep on the narrow floor in a supine position and could not turn over during sleep. Furthermore, they hesitated to cough to avoid making noise in the shelter. Most of the individuals did not pay attention to oral care such as tooth brushing or cleaning false teeth. Oropharyngeal secretions containing bacteria might easily have gone down along the bronchial trees by gravity to the back and augmented pneumonia during sleep.

A previous survey reported that the major illnesses leading to hospital admission after the devastating earthquake were pneumonia, dehydration, heart failure, asthma attacks, peptic ulcer, cerebrovascular diseases, and ischemic heart disease.[2,3] This report focused on the cause of pneumonia and found that pneumonia in older refugees might have occurred because of impaired oral hygiene, frequent aspiration, undernutrition, and cold temperatures under unfavorable circumstances. It has previously been shown that oral care can decrease the prevalence of pneumonia in older institutionalized individuals.[4] Oral care might be important for preventing pneumonia in refugees living in shelters.

The final incidence of pneumonia in older refugees living in shelters remains unknown because the number of individuals is still increasing, but a previous report described that the hospital admission rate due to pneumonia was significantly correlated with destruction ratios of dwellings, suggesting that pneumonia occurred frequently in refugees living in shelters.[2] Furthermore, morbidity in those living in shelters was five times as high as in persons who remained in their own dwellings.[2] This current observation might provide additional insight into how life in a shelter affects the onset of pneumonia.

Insufficient support for many dependent older people and those with dementia who live in shelters will be a major concern in the near future. Investigation of a continuous care delivery system for these people will be a new challenge. We sincerely need your suggestions and ideas to allow us to facilitate long-term medical support to elderly refugees living in shelters.

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POPULATION-BASED SMOKING TRENDS IN OLDER ADULTS: THE MINNESOTA HEART SURVEY

To the Editor: As the population ages, there is a need to reevaluate current cardiovascular disease (CVD) prevention practices in older adults. Although the benefits of smoking cessation and of smoking abstinence in older adults are well established,[1–3] physicians are less likely to assess smoking status in older adults,[4] advise older adults to quit,[5] or introduce lifestyle modification for CVD prevention in older adults.[2] The study of smoking practices and their trends in older adults may help illustrate the importance of addressing smoking in this population. The present study examined cigarette smoking trends in a population-based sample of Minnesotans aged 75 to 84.

The Minnesota Heart Survey (MHS) has been described previously.[6] Briefly, it is a population-based surveillance study of CVD risk factors in residents of Minneapolis and Saint Paul (2000 census: 2.6 million). MHS has completed six surveys (1980–1982, 1985–1987, 1990–1992, 1995–1997, 2000–2002, and 2007–2009); the last four surveys included participants aged 75 to 84. The institutional review board of the University of Minnesota provided ethical approval, and participants provided informed consent.

Population-based sampling involved a two-stage strategy. The metropolitan area was divided into census-defined clusters, and households were then randomly selected within included clusters. Participants completed a home interview and a clinic visit. A total of 268, 318, 142, and 145 adults aged 75 to 84 participated in both components of each of the four most recent surveys, respectively.

Smoking status was assessed according to self-report. In earlier surveys, smoking status was validated using serum thiocyanate level. Validation was not performed in the 2007–2009 survey because of high concordance with self-report in previous surveys.[6] Sex-specific trends were examined using generalized linear mixed models that contained a random effect to account for the clustered sampling. Age-adjusted prevalence was estimated for an age of 80.

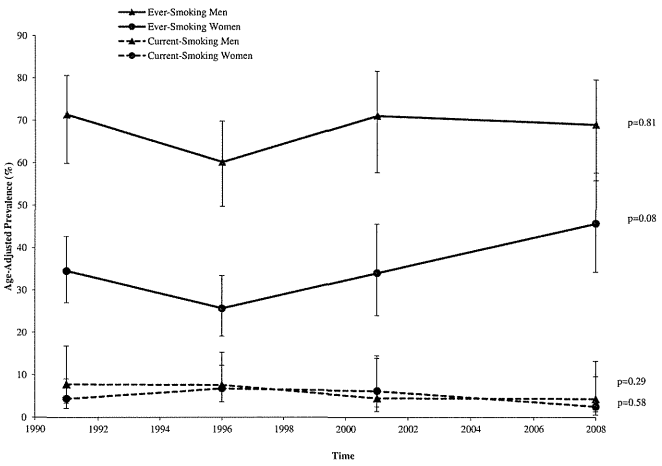

Figure 1. Population-based trends in age-adjusted prevalence of current and ever smoking in men and women aged 75 to 84 participating in the Minnesota Heart Survey. Data were plotted at the midpoint of each survey, and models were age-adjusted using generalized linear mixed models and setting the age term to 80. *P*-values are for linear trends.

Participants were predominantly Caucasian (range: 98.5–100%), and the majority were women (53.8–67.9%). The median age varied from 77.4 to 78.9.

The overall prevalence of current cigarette smoking was less than 8% in all surveys and did not change substantially over time ($P = .36$). In the 1990–1992 survey, the prevalence of current smoking was 7.8% in men and 4.4% in women (Figure 1). By the 2007–2009 survey, it was 4.3% ($P = .29$) and 2.5% ($P = .58$), respectively. Combining the four surveys, 20 of 23 currently smoking men and 27 of 28 currently smoking women smoked 20 cigarettes or fewer per day.

The prevalence of ever smoking increased in women across surveys ($P = .08$) (Figure 1). This increase was due to a greater prevalence of past smoking ($P = .04$). In contrast, the prevalence of ever ($P = .81$) and past ($P = .44$) smoking was consistent across surveys in men.

Past smokers reported quitting at increasingly younger ages. In men, the reported quitting age decreased from 50.7 in the 1990–1992 survey to 44.6 in the 2007–2009 survey ($P < .001$). In women, it decreased from 56.0 to 45.7 ($P < .001$). The prevalence of quitting for health reasons was 25.0% in the 1995–1997 survey and 38.2% in the 2007–2009 survey in men ($P = .38$) and 45.5% and 40.7% in women, respectively ($P = .86$).

The benefits of smoking cessation and abstinence in older adults include lower morbidity and mortality due to CVD and smoking-related cancers, better physical function, and higher quality of life.[1–3] Many of these benefits occur within 1 to 2 years of quitting.[1,3] Although the prevalence of smoking has remained consistent over the last 20 years, the absolute number of elderly smokers is increasing as the population ages. Given the high underlying CVD risk in older adults, the absolute number of

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〔原著〕

市川市基本健康診査受診者血清脂質の検討：nonHDLコレステロールに着目して
－市川市基本健康診査の解析（3）－

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（2010年8月30日受付，2011年2月17日受理）

要　旨

本研究は動脈硬化性疾患のリスクとなる脂質代謝異常の特徴と脂質代謝異常の脂質管理におけるnonHDLの有用性について検討することを目的とした。市川市基本健康診査受診者のうち高血圧，脂質代謝異常症，糖尿病の薬物治療を受けていない男性2,086名（平均年齢58.0歳）と女性4,357名（平均年齢55.6歳）の血清脂質を検討した。年代別血清脂質の平均値でみると，男性の総コレステロール，LDL，nonHDLは50歳代が最も高く，中性脂肪は40歳代が最も高かった。女性の総コレステロール，LDL，nonHDL，中性脂肪は年代が上がると高くなり，HDLは60歳代で低くなった。男性のメタボリックシンドローム群ではノンメタボリックシンドローム群と比較して，総コレステロール，nonHDL，は有意に高く，LDLは両群間に差を認めなかった。男性のnonHDLはLDLと高い相関を認め，LDL140mg/dLに相当するnonHDLは165mg/dLであった。女性のnonHDLもLDLと高い相関を認め，LDL140mg/dLに相当するnonHDLは156mg/dLであった。以上の結果より動脈硬化のハイリスクとして知られているメタボリックシンドローム群では，LDLは変わらずnonHDLは高くなりHDLは低くなった。nonHDLを構成するレムナントや小型LDLの増加とHDLの低下が日本人のメタボリックシンドロームに見られた事は，メタボリックシンドロームの経過を追っていく際LDLだけでなくnonHDLにも注意をする必要があると思われる。

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Key words: 住民健康診査，脂質代謝異常，メタボリックシンドローム，LDLコレステロール，nonHDLコレステロール

略語一覧: LDLコレステロール（LDL），HDLコレステロール（HDL），nonHDLコレステロール（nonHDL），レムナントリポ蛋白（レムナント）

Ⅰ．緒　言

メタボリックシンドロームは高LDL血症だけでは説明できないハイリスクグループとして提案された[1]。メタボリックシンドロームなど内臓脂肪の蓄積やインスリン抵抗を示す病態では，高LDL血症だけでは語ることができない脂質代謝異常を合併する事が多く[2]，現在様々な研究が行われている。今回我々はメタボリックシンドロームの脂質代謝異常について検討した。肥満，メタボリックシンドローム，Ⅱ型糖尿病などの脂質管理を行ううえでLDLの値のみでなく，レムナントなどあらゆるリポ蛋白に含まれるコレステロールの総量を表すnonHDLが注目されている[3]。今回我々はnonHDLの有用性について検討した。

Ⅱ．対象と方法

調査の対象は2006年11月１日より2007年10月30日までの１年間に市内28医療機関（26診療所，２病院）で市川市の成人病健診を空腹時に受け，かつ高血圧，脂質代謝異常症，糖尿病のいずれの薬物治療も受けていない40歳より69歳までの受診者とした。メタボリックシンドロームの診断のために，肥満症治療ガイドライン2006[4]に従ってウエスト周囲径を測定した。LDLコレステロールはFriedewaldの式により，nonHDLコレステロールは総コレステロール－HDLコレステロールにより算出した。メタボリックシンドロームの診断はメタボリックシンドローム診断基準検討委員会2005[5]により診断した。本研究は市川市医師会に帰属する倫理委員会の承認を得た。

統計解析

結果は平均値±標準偏差で表現した。二群間の比較検定にMann-Whitney検定及びχ二乗検定を，相関はPearsonの相関検定を用いた。統計処理は全てSPSS（ver15.0J）を使用した。$P<0.05$を有意差有りと判定した。

Ⅲ．結　果

今回の調査対象は，男性2,086名（平均年齢58.0歳），女性4,357名（平均年齢55.6歳）であった。全健診受診者のうちで，男性の高血圧，脂質代謝異常症，糖尿病のいずれの薬物治療も受けていない調査対象者の年代別割合は，40歳代は83.8％，年代が上がると対象者の割合が低くなった。メタボリックシンドロームの頻度は，全世代20％以下であり，50歳代が最も高く18.5％であった（表１）。

女性の高血圧，脂質代謝異常症，糖尿病のいずれの薬物治療も受けていない調査対象者の年代別割合は，40歳代は92.2％，年代が上がると対象者の割合が低くなった。メタボリックシンドロームの頻度は，全世代５％以下で，年代が上がると頻度が高くなった（表１）。

男性nonHDLの平均は149.3mg/dLで，年代

表１　男女年代別一覧

	40-49歳	50-59歳	60-69歳	全体
		男性		
対象人数（人）	306	372	782	1,462
無治療者割合（％）	83.8	61.8	53.9	60.5
メタボリックシンドローム頻度（％）	15.4	18.5	16.8	16.9
		女性		
人数（人）	975	1,090	1,329	3,394
無治療者割合（％）	92.2	73.5	57.4	69.7
メタボリックシンドローム頻度（％）	1.2	2.2	4	2.6

表2　男性年代別と全体の平均

	40-49歳	50-59歳	60-69歳	全体
総コレステロール（mg/dL）	207.6±34.7	209.6±36.3	207.6±35.2	208.1±35.4
HDL（mg/dL）	59.3±19.1	58±15.1	60.2±17.5	59.5±17.3
中性脂肪（mg/dL）	147.5±120.2	138.1±96.2	126.4±85.3	133.8±96.6
LDL（mg/dL）	121±32.6	125.6±32.5	123.5±31.5	123.5±32.0
nonHDL（mg/dL）	149±37	152.4±36.8	147.9±35.1	149.3±36.0

表3　女性年代別と全体の平均

	40-49歳	50-59歳	60-69歳	全体
総コレステロール（mg/dL）	199.3±34.1	224.5±36	230±34.5	219.4±37.2
HDL（mg/dL）	72.9±16.6	73.1±19.4	70.3±17.4	71.9±17.9
中性脂肪（mg/dL）	81.3±63.3	98.1±66.5	102.8±65.6	95.1±65.9
LDL（mg/dL）	111.2±30.5	133.6±32	139.7±32.1	129.6±33.8
nonHDL（mg/dL）	126.7±33.7	152.7±35.5	160±35.6	148.1±37.7

表4　男性メタボリックシンドローム群とノンメタボリックシンドローム群の比較

	メタボリックシンドローム群	ノンメタボリックシンドローム群	有意差
人数（人）	247	1212	
年齢（歳）	58.0±8.4	58.0±8.9	N. S
総コレステロール（mg/dL）	216.9±39.1	206.3±34.3	$P<0.001$
HDL（mg/dL）	50.8±12.5	61.2±17.6	$P<0.001$
中性脂肪（mg/dL）	221.6±141.0	115.9±72.9	$P<0.001$
LDL（mg/dL）	125.6±35.6	123.1±31.3	N. S
nonHDL（mg/dL）	166.0±38.4	145.9±34.4	$P<0.001$

別では50歳代が最も高く，総コレステロールやLDLと同じ傾向であった。中性脂肪は40歳代が最も高く，年代が上がると低くなった（表2）。

女性nonHDLの平均は148.1mg/dLで，年代別では年代が上がると高くなり60歳代が最も高く，総コレステロールやLDLと同じ傾向であった。HDLは60歳代で低くなった。中性脂肪は年代が上がると高くなった（表3）。

男性をメタボリックシンドローム群とノンメタボリックシンドローム群の2群に分け，その血清脂質値を比較検討した。メタボリックシンドローム群では総コレステロール，中性脂肪，nonHDLは有意に高く，HDLは有意に低かった。LDLは両群間に差を認めなかった（表4）。

男性nonHDLの相関を検討した。nonHDLはLDLと正の相関（図1－A），総コレステロールと正の相関（図1－B），HDLと負の相関（図1－C），中性脂肪と正の相関（図1－D）を認めた。

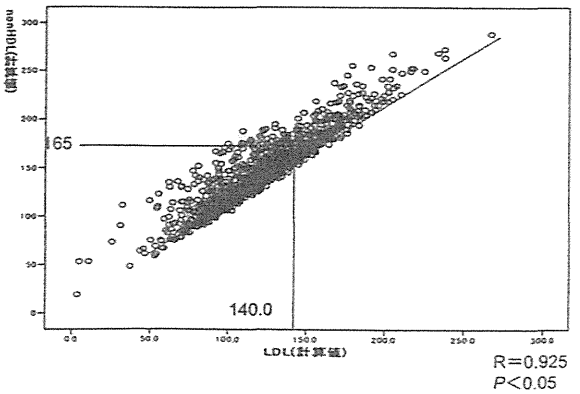

図1－A　男性nonHDLとLDL相関

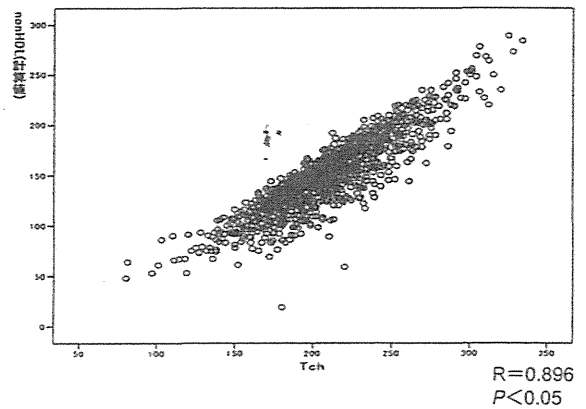

図1－B　男性nonHDLとTch相関

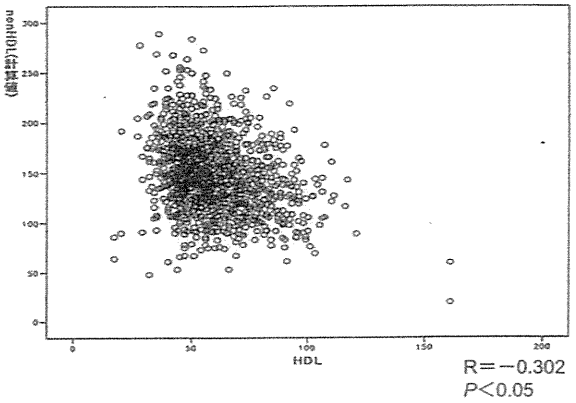

図１－C　男性nonHDLとHDL相関

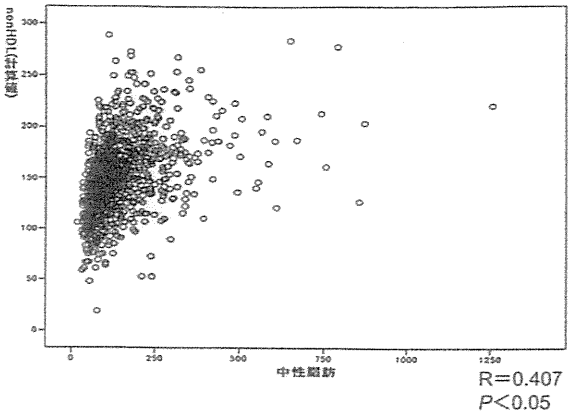

図１－D　男性nonHDLと中性脂肪相関

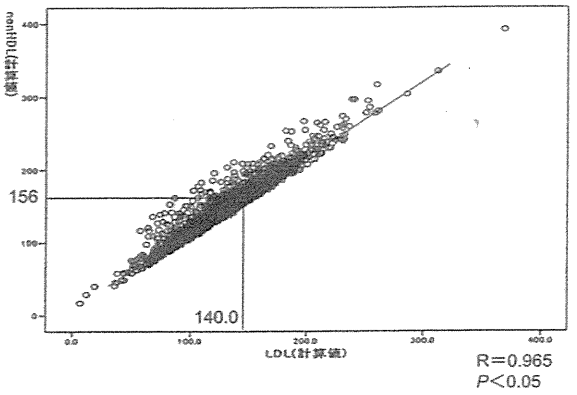

図２－E．女性nonHDLとLDL相関

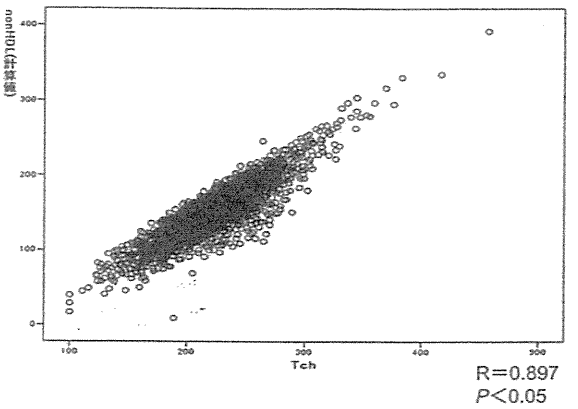

図２－F．女性nonHDLとTch相関

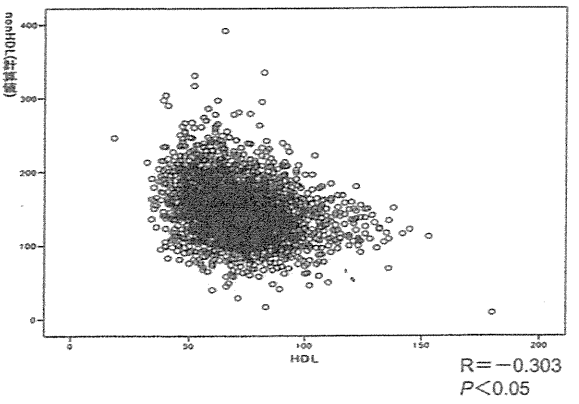

図２－G　女性nonHDLとHDL相関

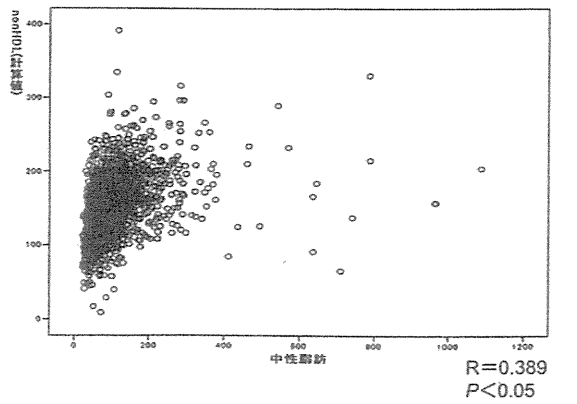

図２－H　女性nonHDLと中性脂肪相関

nonHDLはLDLと最も高い相関を認め，nonHDLとLDLの分散図よりLDL140mg/dLに相当するのはnonHDL165mg/dLであった（図１－A）。

女性nonHDLの相関を検討した。nonHDLはLDLと正の相関（図２－E），総コレステロールと正の相関（図２－F），HDLと負の相関（図２－G），中性脂肪と正の相関（図２－H）を認めた。nonHDLはLDLと最も高い相関を認め，nonHDLとLDLの分散図よりLDL140mg/dLに相当するのはnonHDL156mg/dLであった（図２－E）。

Ⅳ．考　察

住民健診よりみた40歳代から60歳代男性は，約

4人に1人がメタボリックシンドロームに該当し，成人男性ではメタボリックシンドロームや高中性脂肪症を中心にした脂質代謝異常に対する取り組みが重要であると報告されている[6]。今回我々は，高血圧，脂質代謝異常症，糖尿病の薬物治療者を除いた住民基本健康診査受診者の血清脂質についてnonHDLを中心に検討した。米国[7]では高中性脂肪血症の脂質管理にnonHDLの利用が推奨され，日本の脂質代謝異常症ガイドライン[8]でも脂質代謝異常症合併糖尿病患者の冠動脈疾患の予防にnonHDLの利用が推奨されている。日本の脂質代謝異常症ガイドライン[8]では中性脂肪が高い場合にはnonHDLを管理目標とすることも可能としている。最近高中性脂肪血症やメタボリックシンドロームでは，動脈硬化作用を有するレムナントの増加が問題となっている。NonHDLはLDLに加えレムナントなどあらゆる動脈硬化惹起性リポ蛋白のコレステロールを含むため，メタボリックシンドロームの該当者が多く，高中性脂肪血症を合併しやすい日本人男性の脂質管理には，LDLとともにnonHDLに配慮することが推奨される。

メタボリックシンドロームに認められる脂質代謝異常の特徴に高中性脂肪，低HDLとLDLの小型化がある。今回の検討ではメタボリックシンドローム群ではHDLは低く，中性脂肪と総コレステロールとnonHDLは高いが，LDLは両群間に差を認めなかった。平野[9]はメタボリックシンドロームではLDLや正常サイズのLDLは増加しないが，小型で高密度のLDL（small dense LDL）は著明に増加すると報告した。メタボリックシンドロームで増加するsmall dense LDLをLDL濃度では，正確に評価することができない。従ってメタボリックシンドロームの脂質管理にはLDL以外の指標が必要であると思われる。メタボリックシンドロームでLDLが増加しない理由は，インスリン抵抗性によるVLDLの合成亢進とリポ蛋白リパーゼ活性低下によりLDLへの中間代謝産物であるレムナントの増加，LDLへの代謝停滞が考えられる[10]。Chan[11]やSatoh[12]はメタボリックシンドロームではレムナントが上昇すると報告し，Nakamura[13]はメタボリックシンドロームではレムナントが上昇し，上昇したレムナントが冠動脈疾患の危険因子と報告している。今回の研究において，メタボリックシンドローム群ではHDLが低く，総コレステロールが高い事は，nonHDLつまりLDLに加えレムナントなどあらゆる動脈硬化惹起性リポ蛋白の増加を反映していたと思われる。nonHDLとLDLの差がメタボリックシンドローム群では約40mg/dL，ノンメタボリックシンドローム群では約22mg/dLである事もメタボリックシンドロームにおけるnonHDLの有用性を反映していると思われる。

日本と米国ともにnonHDLの管理目標をLDL＋30mg/dLと設定している。Sugimoto[14]もnonHDLとLDLは密接に相関し，nonHDLをLDL＋30mg/dLと設定している。Friedewaldの計算式より考えると，中性脂肪の基準上限値の150mg/dLの5分の1の30mg/dLをLDLに加えた値がnonHDLの理論上の目標値となると思われる。今回我々の検討でもnonHDLとLDLは密接な相関を認め，相関直線よりLDL140mg/dLに相当するnonHDLは男性165mg/dL，女性156mg/dLであり，男女ともにLDL＋30mg/dLより少なかった。

nonHDLをLDL＋30mg/dLとするのは理論上の値であり，nonHDLとLDLは密接な相関を認めるので，対象数を増やせばLDL140mg/dLに相当するnonHDLの管理目標値が推定できると思われる。Shimano[15]はnonHDLとLDLは相関し，nonHDLが脂質代謝異常治療の第一管理指標になりうる可能性を報告した。LDLについてはエビデンスも多く，最も強力な動脈硬化惹起性を認め，脂質代謝異常治療の第一管理指標となっている。一方nonHDLについてはエビデンスが少ないが，Yadong Cui[16]はnonHDLはLDLより心臓血管死亡のよい指標になると，Kastelein[17]はnonHDLはLDLより心臓血管疾患の発生に密接に関係すると報告している。Shimano[15]はnonHDLは高中性脂肪とLDLの両方の危険性を反映する全ての脂質異常因子の指標になり得ると述べている。今後はnonHDLの動脈硬化の危険因子としての検討も必要であると思われる。

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