COMMENTARY

Nutrition and Physical Activity and Chronic Disease Prevention: Research Strategies and Recommendations

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A shortage of credible information exists on practical dietary and physical activity patterns that have potential to reverse the national obesity epidemic and reduce the risk of major cancers and other chronic diseases. Securing such information is a challenging task, and there is considerable diversity of opinion concerning related research designs and priorities. Here, we put forward some perspectives on useful methodology and infrastructure developments for progress in this important area, and we list high-priority research topics in the areas of 1) assessment of nutrient intake and energy expenditure; 2) development of intermediate outcome biomarkers; 3) enhancement of cohort and cross-cultural studies; and 4) criteria for and development of full-scale nutrition and physical activity intervention trials. [J Natl Cancer Inst 2004;96:1276–87]

It has been hypothesized that changes in nutrition and physical activity patterns could reverse the obesity epidemic in the United States and elsewhere and reduce the risk of chronic diseases such as cancer, cardiovascular disease, osteoporosis, and diabetes. However, there is little consensus within the research community concerning either the study designs needed to provide reliable tests of disease prevention hypotheses or the developmental infrastructure needed to provide new hypotheses and interventions in a timely manner.

A variety of study designs, including analytic observational studies, randomized controlled trials, and population comparisons can be used for testing hypotheses related to changes in nutrition and physical activity and chronic disease prevention. Some scientists believe that observational studies provide reliable tests of hypotheses if the associations are strong and that controlled trials may be too expensive or impractical. Others hold that observational studies generally fulfill an important hypothesis-generating role but that randomized intervention trials are needed for definitive testing. Although it seems evident that both observational studies and randomized controlled trials have an important place in determining the association between nutrition and physical activity patterns and health, persons favoring either of the two approaches tend to travel in different circles and to participate in meetings of different research societies (e.g., epidemiologic societies versus clinical trial societies); thus, they have few forums for meaningful discussion of the interplay between the two study types.

It is clear that dietary and physical activity intervention trials with disease prevention outcomes are very costly; therefore, only a few trials can be conducted. Consequently, a well-thought-out program is needed for screening and pilot testing interventions that may become the subject of a prevention trial. Behavioral and pharmacologic nutrition and physical activity–related preventive research has great potential to lead to reductions in chronic disease burden; therefore, related hypothesis development research deserves substantial emphasis. Unfortunately, relatively few researchers are conducting small-scale human nutrition and physical activity intervention studies (with biomarker outcomes) that could yield new behavioral interventions.

Various scientific organizations and societies support deliberative processes for developing nutrition and physical activity recommendations and guidelines. To date, however, studies on chronic disease prevention have had limited impact on such recommendations, primarily because of gaps in available re-

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search data. The U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention, and other government agencies have regulatory responsibility for public safety with regard to foods and dietary supplements in the United States, but research data that would help those agencies fulfill their responsibilities are often lacking.

The purpose of this commentary is to provide some perspective on the research agenda and infrastructure developments that are needed to ensure the reliability and usefulness of advice provided by primary care physicians, the food production and fortification choices made by agriculture and industry, administrative influences (e.g., city planning choices) on physical activity patterns, the content of school-based nutritional and physical education curricula, and the dietary and physical activity patterns chosen by individuals.

This perspective emerged from a workshop titled "Research Strategies for the Study of Nutrition, Physical Activity and Chronic Disease," held May 28–30, 2003, in Seattle, Washington. The aims of the workshop were to discuss design strengths and weaknesses of different types of studies of nutrition and physical activity patterns and chronic disease prevention and to explore ways to strengthen these types of studies. The participants also discussed the role of biomarkers in such studies, including high-dimensional genomic, transcriptomic, proteomic, and metabolomic (the simultaneous study of a large number of small molecules from a biologic sample) measures. The group comprised epidemiologists and biostatisticians, along with nutritional, clinical, and basic science researchers, who have expertise and interest in the areas of nutrition and physical activity.

Workshop Background and Goals

Progress in Chronic Disease Prevention Research

The workshop co-organizers (R. Prentice, W. C. Willett, and P. Greenwald) described aspects of the history and status of nutrition and physical activity and chronic disease research. Interest in these topics has been stimulated by the high incidence of chronic disease and the rapidly increasing rate of overweight and obesity in the United States *(1)* and other Western countries and by studies indicating that immigrants from low-incidence countries experience elevated rates of age-specific incidence, often within a few years of immigration *(2)*.

Although the U.S. program for chronic disease prevention research remains small, evidence from randomized controlled trials strongly supports the prevention concept for several chronic diseases: tamoxifen for breast cancer *(3)*, calcium and aspirin for colorectal adenomas *(4,5)*, combined hormones for colorectal cancer *(6)*, finasteride for prostate cancer *(7)*, and statin family drugs for lowering cholesterol *(8)*, as well as anti-inflammatory and anti-hypertensive drugs for coronary heart disease, alendronate *(9)* and calcium and vitamin D *(10)* for fractures, calcium for kidney stones *(11)*, and metformin and lifestyle changes *(12)* for diabetes. This last example is interesting in that a combination of dietary and physical activity changes yielded an estimated 58% reduction in the incidence of type 2 diabetes among study subjects having abnormal glucose tolerance—a statistically significantly greater reduction than that for metformin—whereas the other studies involved only oral medication interventions. A number of major ongoing chronic disease prevention trials involve nutrition and physical activity interventions, including studies of selenium and vitamin E supplementation for prostate cancer prevention, glucosamine sulfate and chondroitin sulfate for arthritis prevention, a low-fat diet for breast and colorectal cancer prevention, and calcium and vitamin D supplementation for fracture and colorectal cancer prevention.

Research Design and Agenda

Developing evidence-based recommendations for dietary and physical activity pattern changes is an important long-term target of chronic disease prevention research. However, as previously mentioned, development of such recommendations is challenging, and there is considerable diversity of opinion concerning the most appropriate agenda for research. Perhaps because of the results from animal feeding trials dating back to the 1940s *(13)* and earlier, the hypothesis that reducing dietary fat may prevent breast cancer has served as a focal point for much of the discussion about methodology and the research agenda over the past 25 years *(14,15)*. This hypothesis has been the subject of extensive, state-of-the-art observational studies and meta-analyses *(16–18)*, as well as ongoing intervention trials *(19–21)*. Opinions on the viability and importance of this hypothesis differ, mainly because of different assumptions about the measurement properties of food frequency questionnaires (FFQs) and other dietary self-report instruments, along with the absence of an accepted biomarker of fat consumption. Some also believe that genetic background may be important in determining response to dietary fat. Recent reports of a positive association between animal, but not vegetable, fat and premenopausal breast cancer risk in the Nurses Health Study II cohort *(22)*, and of differing results on fat and breast cancer in the Norfolk component of the European Prospective Investigation of Cancer (EPIC), depending on whether FFQs or food diaries were used for dietary assessment *(23)*, have further fueled this debate.

For a small number of disease prevention hypotheses, a substantial body of observational studies and one or more randomized controlled trials have been reported. Some of the results of these two types of studies suggest health effects in opposing directions. Reports of beta-carotene supplementation for lung cancer prevention *(24–27)* and combined postmenopausal hormone therapy *(6,28–30)* and vitamin E supplementation *(31,32)* for coronary heart disease prevention have heightened interest in the methodologies used for designing, conducting, and reporting these types of studies and in establishing a research agenda for making credible recommendations for chronic disease prevention. Related methodologic considerations include the development of additional biomarkers of nutrient consumption and energy expenditure, with associated validation studies.

Nutrition and Physical Activity and Chronic Disease Hypothesis Testing: Observational Studies

Study Design

A number of salient points emerged concerning the strengths and weaknesses of analytic observational studies (i.e., studies based on individual exposure data) of nutrition and physical activity and concerning the potential to improve their reliability and interpretation. Observational studies, especially cohort studies, have a number of benefits: 1) They tend to be less expensive

than intervention trials, though cost differences depend on the intensity and frequency of data collection. 2) They permit the simultaneous study of disease associations with many different nutrition and physical activity patterns, including those that may not be practical or ethical as the focus of intervention trials. 3) Their typical size and duration permits study of interactions among dietary and physical activity exposures and interactions of these exposures with genetic factors *(33,34)* in populations that are representative of the general population. On the other hand, observational study associations may be confounded if people who have certain dietary or physical activity patterns also have other disease risk factors (including other nutrition and physical activity factors) or disease screening patterns that cannot be fully accounted for in data analysis. Moreover, nutrition and physical activity patterns are among the most difficult epidemiologic factors to measure in an unbiased and reliable fashion.

Measurement Issues

Dietary assessment has been the focus of a number of specialized meetings and forums, including five international conferences *(35).* Early studies examined the correlation between estimates of nutrient intake from different self-report instruments (e.g., food records, FFQs, food recalls) or from repeated application of the same instrument *(36).* More recent data comparing estimates of nutrient consumption from self-reports and objective biomarkers suggest that measurement errors for a specific nutrient from multiple self-report dietary assessments from a single individual are large and may be strongly positively correlated with each other *(37–39),* though further study is clearly needed *(40,41).* The importance of the measurement error issue and the potential for severe bias in traditional multivariable analyses are reinforced by the fact that nutrient intake distributions may be fairly narrow within study populations, and intakes of various nutrients may be highly correlated *(42).* Even if long-term intakes could be estimated precisely over the years or decades that may have an effect on chronic disease risk, it would be a difficult task to ascertain the statistical relationship between specific nutrients and chronic disease from large-scale observational studies because of the instability of analyses that regress on highly correlated variables.

Consequently, nutritional epidemiology observational studies rely increasingly on nutrient consumption biomarkers *(43).* A suitable biomarker for nutrient consumption should provide an unbiased estimate of actual nutrient consumption, with measurement error variance that is not large (e.g., $<50\%$) relative to that for actual consumption. It should also be unrelated to study subject characteristics (e.g., genetic, anthropometric, or behavioral) and to corresponding self-report assessment measurement error *(44).* These criteria appear to be met, at least in relation to short-term consumption in weight-stable persons, by using doubly labeled water to measure energy consumption *(45),* urinary nitrogen and sodium to measure protein and sodium intake, respectively, and possibly by using urinary potassium to measure potassium intake *(46).* These "recovery" biomarkers *(37)* evidently satisfy the criteria for suitable biomarkers. When collected from a subset of study participants, such biomarkers can allow corresponding self-report assessments to be properly calibrated and can lead to more reliable tests and better estimators of the associations between nutrients and disease. However, biomarkers adhering to this type of simple measurement model have not been developed for most nutrients. Thus, there is strong need for research on biomarker development and validation and for further development of associated calibration and data analysis procedures. For a number of nutrients (e.g., antioxidant vitamins), a biomarker correlate of consumption is available, typically from the blood concentration of a nutrient's metabolite. Methodologic research that includes carefully designed human nutrition intervention studies is needed to determine whether or not such biomarkers, which typically do not adhere to a simple measurement model, can be used to strengthen study reliability. For example, it may be possible to develop measurement models for concentration biomarkers for certain nutrients in conjunction with recovery biomarkers for other nutrients.

Observational studies of physical activity and chronic disease have many of the same problems as studies of dietary patterns and chronic disease—most notably, exposure assessment and confounding issues. In fact, the combination of dietary and physical activity patterns (e.g., energy balance) over a sustained period of time is the major determinant of body mass and obesity and is an important determinant for a broad range of obesity-related diseases. Physical activity and related energy expenditures can be directly assessed using activity records or logs, accelerometers, observation, direct calorimetry, or doubly-labeled water *(45);* they can be indirectly assessed using physiologic methods (e.g., cardiorespiratory and muscular function) or health status questionnaires or surveys. For example, measures of cardiopulmonary fitness, such as maximum oxygen output volume, can yield estimates of normal physical activity *(47),* although such measures may not adequately reflect low-intensity or longer term activity levels. Observational studies typically use personal interviews, mailed surveys, and recall of historic information to construct estimates of energy expenditure patterns and of physical activity patterns over time. The doubly-labeled water technique provides a valuable but expensive biomarker of total short-term energy expenditure and of physical activity-related energy expenditure when combined with resting energy expenditure measurements (i.e., those obtained using indirect calorimetry). Less expensive physical activity biomarkers and self-report assessments of physical activity generally require careful validation and calibration.

In response to a need for research on these important measurement topics, the National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Aging, and National Institute of Nursing Research (all part of the U.S. National Institutes of Health [NIH]) have issued program announcements to encourage research on methods for improving diet and physical activity assessment.

Analysis and Reporting

Another approach to strengthening the body of epidemiologic evidence on nutrition and physical activity and to improving the interpretability and credibility of observational study reports involves improving data analysis and reporting standards. Although many studies report the relative risk of disease as a function of exposure rank (e.g., top quartile versus bottom quartile of estimated exposure), it is also useful to report risk as a function of exposure estimated on an absolute scale. For example, disease risks across populations that have different exposure distributions may be nonlinear, perhaps because of risk

exposure thresholds. The relationships between selenium consumption and blood levels of glutathione peroxidase and between dietary folate and DNA damage, for example, are both apparently nonlinear. Special efforts to obtain comparable measures of absolute nutrient intake and physical activity–related energy expenditure across studies may be needed because studies sometimes use different assessment tools and may be conducted in disparate populations. Measuring biochemical markers using similar methods and quality assurance procedures across studies is useful in calibrating self-report estimates of nutrient consumption and physical activity.

The reliability of data analyses from observational studies and from meta-analyses of such studies can also be enhanced by using prespecified analysis plans and reporting schedules that appropriately account for multiple testing. Although not common in observational studies, periodic monitoring of emerging data pertinent to a prespecified set of hypotheses, as is now standard in clinical intervention trials, may be useful. The quality of primary data analysis may also be enhanced by giving other research groups access to those data.

Controlled Intervention Trials

Randomized controlled trials (RCTs) with disease occurrence outcomes are considered the gold standard for testing chronic disease prevention hypotheses. RCTs avoid confounding by pre-randomization risk factors, whether or not such risk factors can be measured or even recognized. Furthermore, there is no measurement error in the randomization assignment, and an RCT typically provides a clinical context for ensuring consistent ascertainment of outcomes among randomly assigned groups. One benefit of an RCT is that it can focus specifically on the health benefits and risks of a prescribed change in dietary habits or physical activity patterns over a specific time period.

Design and Conduct

Despite the strength of RCTs for testing nutrition and physical activity hypotheses, they are likely to be very expensive, and study subjects may need to be followed for a long period of time before intervention effects become evident. Thus, it is valuable to have observational data on the precise nutrition and physical activity interventions (e.g., doses, schedules) to be tested before proceeding with an RCT. Cost considerations may limit testing to interventions that may have major public health benefits.

One consequence of testing nutrition and physical activity hypotheses using an RCT is that healthy volunteers have to make major changes in dietary and/or physical activity patterns and maintain those changes for a number of years. It may take considerable effort for participants to adhere to intervention goals, especially for interventions that require major lifestyle changes. Assessing their adherence may also be a challenge, because of the difficulties associated with measuring nutrition and physical activity. Although assessing adherence is not needed for valid disease rate comparisons among randomized groups, it does come into play in the interpretation of trial results. With null results, it may be difficult to distinguish an intervention's lack of health effects from inadequate testing as a result of loss of power from poor intervention adherence. Similarly, differential adherence reporting between intervention and control groups could lead to inaccurate recommendations following a positive trial result.

Monitoring and Reporting

The interpretation and generalizability of intervention trial results raise additional issues. Trials of nutritional supplements may, for example, give a reliable answer but only to a very specific question, while hypotheses concerning other supplement dosages or preparations or how they apply to other populations remain untested. Intervention trials of nutrition and physical activity patterns aim to test the entire set of consequences of the intervention over the trial follow-up period and may therefore not specifically test etiologic hypotheses of interest. For example, a dietary fat reduction intervention may induce changes in the consumption patterns of other nutrients, which are not separately assessed by overall intervention group versus control group comparisons. Furthermore, sample size, study duration, and cost issues may render RCTs impractical for testing certain hypotheses, such as prevention hypotheses aimed at the early stages of carcinogenesis or hypotheses concerning childhood or early adulthood nutrition and physical activity in relation to chronic disease.

Monitoring for safety and efficacy is an important and challenging aspect of conducting chronic disease prevention trials. Interventions could affect a number of chronic disease outcomes, each with its own time course. For example, it may be difficult to design and monitor a general population trial of the impact of a weight loss intervention on longer term cancer outcomes because of the likelihood that emerging results on cardiovascular diseases and diabetes would lead to early termination of the trial. Anticipated and unexpected intervention effects may need to be integrated into summary benefits versus risk indices, and overall trial results and implications may depend on the duration of the intervention and follow-up. Indeed, multiple clinical outcomes in disease prevention RCTs must be ascertained so that overall benefits versus risks can be meaningfully assessed. Additional issues relate to premature trial stoppage: the continuation of intervention may be deemed inappropriate if there is evidence of an early adverse outcome or if external data suggest some unfavorable consequence of a related intervention under test, even if trial data suggest overall favorable benefits versus risks.

Trial Initiation

Establishing the criteria for the initiation of a full-scale disease prevention trial is itself an important methodologic goal. Pertinent criteria include documenting the biologic plausibility and public health potential of an intervention, establishing the practicality of the intervention in a study of the appropriate size and duration, providing adequate assurances concerning study subject safety and intervention equipoise, and considering the merits of the contemplated intervention compared with the merits of other potential interventions that may be practical now or in the near future.

Intermediate Outcome Clinical Trials

Role and Timing

One way to capitalize on the rigor of an RCT is to use one or more intermediate outcome comparisons for evaluating the intervention rather than comparing the rates of the disease or diseases targeted for prevention. This approach could reduce sample size, study duration, and cost.

Intermediate outcome clinical trials can be used at any stage of preventive intervention development and testing. Phase II trials, which typically have small sample sizes and short-term outcomes, may play a valuable role in intervention screening and development because they can evaluate the impact of candidate interventions on molecular targets and indices of disease pathways and processes. Intermediate outcome trials can also be conducted as feasibility or pilot studies of a particular intervention (or a small number of interventions) before beginning a full-scale (phase III) intervention trial. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, for example, was initiated by the National Heart, Lung, and Blood Institute around 1990 to examine the effects of estrogen and combined estrogen–progestin hormone therapies on blood lipids, coagulation factors, bone metabolism, and endometrial histology. This trial *(48)* suggested the need for a long-term, full-scale trial to assess the benefits and risks of combined postmenopausal hormone therapy and of estrogen alone, with the latter being practical only for women who have had a hysterectomy, in view of unfavorable endometrial histology results and poor adherence among women with a uterus who were assigned to the estrogen-alone regimen.

This example raises several important points concerning the timing and context of intermediate outcome studies. Postmenopausal hormone therapy has been used in the United States and elsewhere since the 1960s and 1970s. Is there a need to conduct intermediate outcome trials for agents that may have major public health benefits and risks during the early decades of use? If so, what type of forum will be required to identify which interventions should be tested with intermediate outcome trials? The PEPI example also illustrates the need to test a comprehensive battery of intermediate outcomes and disease risk factors, especially for interventions that could affect different body organs and systems favorably or unfavorably. The PEPI trial is a good example because outcomes generally supported the cardioprotection hypotheses for combined hormones, whereas a subsequent full-scale clinical trial of the combined hormone therapy most commonly used in the United States indicated unfavorable effects on coronary heart disease over an approximately 5-year follow-up period *(6)*. This full-scale trial indicated favorable effects of combined postmenopausal hormone therapy on fractures and colorectal cancer but unfavorable effects on stroke, venous thromboembolism, and breast cancer, and on a global index that combines these outcomes with those for cancer of the endometrium and mortality from all other causes.

In general, phase II trials with a well-selected set of outcomes constitute important steps in establishing the biologic plausibility of a preventive intervention. Such trials could yield insights into key pathways for intervention effects and may help select the most appropriate intervention agents, dosages, schedules, and intervention combinations. These characteristics seem especially important for nutrition and physical activity interventions, since hypotheses often arise primarily from observational studies that are unable to distinguish between closely related dietary or physical activity patterns. The value of intermediate outcome RCTs depends entirely on the availability of suitable measures, such as validated biomarkers, of the intermediate outcomes.

Another type of intermediate outcome trial has outcomes that mediate intervention effects on the targeted diseases. This type of trial has been used with some frequency in nutrition and cancer studies, particularly with colorectal adenoma recurrence as the primary intermediate outcome *(4,49–51)*. Other well-known examples of this type of trial include Barrett's esophagus as an intermediate outcome for esophageal adenocarcinoma; actinic keratosis incidence, for non-melanoma skin cancer; dysplastic nevi incidence, for malignant melanoma; high-grade prostatic intraepithelial neoplasia, for prostate cancer; and cervical intraepithelial neoplasia and carcinoma *in situ*, for invasive cervical cancer. Each of these involve lesions that are believed to be on the pathway to the development of the related malignancy, and from which most of the malignancies are believed to arise. Other promising intermediate outcomes include radiographically estimated breast density as an intermediate endpoint for breast cancer *(52)* and quantitative karyometric analysis of cellular nuclear abnormalities as an intermediate for various cancerous and precancerous lesions *(53)*.

Potential Implications of Intermediate Outcome Trial Results

Although knowledge of nutrition and physical activity intervention effects on intermediate outcomes is valuable, a test of no intervention effect on an intermediate outcome will provide a valid test of the hypothesis of no intervention effect on a targeted clinical disease only under limited conditions (e.g., a change in the biomarker if and only if there are corresponding changes in clinical outcome). An intermediate outcome with this property is often referred to as a surrogate outcome. Surrogate outcome criteria require that intermediate outcomes be related to the targeted disease risk and, importantly, that the surrogate fully mediates the relationship between the intervention and the targeted disease *(54)*. These criteria require that the intervention not affect the target disease via pathways that bypass the surrogate, and they imply that the suitability of an intermediate outcome as a surrogate for a given disease occurrence may depend on the intervention, or class of interventions, under study *(54–57)*. Within the framework of these criteria, validation of a surrogate outcome requires data on both the intermediate and the clinical outcomes in relation to the intervention of interest in a trial cohort of suitable size, precluding the sample size and study duration reductions that surrogate outcomes aim to deliver. If a validation study supports the surrogacy of an intermediate outcome, it may be sufficient to focus subsequent trials of similar interventions on the surrogate outcome alone.

Another approach to assessing the utility of an intermediate outcome involves meta-analyses of trials that include both the intermediate outcome and the clinical disease of interest, with emphasis on the agreement between intervention effects based on the intermediate and the clinical outcomes *(58)*. The required meta-analytic data often may not be available for nutrition and physical activity interventions. As with RCTs that have clinical outcomes, an interesting research possibility would be to combine surrogate outcome RCT results with results from observational studies to yield public health recommendations. Such an approach could be used in trials of calcium consumption for colorectal adenoma and colorectal cancer prevention.

Intermediate outcome trials can usually be carried out with a much smaller sample size than an RCT with chronic disease outcomes, but they may not comprehensively address corresponding public health issues. Depending on the biologic effects of an intervention, high-risk individuals or those with prior disease history may not benefit as much from an intervention being tested as do other individuals. Trials in populations at high

risk for certain diseases may provide limited information on intervention effects for other diseases that might be helpful for benefit-versus-risk projections for healthy people. Hence, designing trials for high-risk subjects involves careful consideration of such tradeoffs and of the costs of identifying and managing high-risk study subjects versus subjects from the general population.

Studies in Special Populations and Population Comparisons

Observational studies, particularly cohort studies, complement intervention trials for testing nutrition and physical activity and chronic disease hypotheses but, as discussed above, confounding and measurement error biases may limit their reliability for testing such hypotheses. Judicious selection of a study population can help control these biases; for example, populations that have unusually broad distributions of food consumption and physical activity patterns may be particularly valuable because disease risk trends across exposure levels may be large relative to measurement error and confounding influences. Individuals in certain carefully selected populations could be comparatively good providers of data on dietary and physical activity patterns and may generally be highly reliable study participants.

One example is the Adventist Health Study, a cohort study of 125 000 Seventh-day Adventists in the United States, which focuses on diet and cancer and involves an unusually broad range of nutrition and physical activity exposures compared with other U.S. cohorts, partly because about one-third of Adventists are vegetarian. Indeed, this cohort includes large populations of whites and blacks who consume soy protein at levels similar to that of Asians. A second example is the Multiethnic Cohort (MEC) study in Hawaii and Los Angeles (approximately 215 000 study subjects), which includes approximately equal numbers of white, Latino, African-American, and Japanese-American subjects, along with a smaller number of native Hawaiians. This cohort study has a major focus on nutrition and cancer, and the subjects have considerable variation in their nutrient consumption and dietary patterns, with some noteworthy variations among ethnic groups. The MEC study allows nutrient–disease associations to be examined within ethnic groups and provides a type of built-in replication of study findings that is enhanced by variations in tumor characteristics and genetic susceptibility characteristics among ethnic groups.

A third example is the European Prospective Investigation into Cancer and Nutrition (EPIC), which comprises cohorts in several western European countries that have wide variations in cancer incidence rates. The cohorts combined include more than 500 000 study subjects. Different dietary data collection instruments across populations are calibrated using standardized 24-hour dietary recalls as a common instrument, with some additional calibration using urinary nitrogen as an objective marker of recent protein consumption. The various dietary questionnaires are administered in each country's language, and they assess country-specific foods and dietary patterns. The EPIC study is an excellent example of what is achievable (a large sample size, a wide range of dietary intake patterns, and an ability to make absolute intake estimates) only if mutually comparable calibration activities are funded and prospectively built in to observational studies. In addition, the effectiveness of a relatively short physical activity questionnaire was compared with more extensive questionnaires in the EPIC study *(59)*.

Other Research Designs and Opportunities

In contrast to a typical ecologic study, which relates population estimates of mean nutrient consumption and estimates of mean confounding factors to disease rates, an aggregate data study relates individual-level nutrition and physical activity exposures and confounding factor values from representative surveys in each population to corresponding population disease rates *(60–62)*. The aggregate data study design is robust to classical additive measurement error in primary exposure and confounding factors and may also offer some robustness to systematic measurement error if there are disparate nutrition and physical activity patterns among the populations being compared. On the other hand, it may be difficult to ascertain exposure data in a uniform and comparable manner across diverse populations, and there is little experience to guide data collection and analytic procedures to control between-population confounding. Thus, it seems reasonable to conduct an aggregate data study within existing multi-population cohort studies (e.g., in the combined EPIC and MEC populations), even though the power for examining many nutrition and physical activity associations may be limited. Analyses that examine the consistency of associations within and between populations may help determine the potential of a more worldwide aggregate data study of diet and cancer (NIH funding for such a study has previously been requested by a subset of this commentary's authors). Studies that involve population comparisons may improve our understanding of the considerable variations in incidence rates of various cancers in relation to nutrition and physical activity exposures and of the genomic and proteomic biomarkers from blood specimens and shed cells; this type of study might also be useful for comparing histologic and molecular characteristics of diseases across populations.

Studies of migrant populations provide unique opportunities to examine chronic disease associations. Not only do such populations tend to have unusually broad exposure distributions, they are also suited to the examination of temporal relationships between ages at and durations of exposures and chronic disease risk. Two examples are the nutrient and disease associations among Japanese subjects in the MEC who migrated to the United States and the breast cancer incidence among Asians who migrated to the United States, according to age at and years since migration *(2)*. To date, however, few cohort or case–control epidemiologic studies have been conducted among migrants. It should also be noted that time for insightful migrant studies may be limited; for example, colorectal cancer incidence rates in Japan now exceed those in the United States *(63)* and, thus, colorectal time-trend studies within Japan may now be preferable to studies of Japanese migrants.

Nutrition and Physical Activity and Chronic Disease Hypothesis Generation

Traditional sources of hypotheses in the areas of nutrition and physical activity and chronic disease areas have included observational epidemiology and therapeutic trials. Although both sources are valuable, the former may lack specificity, given the highly correlated patterns for the consumption of various nutri-

ents and the measurement error issues previously discussed. Additionally, hypotheses from therapeutic trials cannot be expected to include interventions that act predominantly at the early stages of disease development and are likely to be pharmaceutical rather than lifestyle interventions. Given that practical and specific nutritional and physical activity approaches to obesity and chronic disease prevention have important potential for improving public health, basic research programs that include preclinical and early-stage clinical intervention trials for generating and screening hypotheses seem essential.

Role of Preclinical Studies and Early-Stage Trials

Preclinical and early-stage clinical trials of nutrition and chronic disease can focus on the interaction between consumption of bioactive food components and genomic DNA (nutrigenomics); on the interaction between bioactive food components and DNA methylation and other epigenomic events; on gene expression changes in relation to dietary patterns; on corresponding proteomic changes, since there tends to be a modest correlation between mRNA and protein expression and posttranslational modifications; and on metabolomics to incorporate aspects of metabolite regulation and metabolic pathways. For example, diet and physical activity may influence genetic and epigenetic events associated with several cancer processes, including carcinogen metabolism, hormone regulation, cell differentiation, apoptosis, and cell cycle regulation. Identification of nutrition and physical activity interventions that have favorable effects on cancer processes and on corresponding processes for other chronic diseases (e.g., lipoprotein synthesis and inflammation, fibrinolysis, and thrombosis in cardiovascular diseases) has the potential to yield dietary and physical activity hypotheses suitable for further testing.

One interesting hypothesis that arose from rodent models is that dietary (caloric) restriction reduces the incidence of various chronic diseases and increases lifespan. This hypothesis has stimulated research to identify a metabolic serotype for dietary restriction in rodents *(64)*, to identify the disease prevention mechanism, to extend the results to nonhuman primates on defined diets, and to identify humans whose disease risk can be modified by changing their energy consumption. Termination of dietary restriction leads to a rapid return to insulin resistance and to pre-restriction gene expression patterns; thus, continued restricted caloric intake over most of the lifespan may be needed for the full benefits associated with lowered caloric intake to be realized. If dietary restriction begins during early adulthood, rodents do have increased longevity, though the effects are considerably smaller than with lifelong dietary restriction *(65)*. Intermittent dietary restriction—as little as 1 day in 4—increases longevity in rats *(66)*, and both adult onset dietary restriction and fasting for 1 day in 7 have been shown to delay tumor onset in p53-deficient transgenic mice *(67)*.

Studies in rodent models, as well as in other model systems, can provide a valuable tool for the initial assessment of nutrition and physical activity hypotheses to define intervention mechanisms. Simple, low-dimensional surrogate endpoints are unlikely to be available for this purpose, especially if chronic disease outcomes of interest include multiple biologic entities. Effective data analysis methods are needed to bring intervention effects for multiple intermediate markers into summary indices to be used for interpreting study results. For example, in global gene expression studies, dietary modification (e.g., dietary restriction) may result in changes in the expression of several hundred genes. These genes can be organized into functional categories (e.g., proliferation, cell cycle, metabolism, apoptosis, angiogenesis, stress response, antioxidant, detoxification, transcription, and signal transduction) to aid in summarizing intervention effects. The voluminous information on gene expression, proteomics, and metabolomics that is emerging relative to dietary restriction and other nutrition and physical activity hypotheses is difficult to assimilate because numerous metabolic pathways are likely to be involved for many diseases. Fortunately, a variety of new bioinformatics and data analysis tools for this type of task (e.g., www.bioconductor.org) are being developed.

Small-scale Human Intervention Trials

Human nutrition intervention studies are well-suited to improving the understanding of the effects of dietary patterns on metabolism and on biomarkers of disease susceptibility. Such studies involve a controlled, administered diet and are typically limited to a few weeks or months. Crossover designs, in which study subjects are exposed to more than one of the dietary patterns under study for part of the follow-up period, are frequently used in these studies. Human nutrition intervention studies can provide an early evaluation of the plausibility of hypotheses generated from observational studies or from model systems. They can also provide a useful setting to identify exposure biomarkers, to study exposure bioavailability, and to identify nutrient–gene interactions. Human nutrition intervention studies can be used to generate new hypotheses and can serve as pilot studies for larger scale intervention trials. Outcome measures may derive from tissue samples from organs of interest or peripheral tissues, including exfoliated cells. A broad range of biomarkers, including those for gene expression, protein expression, and epigenetic changes may be considered. For example, as the technical aspects of high-dimensional protein expression measurements become more refined, and as protein patterns that indicate susceptibility for specific chronic diseases are identified, human nutrition studies to broadly determine the relationship between diet and protein expression may become possible.

Small-scale physical activity intervention trials with biomarker or intermediate outcomes likewise have a role in physical activity hypothesis generation and development. Such studies involve controlled physical activity interventions and could examine the same range of gene expression, protein expression, and epigenetic biomarkers as nutrition trials. Intermediate outcome physical activity intervention trials to date have had somewhat larger sample sizes (i.e., a few hundred subjects) and have focused on clinical and anthropometric parameters. For example, a recent exercise intervention trial *(68)* was conducted in 173 sedentary, overweight postmenopausal women randomly assigned to a moderate-intensity exercise program or to a control group, with outcomes that included sex hormone concentrations and body fat distribution *(69,70)*. Such physical activity hypothesis generation efforts need to consider both acute and chronic effects of physical activity.

Classes of Nutrition and Physical Activity Hypotheses

Hypothesis development research in the nutrition and physical activity area needs to target both a medical model that aims

to provide interventions for individuals according to their genotype and specific exposures and a public health model that aims to develop nutrition and physical activity interventions and recommendations that are applicable to the general population, or major segments thereof. Each model has its own infrastructure and funding needs. Specifically, cooperative therapy groups may be well-suited for conducting trials under a medical model, but a different type of population-oriented structure may be better suited for screening and testing nutrition and physical activity public health interventions.

Nutrition and Physical Activity Recommendations and Regulations

Nutrition and Physical Activity Recommendations

Dietary and physical activity guidelines for health promotion and disease prevention have been promulgated by various government agencies, scientific panels, and professional groups *(71–79).* For example, the Food and Nutrition Board of the Institute of Medicine periodically assembles expert panels to review the scientific literature and establish recommended dietary allowances *(74)* and has expanded its efforts to establish dietary reference indices for a broad range of nutrients. The recent report on macronutrients *(75)* includes recommendations for physical activity that are somewhat different from those given earlier *(76);* it also reinforces the need for coordinated objectives in making public health recommendations on nutrition and physical activity.

The dietary reference indices for a given nutrient include a recommended dietary allowance based on an estimated average requirement. When available scientific data are inadequate for establishing an average requirement, an adequate intake is given. An upper limit of consumption that acknowledges safety concerns is also specified whenever practical. Reference intake levels are given separately by age and sex and for pregnant and lactating women and are used as the basis for determining the standards for nutritionally adequate diets for many federal assistance programs. The scientific studies used to establish the dietary reference index include depletion/repletion studies, case reports of adverse effects resulting from overconsumption, observed intakes in healthy populations, and epidemiologic observations. In evaluating nutrient requirements, an important question often asked is, "Adequate for what?" Chronic disease data are not always sufficiently definitive in providing outcome data at multiple levels of intake to be used as the basis for a quantitative recommendation. Thus, the recommended allowances for specific nutrients, which are based on estimates of average requirement, are intended primarily to prevent deficiency syndromes. When a recommended allowance is not available, observed intakes in healthy populations are used as a basis for recommending adequate intake.

Likewise, human data on which to base tolerable upper intake levels are often sparse, and when uncertainty factors (used to adjust from lowest observed adverse effects levels) are applied to compensate for that lack, there may be some overlap between recommended intakes and upper intake limits. Thus, research studies that aim to close gaps in the scientific database for setting dietary reference indices related to chronic disease prevention would be useful. The panel also considers nutrient interactions and susceptible subpopulations when setting dietary reference indices and is moving toward a greater emphasis on the whole diet.

Similarly, recommendations for using physical activity and weight control to reduce the risk of cancer and other diseases have been made by several groups *(76,77,79).* Again, important knowledge gaps exist, both for individual disease outcomes and for overall health and, to date, no physical activity intervention trial with chronic disease outcomes has been conducted in the general population.

Labeling and Regulation

The FDA has regulatory responsibility for health claims (i.e., food substance and disease risk reduction claims) on labels for food and for dietary supplements. In implementing the Nutrition Labeling and Education Act (NLEA) of 1990, FDA used the statutory concept of "significant scientific agreement among experts qualified by training and experience" to evaluate the scientific evidence when deciding whether a claim should be authorized for use on food labels. This scientific standard was also extended to health claims on dietary supplements following passage of the 1994 Dietary Supplement Health and Education Act (DSHEA). Congress subsequently provided a mechanism whereby recommendations from authoritative bodies (e.g., the Food and Nutrition Board of the Institute of Medicine and the National Academy of Sciences; U.S. Dietary Guidelines) could serve as the source for authorized health claims in lieu of FDA review. More recently, judicial decisions have confirmed the right of manufacturers, under the free speech protections of the Constitution, to make truthful and not misleading claims about substance and disease relationships that are based on preliminary evidence. Accordingly, the FDA has developed an evidence-based ranking system to rate the level and quality of scientific evidence available for a specific relationship. These ratings, or "grades" of evidence, are to be combined with food label statements about the substance and disease relationship to ensure that consumers are not misled regarding the relative strength or weakness of the available scientific evidence.

Health claims on food labels have the potential for (a) helping consumers identify and use healthful foods as part of a lifestyle pattern that is effective in reducing the risk of chronic diseases, (b) increasing consumer awareness about the role of a healthful diet in disease risk reduction, and (c) motivating manufacturers to formulate and market healthful foods. Unfortunately, to date, the preliminary nature of much of the scientific information on food substance and disease relationships has limited the number of claims that can meet the evidentiary standard of significant scientific agreement. Improved approaches for facilitating research on the nutrition and disease relationships discussed here could have significant impact on public health via food labeling provisions under the jurisdiction of the FDA.

Discussion and Recommendations

The workshop participants agreed on 10 general points regarding nutrition and physical activity and chronic disease from the topics discussed above, along with more specific research recommendations in four areas.

Consensus Points

1) Changes in nutrition and physical activity patterns may be key to reversing the obesity epidemic in North America and elsewhere and to reducing the risk of various chronic diseases in developed countries.
2) Related basic, epidemiologic, and public health research toward identifying practical nutrition and physical activity interventions and patterns that will benefit health should have a high priority on national and international health research agendas.
3) Highly credible research results are needed to favorably influence individuals' choices about nutrition and physical activity, advice given by primary-care providers, agricultural policies, food production and processing choices, environmental design, educational choices, and food fortification and regulation. The conduct of the needed research should be recognized as a demanding task that is now becoming scientifically achievable.
4) In view of numerous methodologic challenges, a varied nutrition and physical activity research agenda is needed that includes large studies of long duration. Major research funding organizations should acknowledge these requirements.
5) The nutrition and physical activity research agenda, as with other chronic disease prevention efforts, should emphasize overall health benefits versus risks, with implications for funding opportunities and mechanisms.
6) The nutrition and physical activity research agenda needs to include the following components: biologically based hypothesis generation and initial testing, observational studies of the association of nutrition and physical activity with chronic disease, screening and testing of promising interventions using intermediate outcomes, and full-scale nutrition and physical activity intervention trials with disease outcomes that are supported by earlier phase studies and that have potential for improving public health.
7) The relative emphasis among the listed program components should depend on the ability of specific research initiatives to address pertinent nutrition and physical activity questions in a reliable and interpretable fashion, while taking advantage of emerging technologies and research opportunities.
8) Methodologic research that strengthens the efficiency and reliability of major study designs and elucidates the interplay among designs in the context of nutrition and physical activity and chronic disease should be a key element of the research agenda. Methodologic research on suitable biomarkers and measurement error models for self-report assessments of nutrition and physical activity is clearly needed.
9) Research that could inform nutrition and physical activity recommendations and regulations should be encouraged.
10) The implications for improved public health and the research opportunities related to nutrition and physical activity are large and warrant the energies of a large cadre of basic, clinical, and population scientists, working across disciplines *(80)*.

More specific research recommendations, following small-group and full workshop discussions, are given below for measures of nutrition and physical activity patterns and status, hypothesis development and phase II trials, cohort and cross-sectional studies, and criteria and strategies for initiating full-scale phase III trials with disease outcomes.

Nutrition and Physical Activity Measurement and Biomarker Development

Recommended research on markers of food consumption and health status would include studies of the tissue distribution and speciation of nutrients and research on non-nutrient biology in humans and in model systems. Similarly, augmented exercise physiology research in humans and model systems is needed. Recommended human research would aim to better describe and accommodate biases in self-reports and would study measurement error correlations across various self-report instruments. Research on cognitive and behavioral methods to reduce bias and measurement error would also be desirable. Methods that combine dietary and physical activity recall, records, frequencies, and histories with multiple measurements using specific instruments in cohort studies would be helpful. Pattern recognition studies using high-dimensional biologic data (e.g., proteomic, metabolomic) to identify indirect biomarkers of nutrient consumption or physical activity-related energy expenditure are needed, as are direct measures of nutrient status in exfoliated cells and fluids. Additional studies of variability are needed for many biomarkers, whether or not they have been validated for assessing nutrient consumption or physical activity. For some bioactive food components, biomarkers may provide the only way to assess intake or nutritional status.

Nutrition and Physical Activity and Chronic Disease Hypothesis Development

More basic research, especially small-scale human nutrition and exercise intervention trials with biomarker outcomes, will invigorate hypothesis generation and initial testing of the relationships between nutrition and physical activity and chronic disease. Opportunities for training in clinical nutrition and exercise physiology research with a focus on specific chronic diseases, and directed funding opportunities for high-priority clinical trials to evaluate biomarker efficacy and safety outcomes would be especially welcome. Phase II trials with a comprehensive set of biomarker outcomes are necessary for translating results from laboratory studies to full-scale intervention trials. Phase II trials can also increase the likelihood of a successful health benefit versus risk result in a subsequent phase III trial by refining the interventions, developing adherence strategies, evaluating the translation of efficacy results from studies in cells and animals to humans, developing safety indicators, and studying the relationship between intervention interactions and genetic and environmental factors.

Cohort and Cross-Cultural Studies

Cohort and cross-cultural studies should continue to be a mainstay method for the epidemiologic study of nutrition and physical activity and chronic disease associations. However, the credibility and interpretation of observed associations is diminished by uncertainty concerning the measurement error properties of dietary and physical activity assessment instruments and the extent to which confounding has been controlled—both confounding by other difficult-to-measure nutrition and physical activity variables and residual confounding by non-nutrition and physical activity variables. In response, research on methods for

using validated nutrient consumption and physical activity biomarkers within subcohorts to calibrate self-reports of nutrition and physical activity in cohort studies is strongly indicated. Collaborations among investigators involved in existing cohort studies should be encouraged. Such collaborations could lead to "absolute exposure" biomarker calibration studies across cohorts and ultimately to association analyses based on both within-cohort and between-cohort comparisons. An annual meeting of investigators who are studying cohorts that have collected comprehensive dietary and physical activity data could facilitate such collaboration and could provide a forum for interaction with basic scientists. Additional research efforts are needed to ensure that existing major cohort studies include clinical outcomes that are comprehensive enough to allow meaningful assessments of overall benefit versus risk.

Another issue is whether or not existing cohorts allow a sufficient response to current nutrition and physical activity opportunities. Consideration should be given to whether additional cohort studies having nutrition and physical activity and chronic disease goals are needed among children, in understudied geographic areas (e.g., Latin America), or in populations in nutrition and physical activity transition. Case–control studies may be useful for the initial exploration of some nutrition and physical activity issues, especially those concerning exposures at early ages.

Full-scale Intervention Trial Evaluation

Nutrition and physical activity hypotheses having biologic plausibility and substantial public health potential should be subjected to full-scale (phase III) intervention trials, when practical. Trans-NIH forums need to be established to identify the most promising nutrition and physical activity interventions for phase III trials and to review trial proposals by external investigators. Review criteria would include an assessment of biologic plausibility, an assessment of concordance with observational and other data sources, an evaluation of the public health importance, and a determination that less costly designs will not be able to resolve the benefit-versus-risk question in a reliable manner. For example, the possibility of conducting a phase III physical activity intervention trial is currently of great interest, and the trans-NIH forum suggested above could assess whether a general population trial, say among persons aged 50 years or older, is currently merited. Alternatively, the assessment could consider whether new or additional intervention trials among those at high risk for targeted diseases (e.g., breast cancer, diabetes) or who have a personal history of targeted diseases should first be conducted to refine and evaluate the intervention in a less expensive, more limited fashion. One possibility for the development of a forum for identifying nutrition and physical activity and chronic disease hypotheses that are suitable for phase III testing would be a new nutrition and physical activity and chronic disease cooperative group comprising investigators who have interest and expertise in basic, clinical, and population aspects of nutrition and physical activity and who have interest and expertise in pertinent health-related outcomes. Such a cooperative group could conduct studies of various phases of nutrition and physical activity hypotheses and could receive and evaluate concepts from the scientific community for new studies, including phase III clinical trials. Concepts endorsed by the cooperative group could then be developed into full proposals for appropriate peer review. We recommend that the NIH consider initiating such an entity as a way of stimulating and capitalizing on opportunities in this most important research area.

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NOTES

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