P-07

Blood levels of vitamin C and the subsequent risk of Stroke in cohort studies: A systematic review

Yokoyama T and Tango T

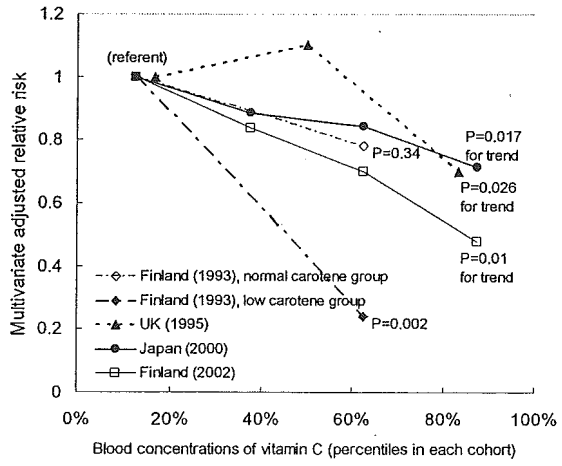
Department of Technology Assessment and Biostatistics, National Institute of Public Health

Background and purpose: There has been a growing interest in the potential role of antioxidative vitamins for the prevention of cardiovascular disease. At least 3 large randomized controlled trials are on-going in the U.S. (WACS and Physicians' Health Study II) and France (SUVIMAX study) to assess the effects of antioxidative vitamins, including vitamin C (VC), for the prevention of stroke. However, the findings from observational studies, especially those based on dietary surveys, are inconsistent. The purpose of the present study is to systematically review the relationship between blood levels of VC and the subsequent risk of stroke (VC-stroke relationship) in observational cohort studies.

Methods: Cohort studies assessing the VC-stroke relationship were identified by a MEDLINE search with key words: cohort studies[MeSH] AND (ascorbic acid[MeSH] OR ascorbic acid[tw] OR ascorbate[tw] OR vitamin c[tw]) AND (cerebrovascular disease[MeSH] OR stroke[tw]), in March 3, 2004.

Results: Four cohort studies were identified: two studies in Finland, a study in Japan, and a study in the U.K. Two studies analysed data by subtypes of stroke and the other 2 studies analysed for all strokes combined. Blood levels of VC were categorized by the quartiles in 2 studies, tertiles in a study, and 'low' vs. 'high' (a cut-off point of 22.7μmol/L) in a study. A significant dose-response VC-stroke relationship was observed in 3 studies; and the other one reported an increased risk of stroke only when blood levels of VC and beta-carotene were simultaneously low (Figure).

Figure. Blood concentrations of vitamin C and the subsequent risk of stroke in 4 cohort studies



Conclusions: Observational cohort studies consistently showed a strong inverse VC-stroke relationship, however, the number of available studies was limited.

Comparison of effects in randomized, controlled trials with observational studies in digestive surgery

Satoru Shikata, M.D.[1,2], Takeo Nakayama, M.D., Ph.D.[3], Hisakazu Yamagishi, M.D.[1], Yoshinori Taji, M.D.[3], and Yoshinori Noguchi, M.D., M.P.H.[4]

1 Department of Digestive Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan
2 Department of Clinical Epidemiology, Kyoto University, Kyoto, Japan
3 Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan
4 Department of Medicine, Fujita Health University School of Medicine, Aichi, Japan

Background: While randomized, controlled trials have been recognized as providing the highest standard of evidence, claims have been made that observational studies may overestimate treatment benefits. This debate has recently been renewed, particularly with regard to pharmacotherapies. To extend perspectives, the present study compared the results of identical meta-analyses (randomized, controlled trials versus observational studies) on digestive surgical topics.

Methods: The PubMed, EMBASE and Cochrane databases were searched to identify meta-analyses of randomized, controlled trials in digestive surgery that had been published up to 2004. We then undertook an exhaustive search of the observational studies for all selected topics and combined various extracted data for every outcome. Summary estimates from randomized, controlled trials were compared with observational studies under equivalent conditions to the maximum extent possible.

Results: This investigation identified 52 outcomes of 18 topics from 276 original articles with a total of 101,170 study participants. Significant between-study heterogeneity was seen more often among observational studies than among randomized, controlled trials (7 of 14 topics vs. 1 of 11 topics, respectively;). In 48 of 52 outcomes compared (9 of 10 primary outcomes), summary estimates of treatment effects were similar.

Conclusions: Meta-analyses of observational studies were not found to overestimate treatment effects relative to randomized, controlled trials in the field of digestive surgery.

P-09

The quality of reporting of randomized controlled trials conducted in Japan: An evaluation based on the consort statement

Uetani K[1], Kimura Y[2], Ikai H[3], Yonemoto N[4], Nakayama T[1]

1 Dept. of Health Informatics, Kyoto University School of Public Health
2 Statcom Co., Ltd.
3 Dept. of Clinical Epidemiology, Kyoto University Graduate School of Medicine
4 Dept. of Biostatistics, Kyoto University School of Public Health

Randomized controlled trials (RCTs) is a means of ensuring the highest scientific validity, and provides essential information for systemic reviews and meta-analyses. They are best used as a source of information, only if researchers conduct and report them with the utmost quality. This study evaluates the quality of RCT reporting from Japan, based on the CONSORT statement.

This study is a descriptive literature review, targeting the RCT reported from Japan. All reports were published in January and March, 2004 and registered to PubMed. Evaluation was based on the CONSORT statement (32 items) and original 3 items: IRB review, informed consent, conflict of interest. A cross-tabulation was used between evaluative item and whether or not the accepting journals supported the CONSORT statement.

The total of 100 reports was reviewed, of which 10 supporting CONSORT, 90 not supporting CONSORT. Among 32 CONSORT items, the mean number of items described was 15 (16.5 items in journals supporting CONSORT, and 15 items in journals not supporting CONSORT). IRB, informed consent, and conflict of interest were described in 83, 92, and 19 reports, respectively.

The quality of reporting of RCTs from Japan is not adequate and further improvement is needed. Having journals comply with the CONSORT statement alone is not sufficient in improving the quality. Further education on international guidelines such as the CONSORT statement are anticipated, and both researchers and writers, should be encouraged to follow them.

(Tentative report as of January 8, 2005. Final analysis is to be completed by February, 2005.)

P-10

A meta-analytic comparison of echocardiographic stressors

Yoshinori Noguchi[1], Shizuko Nagata-Kobayashi[2], James E Stahl[3], and John B Wong[4]

1 Fujita Health University School of Medicine
2 Kyoto University Graduate School of Medicine
3 Massachusetts General Hospital
4 Tufts University School of Medicine

Background: The relative performance of alternative stressors for stress echocardiography for the diagnosis of coronary artery disease (CAD) is not well established.

Methods: All studies published between 1981 to December 2001 who met inclusion criteria were included in this analysis. We performed a summary receiver operator characteristic (SROC) analysis and calculated weighted mean of the likelihood ratio and sensitivity/specificity. A covariate analysis using meta-regression methods was also performed.

Results: Forty-four studies presented data on Exercise, 11 on Adenosine, 80 on Dobutamine, 40 on Dipyridamole, 16 on transatrial pacing transesophageal echocardiography (Tap-TEE), and 7 on transatrial pacing transthorasic echocardiography (Tap-TTE). Summary receiver operator characteristic (SROC) analysis showed that the following order of most discriminatory to least: Tap-TEE, Exercise, Dipyridamole, Dobutamine and Adenosine. Weighted means sensitivity/specificity were Exercise: 82.6/84.4 %, Adenosine: 68.4/80.9 %, Dobutamine: 79.6/85.1 %, Dipyridamole: 71.0/92.2 %, Tap-TTE: 90.7/86.1 %, and Tap-TEE: 86.2/91.3 %. Covariate analysis showed that the discriminatory power of Exercise decreased with increasing mean age.

Conclusions: Tap -TEE is a very accurate test for both ruling in and ruling out CAD although its invasiveness may limit its clinical acceptability. Exercise is a well-balanced satisfactory test for both ruling in and ruling out but performance might be lower for the elderly. Dobutamine offers a reasonable compromise for Exercise. Dipyridamole might be good for ruling in but not for ruling out CAD. The incapability in ruling-out CAD was a major problem in clinical application of the stress. Adenosine was the least useful stressor in diagnosing CAD.

P-11

Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomized controlled trials

L. Bax[1,2], F.Staes[2], A.P. Verhagen[3]

1 Medical Informatics, Graduate School of Medical Sciences, Kitasato University
2 Faculty of Physical Education and Physiotherapy, University of Leuven
3 Department of General Practice, Erasmus MC, University Medical Center Rotterdam

Background: Devices for neuromuscular electrical stimulation are increasingly used by individuals without specific injuries and are standard equipment in most physical therapy practices. The most often stimulated muscle group is the quadriceps femoris. We designed a systematic review and meta-analysis of randomized controlled trials to determine whether neuromuscular electrical stimulation is an effective modality for strength augmentation of the quadriceps femoris.

Methods: A full content search for randomized controlled trials was performed in Medline, Embase, Cinahl, the Cochrane Controlled Trials Register, and the Physical Therapy Evidence Database. Maximum volitional isometric or isokinetic muscle torque in Newton-meter was used as main outcome measure.

Results: Thirty-five trials were included and evaluated. A fundamental distinction was made between the trials using subjects with unimpaired quadriceps femoris muscles and the trials using post-injury or post-operative subjects. In the unimpaired quadriceps subgroup, meta-analyses were performed for the comparisons 'NMES versus no exercises' and 'NMES versus volitional exercises'. All other comparisons were evaluated descriptively. The included trials were generally of poor quality and meta-analytic data indicate that publication bias may be present. The evaluated data suggest that, both for the unimpaired and impaired quadriceps, NMES makes sense compared to doing no exercises but volitional exercises appear to be more effective in most situations.

Conclusions: Based on the available evidence, neuromuscular electrical stimulation may only be preferred over volitional training for within-cast muscle training and perhaps in specific situations where volitional training does not receive sufficient patient compliance. Further research should be directed toward identifying the clinical impact at activity and participation levels and the optimal stimulation parameters of this modality.

The 'MIX' program, an active way of learning about meta-analysis with Excel

L. Bax, H. Tsuruta, M. Shirataka, A. Takeuchi, N. Ikeda

Medical Informatics, Graduate School of Medical Sciences, Kitasato University

Background: Currently, various programs are available for performing meta-analyses. Some are relatively cheap and user-friendly, whereas others are expensive and difficult to use. Even though the number of researchers getting involved in systematic reviews and meta-analyses has grown exponentially in the last decade, there are no statistical programs available that are specifically aimed at educating inexperienced users about what they are doing. Our objective was therefore to fill this niche and to develop a program that could assist those new to meta-analysis in learning about them in a practical, interactive way.

Methods: We started with assessing recent articles about meta-analysis methodology and created a list of all statistical calculations and procedures to be integrated in the program. Ease of use, interactive learning, and flexibility for adding additional options were chosen as central themes for the actual development. Output is being verified with various professional statistical programs.

Status: In contrast to other developers of programs for meta-analysis so far, we decided not to make a stand-alone program, but an add-in for Excel. This has resulted in a familiar working environment for inexperienced users and has allowed us to make use of some of the extensive calculational potential in Excel. To allow the users to learn about "what is what?" and "what is it for?" an extensive Concept Tutor and a Statistics Assistant has been developed with Visual Basic for Applications and can be consulted from within the program. With this interactive learning as primary theme, we named the program MIX: Meta-analysis with Interactive eXplanations. In the current version (part of the development is still ongoing) meta-analyses can be performed with built-in data sets of existing published meta-analyses or with personal data sets created with the data set wizard. It features fixed and random effects analyses and allows the calculation of pooled risk differences, risk ratios, odds ratios, weighted mean differences and weighted Hedges' Gs, based on per group input or comparative input, the latter being analyzed by generic inverse variance methodology. For assessment of heterogeneity as well as publication bias, various test options are available. Current graphical output includes standard and cumulative forest plots, multiple funnel (regression) plots, a Galbraith plot, a L'Abbe plot, an exclusion sensitivity plot, and more.

Conclusion: A beta-version for final testing will be available early 2005 and with the official launch some time later in 2005, we expect the program to become a helpful tool for researchers and clinicians interested in learning about and performing meta-analyses.

P-13

Concerns encountered in the meta-analysis of the causal relationship between coffee consumption and type 2 diabetes

Origasa H and Sakai H

Division of Biostatistics, Toyama Medical and Pharmaceutical University

A prophylactic effect of coffee on type 2 diabetes was reported in 2002 by a Dutch research group. Since then, four prospective cohort studies have presented data on the same topic. All the information finally reached more than 160,000 participants. Insulin secretion by caffeine is considered as a possible mechanism. We performed a meta-analysis on this topic. In the process of this work, we encountered several difficulties to perform the meta-analysis. In this presentation, these are exposed to the audiences of this symposium.

As usual, each article reported an adjusted risk (accurately speaking, odds ratio) and its 95% confidence interval. To combine these reported risk data across the studies, we utilized an inverse variance weighting method. The first issue was that there was inconsistency in the control group with respect to the amount of coffee consumption. Three studies specified the control group to be 2 cups or less; one study set the control to be no coffee drinkers; one study set the control to be 1 cup or less. We determined 2 cups or less as the control group since it was a majority and included coffee consumption of 1 or 0 cup. Second, the risk of developing diabetes was assumed to be linearly decreased upon coffee consumption, although we do not know whether a linear trend is valid. The last issue was that categorization of the amount of coffee consumption was variable among the studies and reported the data for the interval of coffee consumption such as 3 – 4 cups per day. For the cases reported 3 – 4 cups per day, we supposed the risk for 3.5 cups a day. A further problem was how to deal with the last category of coffee consumption that was censored such as 6 cups or more. In any event, several assumptions were necessary to overcome the variability in data presentations among the studies in conducting a meta-analytic research on this topic.

Confidence intervals for the ratio of regression slopes in meta-analysis

Takahashi K and Tango T

Department of Technology Assessment and Biostatistics, National Institute of Public Health

In epidemiological studies of the association between disease and exposure to some agent or hazard, it is often of interest to estimate how much risk increases as exposure increases. Studies that measure the risk at different levels of exposure are usually analysed by trend estimation using linear regression analysis. For instance, we assume that blood pressure y has a relationship with alcohol consumption x. This simple linear regression model is

$$y = \alpha + \beta x + \varepsilon ,$$

where ε is a random error component according to normal distribution $N(0, \sigma^2)$. It can be assumed therefore that another factor (ex. genotypes) may associate with individual differences in sensitivity to alcohol toxicity including the pressor effect, that is, they have the slope β_1 for type 1 and β_2 for type 2 respectively and we have an interest in the ratio of slopes

$$\rho = \frac{\beta_2}{\beta_1} .$$

Confidence intervals of ρ are derived from the data by Fieller's theorem.

Meta-analysis is used to combine together the evidence from several such studies. However, meta-analyses of observational studies often have to rely on the limited data available from research reports. In such cases, it is difficult to estimate ρ and to derive its confidence intervals in regression analysis.

In this study, we suppose cases that we can get several descriptive statistics for each grouped x as follows

	Type1			Type2		
x	No. of cases	Mean of y	S.E.	No. of cases	Mean of y	S.E.
$(I_0, I_1]$	n_1	$\bar{y}_1$	se_1	n_1'	$\bar{y}_1'$	se_1'
$(I_1, I_2]$	n_2	$\bar{y}_2$	se_2	n_2'	$\bar{y}_2'$	se_2'
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$(I_{m-1}, I_m]$	n_m	$\bar{y}_m$	se_m	n_m'	$\bar{y}_m'$	se_m'
Total	N			N'		

and means and variances of x for each type. Then we try to estimate ρ, standard error of an estimator $\hat{\rho}$ and to derive its confidence intervals. We also describe statistics that is necessary to reconstruct the ratio of slopes for meta-analysis.

P-15

Meta-analysis of low does radiation risk: An application of meta-regression model to biological risk evaluation

Ogata H

Section of Knowledge Evaluation, National Institute of Public Health

Linear non-threshold (LNT) model is a basic theory for radioprotection, but the adaptability of this hypothesis to biological responses at low doses or at low dose rates is not sufficiently investigated. In this study, we acquired quantitative experimental data at low doses/low dose rates using micronucleus formation of human osteosarcoma as biological reaction to low dose gamma radiation. To estimate "observed minimum risk level" (OML) of the response for cells irradiated at low doses with a variety of dose rates, we applied meta-regression models to the data and compared them with other statistical models that find values corresponding to "threshold limits".

By fitting a weighted regression model (fixed-effects meta-regression model) to the data, it was found that the log relative risk [log(RR)] decreases as the total exposure dose decreases. The intersection of this regression line with the x-axis denotes the OML. However, as the heterogeneity is present beyond that explained by the total exposure doses, we applied mixed model that includes random-effects considering residue heterogeneity. The confidence intervals of estimated OMLs for mixed model are wider than those for fixed-effects model. Therefore when residue heterogeneity is present, above that explained by doses, it is difficult to find a "threshold". These estimated OMLs remarkably increased with an increase of irradiation time, this shows that the risk is reduced when dose rates are very low. These results suggest that dose response curve of biological reaction is remarkably affected by exposure time, and that dose rate effect changes as a function of dose-rate and irradiation time. Moreover, OMLs and their confidence intervals depended on models used for the estimation.

For scientific discussion on the low dose exposure risk and its uncertainty, the term "threshold" should be statistically defined, and dose rate effects should be included in the risk evaluation model.

Method of correcting for publication bias in meta-analysis

Matsuoka N and Hamada C

Department of Industrial Management and Engineering, Faculty of Engineering,
Tokyo University of Science

The publication bias, the tendency the researches with statistically significant results is more likely to be submitted and to be published than the researches with non-significant results, is a very serious problem in meta-analysis. The most serious consequence of this bias would be an overestimate of treatment effect and lead to an inappropriate decision about the selection of treatment or health policy. Several statistical methods for publication bias have been studied.

The trim-and-fill[1] method was proposed by Duval and Tweedie (2000). This method estimates the number of unpublished studies, based on the property of the funnel plot. The funnel plot is a scatter plot sample size versus treatment effect (eg. log odds ratio) of individual study in a meta-analysis. The shape of this plot like an inverse funnel if there is no publication bias. But, if the probability of publication of studies with positive statistically significant results is greater, the shape of the funnel plot may be skewed and asymmetric. Consequently, the trim-and-fill method estimate the number of studies to be needed for recovering the shape of the funnel plot 'asymmetry' to 'symmetry', then estimate the true effect size based on the artificially symmetrized funnel plot. But, the mechanism of publication that is assumed in the trim-and-fill method is unrealistic, therefore this method could not correct for publication bias appropriately.

Therefore, the new method to correct for publication bias is proposed. Our method assumes that the probabilities of publishing are based on the p-value of individual study in a meta-analysis, and the weight of each study is defined as an inverse of the probability of publishing, then calculate the weighted average for estimating the combined effect.

A simulation study is performed to compare the performance of the proposed method with that of the trim-and-fill method.

Reference: [1] Sue Duval and Richard Tweedie., "A Nonparametric "Trim and Fill" Method of Accounting for Publication Bias in Meta-Analysis". Journal of American Statistical Association. 2000; Vol.95, No.499: 89-97

Development of a Clinical Trials Registry in Japan

Kiichiro Tsutani[1], Takahiro Kiuchi[2], Yasuo Ohashi[3], Eiji Uchida[4], Hisako Matsuba[2]

1. Department of Pharmacoeconomics, Graduate School of Pharmaceutical Sciences, The University of Tokyo
2. University Hospital Medical Information Network (UMIN) Center, The University of Tokyo Hospital
3. Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, The University of Tokyo
4. Clinical Trial Support Center of Showa University Hospital

Background: The needs of the clinical trials registry (CTR) have been discussed, and several projects have started since the 1990s, although they have not been quite satisfactory. After the anti-depressant scandal in New York in June 2004, awareness has rapidly grown and global discussion of the topic as well as a new CTR project was initiated by concerned groups. Presently, however, the situation is still fluid and somewhat chaotic. This study aims to review the global status of CTR and introduce the UMIN-CTR, which is the first attempt to develop the CTR system in Japan using public funds.

Methods: Literature search, internet search, meetings, and interviews with relevant key persons.

Results: The following key global events after the year 2000 led to a growing concern about a more comprehensive clinical trials registry: (1) 2000: Amendment to the Declaration of Helsinki, calling for the publishing of or making public both positive and negative data; (2) June 2004: GSK's scandal on the use anti-depressants for children; (3) September 2004: Statement from the International Committee of Medical Journal Editors (ICMJE) on requiring a registry of clinical trials; (4) October 2004: Ottawa meeting on CTR during the 12th Cochrane Colloquium; (5) October 2004: WHO International Registry Platform Meeting in New York; (6) November 2004: Ministerial Summit on Health Research at Mexico City; (7) January 2005: International Federation of Pharmaceutical Manufacturers Association (IFPMA) statement.

In Japan, a Working Group on CTR was established in October 2004 to develop policy and discuss technical issues on UMIN-CTR. A symposium on CTR to introduce an alpha version of it and to have public comments was held on 2 February 2005. The system is

currently under revision [http://www.umin.ac.jp/ctr/index-j.htm]. Full implementation is scheduled to start in April 2005.

A wide range of opinion was observed both globally and domestically. Ethics, ensuring compliance, and the role of government were among the hot topics.

Conclusion: Close collaboration with international agencies, including WHO, as well as internal collaboration within Japan is strongly recommended for more comprehensive and user-friendly system development.

資料-2. シンポジウム

学際領域における評価のデザイン
-RCTとシステマティック・レビューの現状-

本研究班では、メタ・アナリシスの理論と応用を中心としたEBMツールの広範囲の分野への普及啓発活動の一環として、平成18年2月16日（土）に東京大学大学院薬学系研究科講堂において、「学際領域における評価のデザイン」というタイトルでシンポジウムを開催した。次ページには、そのパンフレットを掲載するが、シンポジウム参加者は80名弱と好評であった。

シンポジウム

学際領域における評価のデザイン
- RCTとシステマティック・レビューの現状 -

日　　時：2006年2月18日（土）13:00-18:00
場　　所：東京大学大学院薬学系研究科・総合研究棟2F講堂（東京都文京区本郷7-3-1）
参 加 費：無　料

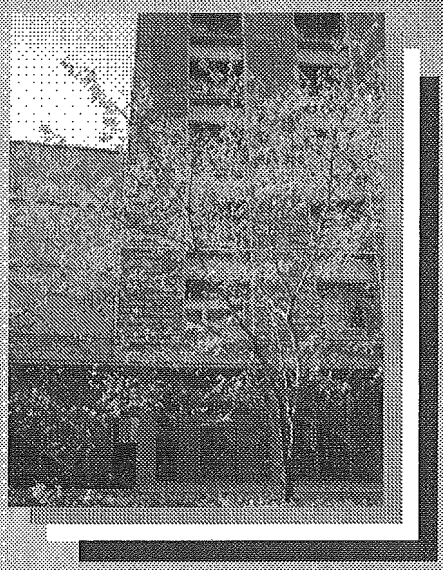
プログラム　座　長　津谷喜一郎（東京大学大学院薬学系研究科）
　　丹後俊郎（国立保健医療科学院）

講演者/タイトル：
13:00　開会
13:10-13:50 1. 山岡和枝（国立保健医療科学院）/ 栄養領域のRCTとSR
13:50-14:30 2. 高橋美絵（身体教育医学研究所）/ 運動による健康教育のSR
14:30-15:10 3. 上岡洋晴（東京農業大学）/ 温泉利用の健康教育のRCT
15:10-15:30　< coffee break >
15:30-16:10 4. 岩崎久美子（国立教育政策研究所）/ 教育領域のSR
16:10-16:50 5. 津富宏（静岡県立大学）/ 司法領域のRCTとSR
16:50-17:30 6. 正木朋也（国際医療福祉大学）/ 国際援助の評価
17:30-18:00 7. パネル・ディスカッション

主　　催：平成17年度厚生労働科学研究補助金医療技術評価総合研究事業
「エビデンスを適切に統合するメタ・アナリシスの理論、応用と普及に関する調査研究」班

後　　援：財団法人日本医療機能評価機構, The Campbell Collaboration Japan

事務局・問い合せ先：国立保健医療科学院技術評価部事務局　根津葉子
埼玉県和光市南2-3-6 tel: 048-458-6223 fax: 048-469-3875
e-mail: yokon@niph.go.jp



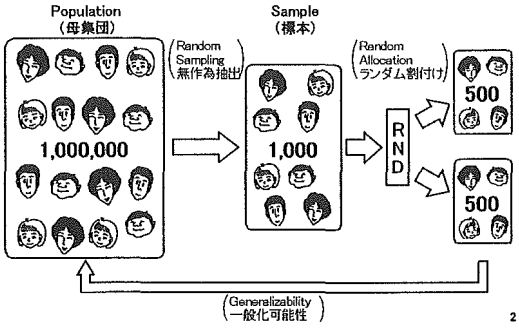
ランダム化比較試験とシステマティック・レビューの過去・現在・未来

シンポジウム
学際領域における評価のデザイン
－RCTとシステマティック・レビューの現状－
2006.2.18(土), 東京大学

東京大学大学院薬学系研究科医薬経済学
津谷喜一郎

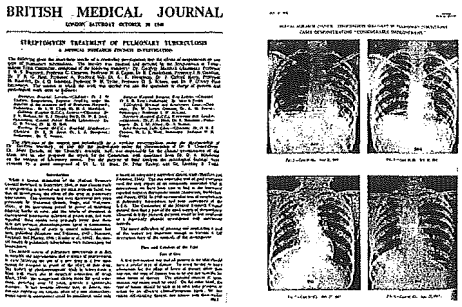
1

Random Sampling & Random Allocation
（無作為抽出とランダム割付け）



2

Streptomycin trial *BMJ* 30 October 1948



Determination of whether a patient would be treated by S or C was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill

3

用語は人と領域によって異なる

- RCT
  - ランダム化比較試験
  - 無作為化比較試験
  - 実験
  - ・・・
- SR
  - システマティック・レビュー
  - 系統的総説
  - メタアナリシス
  - ・・・

4

Systematic Reviewとは？

- Primary Analysis
- Secondary Analysis
- Meta-Analysis
  - → Systematic Review
    - → Clin. Prac. Guidelines

5

Strength of Evidence

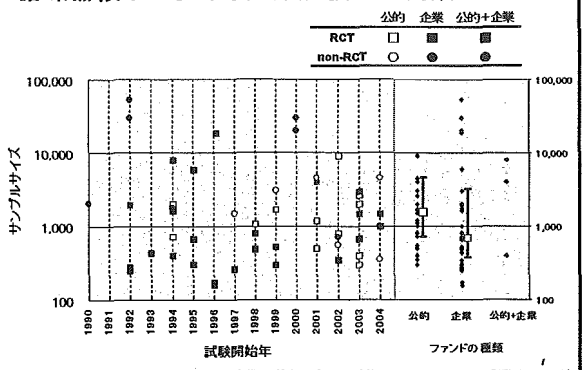
Strength of evidence

- case report
- case series
- case control study
- cohort study
- RCT
- DB-RCT
- meta-analysis

Linear Model

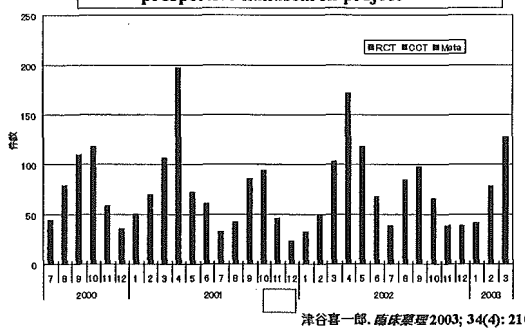
6

循環器領域における臨床試験の症例数とファンド



栗山, 他: JAMP以降の日本での循環器領域における大規模臨床試験のレビュー. 臨床薬理 2005; 36 Suppl: S152, 別刷, 2005.12.3(土)

Number of RCT/CCT/MA in Japan
-prospective handsearch project-



津谷喜一郎. *臨床薬理* 2003; 34(4): 210-6

8

臨床試験参加者

	日本	米国	倍率
人口	1億2千万	2億8千万	2.3倍
治験[1]			
初回届数	60	417	7倍
一品目あたりの必要症例数	約1,000例	約5,000例	5倍
参加者数	4万人	140万人	35倍
国民参加割合	3,000人に1人	200人に1人	15倍
臨床試験			
試験数	1,500	80,000	53倍
一試験あたりの症例数	約100例	約4,000例?	40倍?
参加者数	15万人	230万人	15倍
国民参加割合	800人に1人	120人に1人	7倍

9

1) 山積靛之介, 井上雅夫, 津谷喜一郎. 日本の年間治験参加者の推計数は4万人.臨床薬理 2005; 36 suppl: S295

Jadad Scale (1996)

	Yes	No
1. ランダム化の記載があるか？	1	0
Yesの場合、適切か？	1	-1
2. 二重盲検の記載があるか？	1	0
Yesの場合、適切か？	1	-1
3. 解析除外例、脱落例数、理由の記載があるか？	1	0
total		

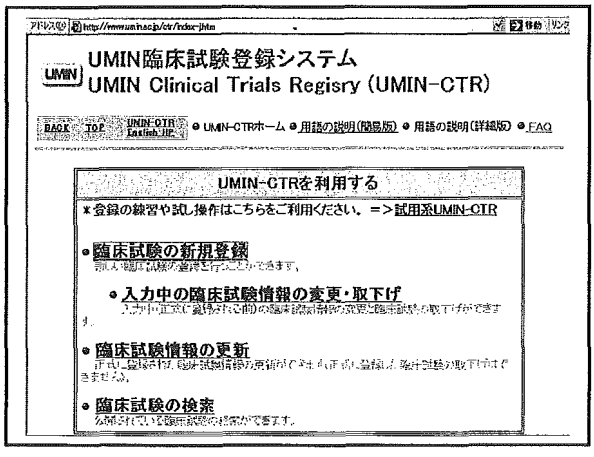
10

レポートの質管理

- RCT - CONSORT 声明
  - 1996
  - 2001 Revised 改訂版 (日本訳あり)
    - Explanation and elaboration 解説と詳細 (日本訳あり)
- SR - QUOROM 声明
  - 1999 QUOROM 声明 (チェックリストの日本訳あり)

http://www.consort-statement.org/
http://homepage3.nifty.com/cont/CONSORT_Statement/menu.html

11



栄養領域のランダム化比較試験(RCT)とシステマティック・レビュー(SR)

シンポジウム
学際領域における評価のデザイン
－RCTとシステマティック・レビューの現状－
2006.2.18(土), 東京大学

国立保健医療科学院技術評価部
山岡和枝, 丹後俊郎

栄養教育のRCT研究

無作為化比較試験による2型糖尿病予防のための新しい栄養教育の評価
渡辺満利子・山岡和枝・横塚昌子・丹後俊郎
(Diabetes Care 26:3209-3214, 2003)

目的 OGTT境界型の日本人男性勤労者を対象とし、FFQW65を利用した「新栄養教育」と「従来型」という2種類の栄養教育法の無作為化比較試験(RCT)により、EBNに基づいた栄養教育効果の評価を行う

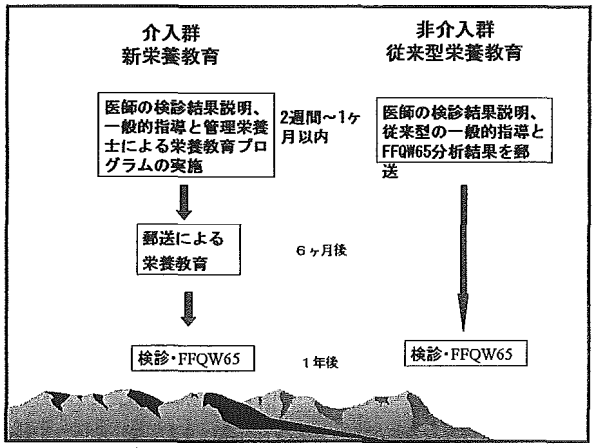
研究仮説 FFQW65を利用した新栄養教育群は、従来型教育群に比べて、1年後の75gOGTT負荷後2時間静脈血漿糖値(2h-PG)の開始時に対する変化率の差が10%以上低下する

研究デザイン 2種類の栄養教育法の評価を、無作為割付に基づく並行群間比較試験にて検討する

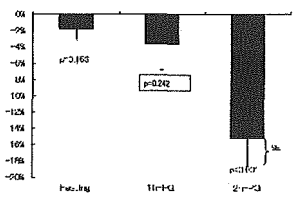
研究対象 平成11年2月から2年間の間に某人間ドック受診のOGTT境界型男子勤労者(35～70歳)173名

RCTによる割付 新栄養教育群:86名, 従来型群:87名

エンドポイント プライマリ=(介入1年後の2h-PGの10%低下)、セカンダリ=(空腹時血糖値、負荷後1時間値、1年後の充足率の改善指数など)



1年後血糖値の変化の差(調整後)



共分散分析により調整した差を検討したところ、有意な低下が認められた。
調整済変化率の差と95%信頼区間:-15.2% (-8.2% ～ -22.0%)

結論 FFQW65を利用した新栄養教育は糖尿病ハイリスク者の血糖値を改善する効果を持つ可能性が示唆された。

栄養領域でのシステマティック・レビューとメタ・アナリシス

生活習慣教育により2型糖尿病を予防できるか？
―RCT研究のメタ・アナリシス
山岡和枝・丹後俊郎
(Diabetes Care 28: 2780-6, 2005)

目的 ハイリスクを対象とした、糖尿病予防に対する生活習慣(食習慣単独も含む)教育に着目し、RCTに基づく介入研究のシステマティック・レビューとメタ・アナリシスにより、生活習慣教育の効果の評価を行うこと。

研究デザイン

システマティック・レビューとメタ・アナリシス。

研究仮説：生活習慣の改善プログラムを行った群は、それを行わなかった対照群に比べて血糖値の改善や糖尿病の罹患率に改善がみられる。

結果変数：負荷後2時間血糖値（mmol/dl）(2hPG)のベースラインからの変化（半年以上の介入期間）と糖尿病の罹患。介入の効果は前者では総変化量として両群でのベースライン値からの1年後の変化の差により、後者は相対危険度(RR)により検討した。

研究対象：糖尿病のハイリスクのグループ（IGT、IFG、境界型）

研究のタイプ：6ヶ月以上の介入期間のあるRCT。

介入のタイプ：生活習慣（含む食習慣単独）の改善を目指したプログラム。対照群は非介入群（従来型など）として比較したもの。

検索方法：電子媒体による検索（MedlineとERIC）で検索用語（テキストとMeSHはMedline検索手順に従った (1966.1- 2004.11)。成人を対象としたもので、言語は英語のみとした。

図1　システマティック・レビューの流れ

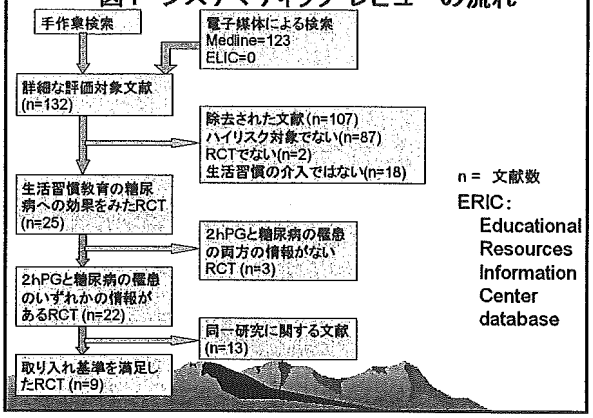
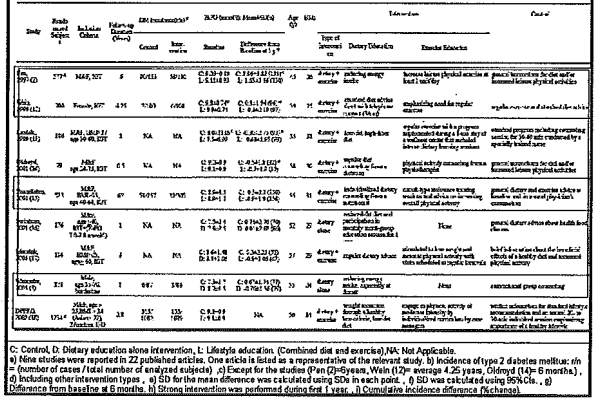
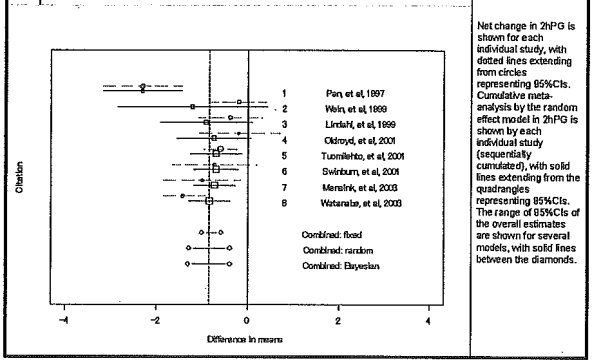


Table 1. Characteristics of the 9 randomized controlled trials)



C: Control, D: Dietary education alone intervention, L: Lifestyle education. (Combined diet and exercise),NA: Not Applicable.
a) Nine studies were reported in 22 published articles. One article is listed as a representative of the relevant study. b) Incidence of type 2 diabetes mellitus: n/n = (number of cases / total number of analyzed subjects) ,c) Except for the studies (Pan (2)=6years, Wein (12)= average 4.25 years, Oldroyd (14)= 6 months.) , d) Including other intervention types , e) SD for the mean difference was calculated using SDs in each point. , f) SD was calculated using 95% CIs. , g) Difference from baseline at 6 months. h) Strong intervention was performed during first 1 year. , i) Cumulative incidence difference (%/change).

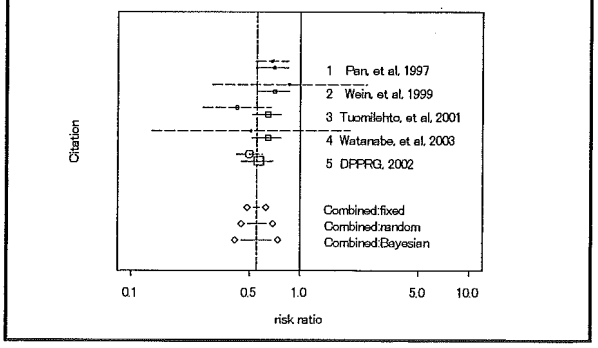
Figure 2. Forest plot for the net change in 2hPG in 8 randomized controlled trials of the effects of dietary education with their 95%CIs: individual and cumulative meta-analysis.



Net change in 2hPG is shown for each individual study, with dotted lines extending from circles representing 95%CIs. Cumulative meta-analysis by the random effect model in 2hPG is shown by each individual study (sequentially cumulated), with solid lines extending from the quadrangles representing 95%CIs. The range of 95%CIs of the overall estimates are shown for several models, with solid lines between the diamonds.

Figure 3. Forest plot for relative risk in 5 randomized controlled trials of the effects of dietary education with their 95%CIs:

individual and cumulative meta-analysis.



まとめ

本研究の結果、検討した研究の多くで生活習慣（食習慣のみを含む）教育方法・内容に相違があったものの、その改善により、教育を行わなかったグループに比べて1年後血糖値および糖尿病罹患のリスクの改善が認められた。

したがって糖尿病ハイリスク群を対照した栄養教育を含む生活習慣教育は、糖尿病予防の効果的戦略となりうる可能性が示唆されたと考える。

運動による健康教育のSR
-生活・運動指導介入の研究と実践における課題-

シンポジウム
学際領域における評価のデザイン
－RCTとシステマティック・レビューの現状－
2006.2.18(土), 東京大学

身体教育医学研究所
高橋　美絵

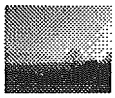
運動による健康教育のSR/RCT

exercise & intervention & health & SR (2002-2006)	
MEDLINE, CINAHL, COCHRANE ALL EBM	407
Web of Science BIOSIS Previews	36

exercise & intervention & health & RCT (2002-2006)	
MEDLINE, CINAHL, COCHRANE ALL EBM	815
Web of Science BIOSIS Previews	258

-生活・運動指導介入の研究と実践における課題-

中高年者を対象とした
ランダム化比較試験による
生活・運動指導の介入研究のレビューを通して



目的

国内外で中高年者を対象に行われたランダム化比較試験(RCT)による生活・運動指導中心の介入研究を、系統的に整理(対象・介入・結果)し、研究の質と、研究と実践における課題を明らかにすることを目的とした

方法：適格基準

1. キーワード	exercise, intervention, random controlled trial, behavior old, elder*, health. 運動、介入、ランダム化比較試験
2. データベース	ISI Web of Knowledge(SCI,SSCI,A&HCI,BIOSIS Previews), PubMed, 医中誌
3. 研究のデザイン	RCT　(研究計画のみのデザインペーパーは除く)
4. 出版の時期	2000年以降
5. 言語	英語、日本語
6. 対象	中高年者　(40歳以上)
7. サンプル数・観察期間	5人以上・1週間以上
8. 評価指標	以下のいずれかを含む 一次指標：日常の身体活動を示す変数 身体活動量、運動習慣、認知行動的変数など 二次指標：心身の健康状態を示す変数 身体組成、血液性状、運動機能、精神心理面など
9. 類似介入、及び効果の許容範囲	介入の数と種類：単独・複数を認め、運動以外の介入を許容する 評価指標：一次指標、及び、二次指標を示す変数を同等に扱う

方法：研究の質評価基準

(PEDro ScaleとCochrane Review の評価ツールの改変版、15項目、15点満点)

ランダム化	1.ランダムなグループ分けがなされたか
	2.対象選定(採用と除外)の基準は明記されたか
	3.両群はベースラインで同等であったか
盲検化	4.対象者は盲検化されたか
	5.評価者は盲検化されたか
	6.介入者は盲検化されたか
介入・測定	7.介入内容(種類、頻度、時間、期間、場所、強度など)の詳細は明記されているか
	8.サンプル数は十分か(ベースラインで各群50以上、又はパワー分析に基づき決定)
	9.観察期間は十分か(3ヶ月以上)
	10.測定・評価方法は明記されているか
分析・結果	11.主な指標においてベースライン時の対象者の85%以上の測定がなされたか
	12.主な指標においてITT分析*がなされたか
	13.主な指標において統計学的群間比較がなされたか
	14.主な指標において点推定値と信頼区間の両方を示しているか
	15.有害事象の有無に関する記述があるか
考察	点数外：結果の一般化可能性(外的妥当性)に関する記述があるか

※12. ITT分析(Intention to treat analysis)：脱落した対象者のデータも含めた分析

検索結果

Database:	Database:
ISI Web of Knowledge*20件, 2005.10.24 PubMed 28件, 2005.11.3	医学中央雑誌18件, 2005.10.24
Keywords: exercise & intervention & random* & control* & trial & behavior* & (old* OR elder*) & health	Keywords: (TH=身体運動/AL=運動、介入、ランダム) & (RD=ランダム化比較試験)

前述の適格基準に基づき選択・除外

RCT 21編

対象者数のべ4888人

米国(8) 日本(7) 英国(2) オーストラリア(2) ニュージーランド(1) カナダ(1)

結果1：研究の質評価

平均得点(15点満点)： 9.2(5-13)点

- 0点の場合、「該当しない」もしくは「記述がない」の2通りがある
- 課題項目： 盲検化、脱落、負の効果の記述

結果2：介入の効果

一次指標： 日常の身体活動

- 総じて効果的、有意な増加や対照群でみられた減少を予防した
- 但し、半年以上のフォローアップ後、効果が消失した報告あり(4)

<測定方法別の結果> ※ 質評価8点以上の研究

機器を用いた測定(歩数計、加速度計)‥	2／4
運動習慣(日記式活動記録)‥‥‥‥‥‥	5／6
運動習慣(回想式質問紙)‥‥‥‥‥‥	4／4
認知行動的変数(質問紙)‥‥‥‥‥‥	5／6

※ 測定方法間の結果の食い違い(Marshallら、高田ら)

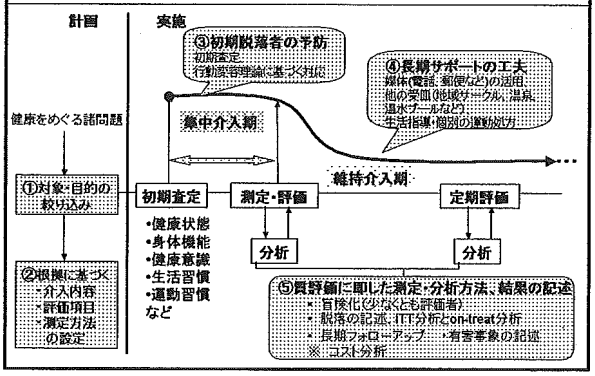
二次指標： 心身の健康状態

- 有意な効果を示した研究と、有意な効果のない研究があった

特徴的な結果：

- 医療機関や職域での介入は、中長期介入でも、脱落が少ない
- 媒体(電話、郵便等)を用いた介入は、中長期介入でも、脱落が少ない

効果的な生活・運動指導介入(啓発)のモデル
例)段階的な中長期介入



まとめ1. 研究の質に関する課題

- 盲検化の工夫
  →困難だが、評価者は努力可能
  →介入者や機関をランダム化
- 脱落を考慮した分析方法の検討
  → ITT分析における欠損データの取り扱い
  →脱落の量的・質的分析
- 負の効果の検討
  →有害事象の有無を記述

まとめ2. 健康による健康教育の研究課題

- 「脱落」と「効果の長期維持」の検討
  →理由を検証し、介入方法や対象の問題を明らかにする
  (介入の問題、身体の問題、家族の世話、仕事等で時間がない、など)
  →長期サポートの工夫
- 「地域と医療の連携モデル」「地域と職域の連携モデル」の介入
- 運動の健康増進効果の理論的根拠の明確化
- 研究の少ない対象に対する介入
  →後期高齢者、虚弱高齢者
- 費用対効果分析
  – 介入コスト－医療費削減効果の検証