National Cancer Institute

Estimating usual total nutrient intakes from supplements and diet

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Slide 1

Hello, and welcome to today's webinar, the fifth in the Measurement Error Webinar Series. I'm Sue Krebbs-Smith, Branch Chief of the Risk Factor Monitoring and Methods Branch at the U.S. National Cancer Institute. I'll be moderating today's webinar, the last of our sessions on estimating usual intake distribution.

A few notes before we get started: The webinar is being recorded so that we can make it available on our Web site. All phone lines have been muted and will remain that way throughout the webinar. There will be a question-and-answer session following the presentation; you can use the Chat feature to submit a question. And, finally, a reminder: You can find the slides for today's presentation on the Web site that has been set up for series participants. The URL has been sent out via the listserv and appears in the Note box at the top left of your screen.

Other resources available on that page include the Glossary of Key Terms and Notation and the recordings of the first four webinars. The link to the National Health and Nutrition Examination Survey dietary tutorial has been added to the recommended resources, as requested during the webinar 4 question period.

Now, I'd like to introduce our presenter for today's webinar. Dr. Regan Bailey is a nutritional epidemiologist in the Office of Dietary Supplements at the National Institutes of Health. Dr. Bailey's research focuses on methodological issues related to dietary assessment. Recently, Regan has worked with Dr. Kevin Dodd and others to apply statistical methods to data from the National Health and Nutrition Examination Survey to estimate total nutrient intake. We're pleased to have Regan present today's webinar on estimating total usual nutrient intake distribution. Dr. Bailey.

Thank you, Sue. And as Sue mentioned, I would like to point out that Kevin Dodd is really instrumental in many of the methods that I will be presenting here today. So I come at this from the perspective of the data user, a nutritional epidemiologist, who is interested in applying some of these principles that have been discussed in the webinar series. *(R. Bailey)*

Presenters and Collaborators

Sharon Kirkpatrick
Series Organizer

Regan Bailey	Laurence Freedman	Douglas Midthune
Dennis Buckman	Patricia Guenther	Amy Subar
Raymond Carroll	Victor Kipnis	Fran Thompson
Kevin Dodd	Susan Krebs-Smith	Janet Tooze

Slide 2

So before I begin, I'd like to acknowledge the other presenters and collaborators in this webinar series and take a moment to say thank you to Sharon Kirkpatrick, the series organizer who has been instrumental in all of the details that bring this webinar series to you.

measurement ERROR webinar series

This series is dedicated
to the memory of

Dr. Arthur Schatzkin

In recognition of his internationally renowned contributions to the field of nutrition epidemiology and his commitment to understanding measurement error associated with dietary assessment.

Slide 3

I would like to remind everyone that this series is dedicated to the memory of Dr. Arthur Schatzkin.

Two main areas of interest

- Describing usual intake distributions: mean, percentiles, proportion above or below a threshold
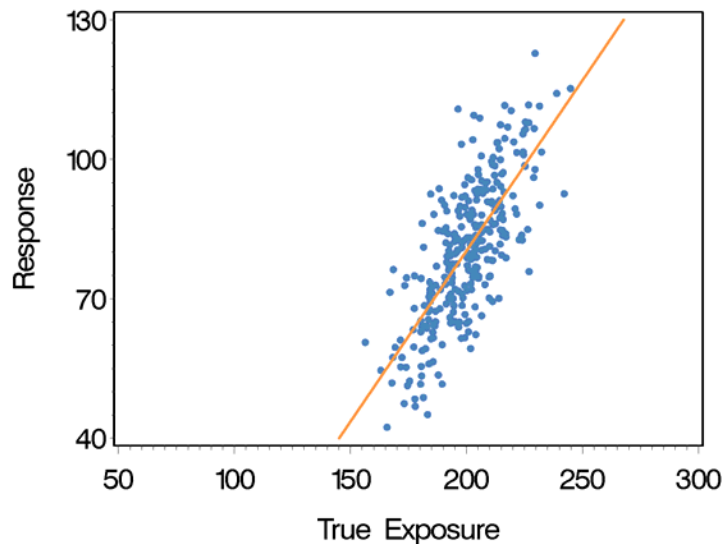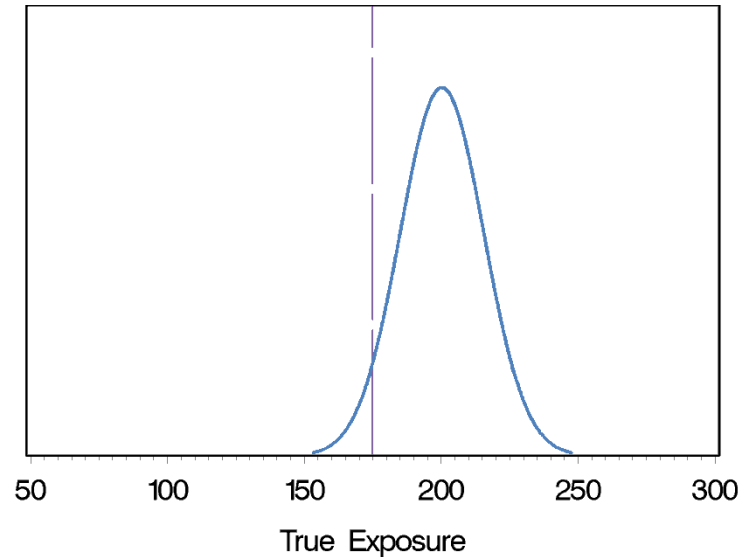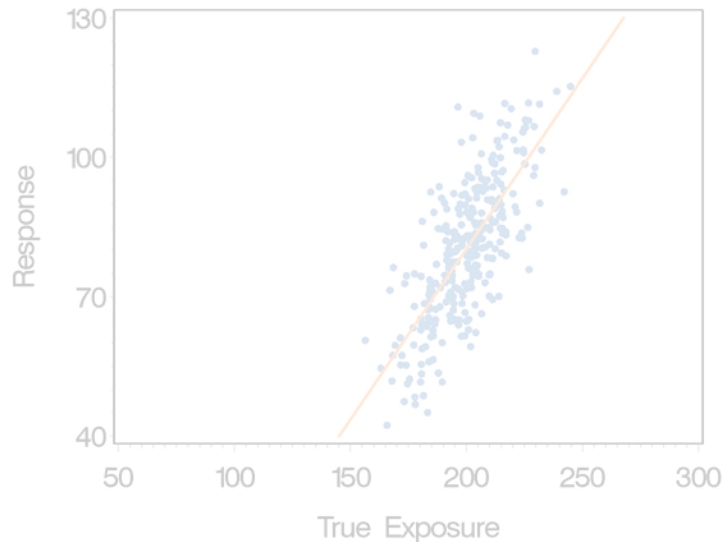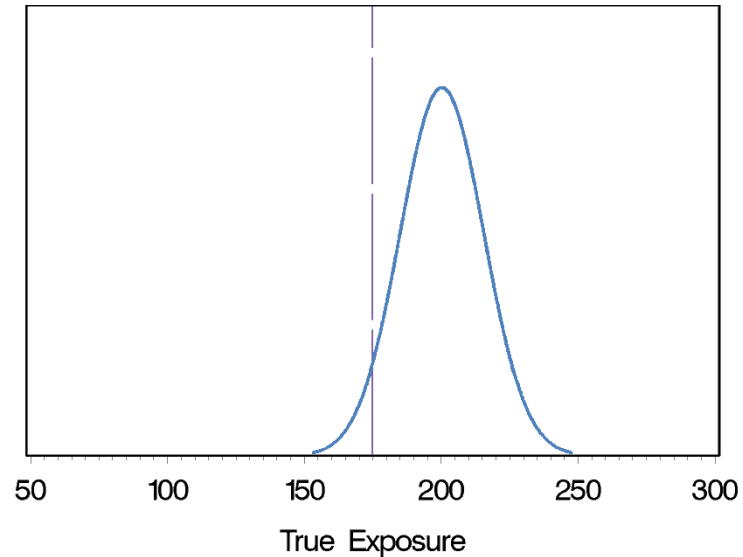
- Estimating diet-health relationships: regression coefficients

Slide 4

So to start out with, some introductory concepts that were considered in structuring the series: The webinars will cover two main areas of interest—the impact of measurement error and ways to account for it when describing usual intakes—for example, when monitoring diet and nutrition among a population of interest—and when assessing relationships between a dietary exposure and a health outcome. In the first case, we are interested in distributions and the associated statistics such as the means, the percentiles, and the proportions above and below a certain threshold or cutpoint, like a nutrient requirement or a food group recommendation. In studying diet-health relationships, we're interested in regression coefficients that describe the relationship between a dietary exposure and an outcome, such as an odds ratio or relative risk.
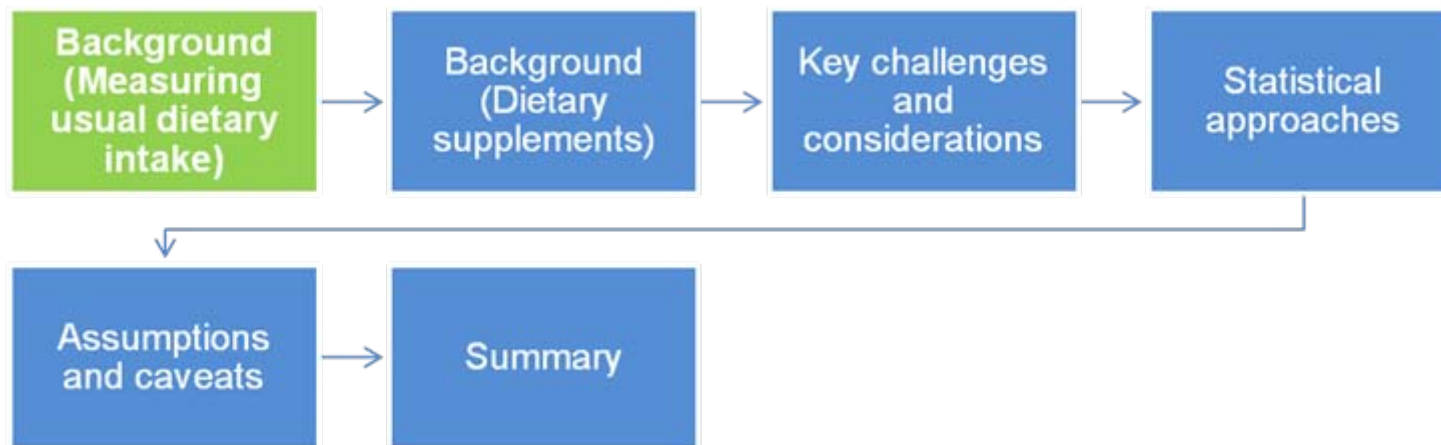
Two main areas of interest

- Describing usual intake distributions: mean, percentiles, proportion above or below a threshold

- Estimating diet-health relationships: regression coefficients

Slide 5

Today, we'll be focusing primarily on the first part of this talk, or the first goal of this webinar series.

BACKGROUND:
MEASURING USUAL DIETARY INTAKE

Before I begin, I would like to go over some of the background in measuring usual dietary intake. So for those of you who have been with us throughout the series, this will be a quick refresher, and for those of you who are new, I hope to address the key concepts necessary to discuss all of the topics that I hope to cover today.

Two types of self-report instruments

- **Short-term instruments**
  (e.g., 24-hour recalls, food records, food diaries)

  – Often used in population surveys for monitoring health and nutrition

- **Long-term instruments**
  (e.g., food frequency questionnaire)

  – Often used in large cohort or case-control studies to examine diet-health relationships

Slide 7

As Sharon described in the first webinar, there are two types of self-reported instruments: short-term and long-term. Short-term instruments—what I'll be talking about primarily today. 24 hour recallsare often used in population surveys for monitoring health and nutrition. Longer-term instruments, usually food frequency questionnaires, can be used in large cohort, or case-control studies, and while they are not as interested in estimating distributions, they are useful in examining diet-and-health relationships.

24-hour recall (24HR)

- Less cognitively challenging (relies on short- term recall)

- Rich detail → fewer assumptions required in converting to nutrient and food group intake

- Aims to capture recent diet

  – Need more than one to assess usual intake

- *Expensive to collect and code (until recently)*

So, just a reminder about the strengths and weaknesses of 24 hour recalls for dietary assessment for foods—we'll think about these also in the context of measuring dietary supplements a little bit later in the talk. So 24 hour recalls are useful in that they are less cognitively challenging and can obtain rich detail about a short-term intake but they are expensive to collect and code. Until recently, when technological advances in the field have made it possible to collect recall data at a lower cost, such as automated Web-based recalls—and work is recently under way to test a module to assess dietary supplements using a Web-based 24 hour recall.

Food frequency questionnaire (FFQ)

- Aims to capture long-term intake

- *Inexpensive to administer*

- Cognitively challenging

- Affected by recent diet

- Finite food list

- Lack of detail → assumptions required in converting to nutrient and food group intake

Food frequency questionnaires are able to capture long-term intake at the expense of some of the rich details that we can get from the 24 hour recall.
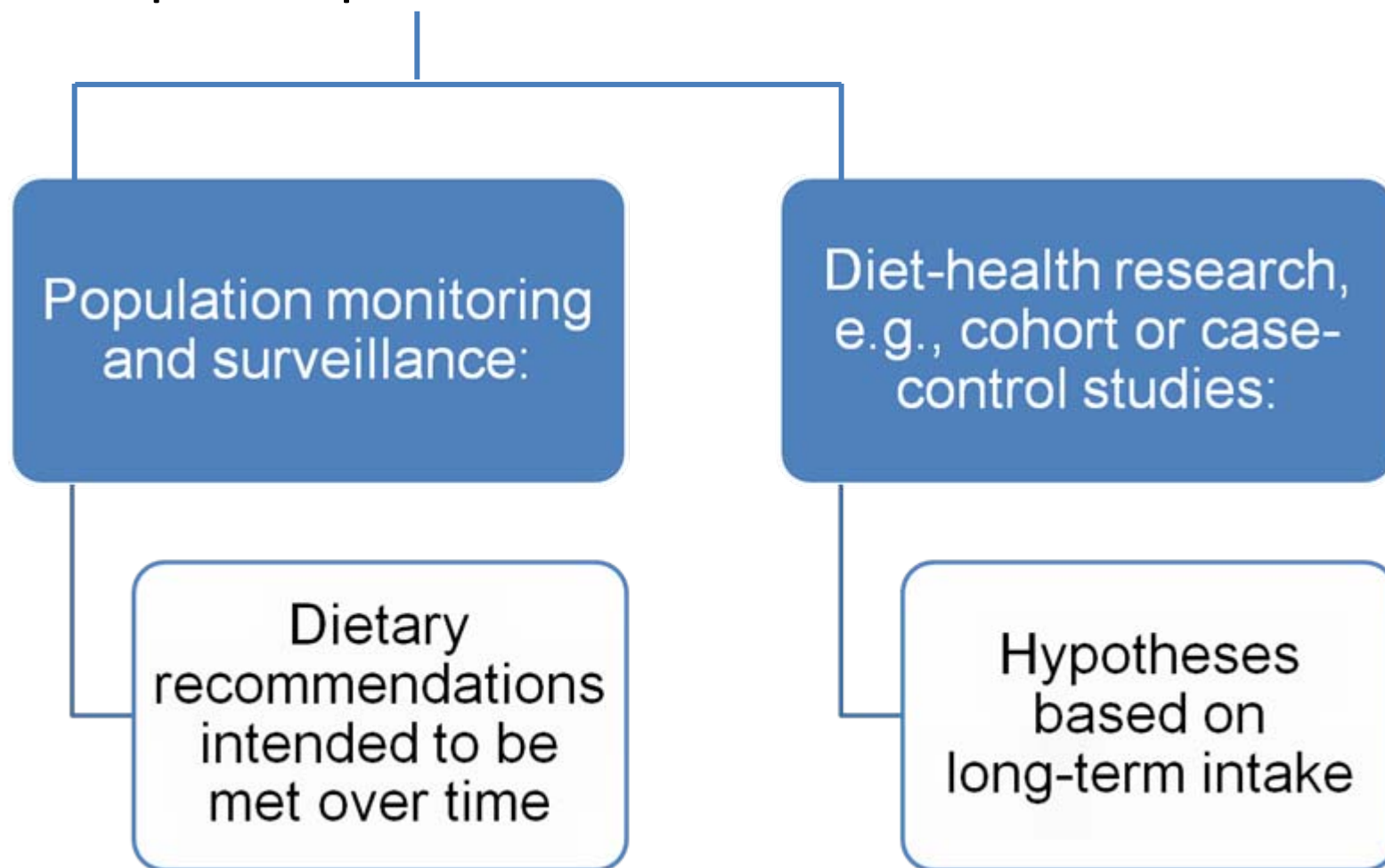
Daily vs. episodic consumption

- **Consumed nearly daily by nearly all persons**

  – E.g., vitamin C, total grains, total vegetables, solid fats, added sugars

- **Consumed episodically by most persons**

  – E.g., vitamin A, whole grains, dark green vegetables, fish

- **Consumed episodically by ? persons**

  – Supplements

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And I'd also like to discuss very briefly something that Dr. Tooze covered in her presentation about daily versus episodic consumption of foods and nutrients. This is *really* important as we consider dietary supplements. So for foods, we have foods and nutrients that are consumed daily by nearly all people. We have foods and nutrients that are consumed episodically by most people. But with dietary supplements, we have both. Some people may use supplements episodically, for example, seasonally. People may use vitamin D only in the winter months. Some people may consume [supplements] episodically—for example, vitamin C—when they are sick. So these are two different supplements that are used in different time periods, and then someone may also use a daily multivitamin/multimineral. So when you're trying to model these intakes, this is a special consideration for supplements.

Usual dietary intake

Average or long-run intake (*habitual intake*)
over a specific period of time

Population monitoring and surveillance:

Diet-health research, e.g., cohort or case-control studies:

Dietary recommendations intended to be met over time

Hypotheses based on long-term intake

Slide 11

So, remember that in monitoring and surveillance, what we typically want is the usual or long-run average intake. In this presentation most of the examples that I will use seek to explain how supplements are used to meet or exceed nutrient recommendations. We will be discussing how to use 24 hour recall data to obtain usual nutrient intake, and then how to expand that to total nutrient intake.

Challenge

Usual intakes are not directly observable

- Self-report dietary assessment instruments measure usual intake with error

- If ignored, this error can bias results

- Statistical modeling methods can be used to correct this bias

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This poses a challenge because usual intakes are not directly observable in practice; 24 hour recalls are good daily measure of intake, but they are not reflective of usual or long-term intake or exposure. We know that regardless of the dietary assessment tool that you use, there is an error associated with the measurement. If ignored, this error can bias the results, whether that is the estimation of the distribution that is biased, or the estimation of the relationship between diet and some health parameter. However, I'm happy to report that the statistical modeling methods that we've been describing in this series can be used to help reduce this bias.

Some existing methods

- U.S. National Research Council (NRC)/ Institute of Medicine (IOM)

- Iowa State University (ISU) Method

- U.S. National Cancer Institute (NCI) Method

- EFCOVAL Consortium Multiple Source Method (MSM)

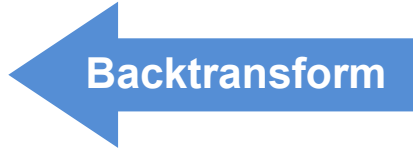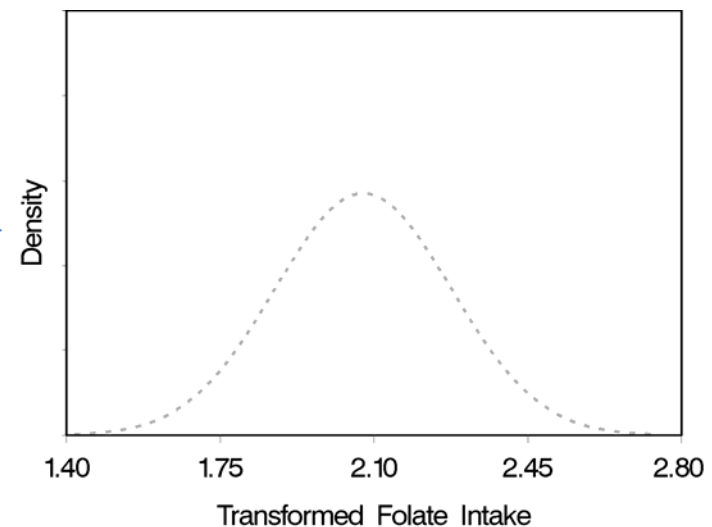- Statistical Program for Age-adjusted Dietary Assessment (SPADE)

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As has been described previously, there are a number of methods that have been in use to assess usual dietary intake, and these are just a few of them.

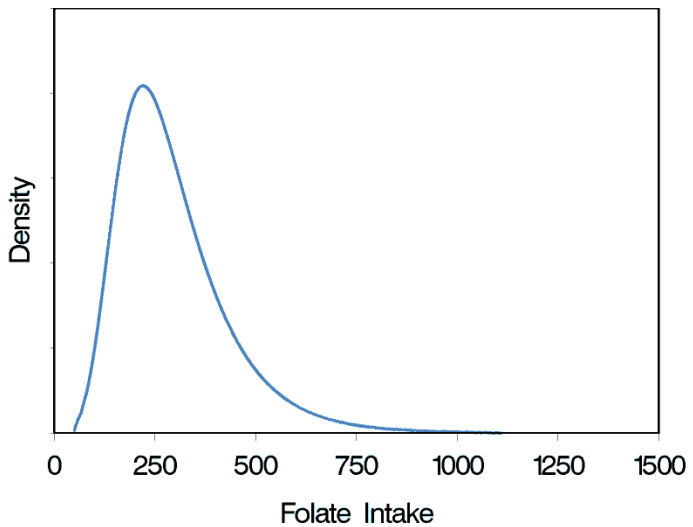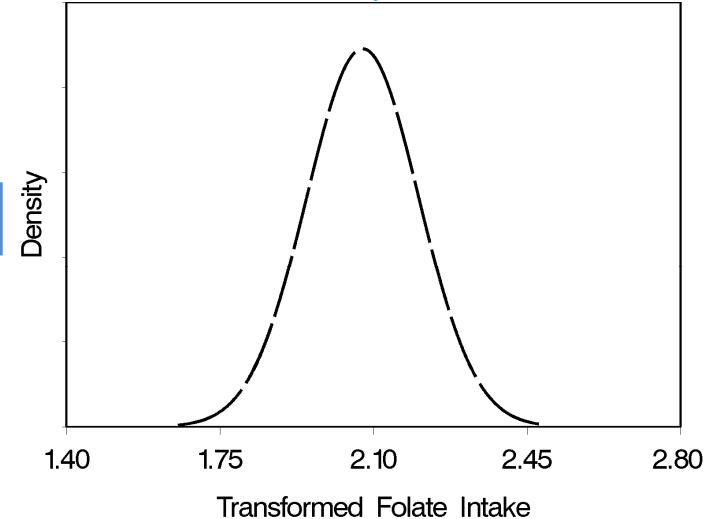# Accounting for nonlinear transformations
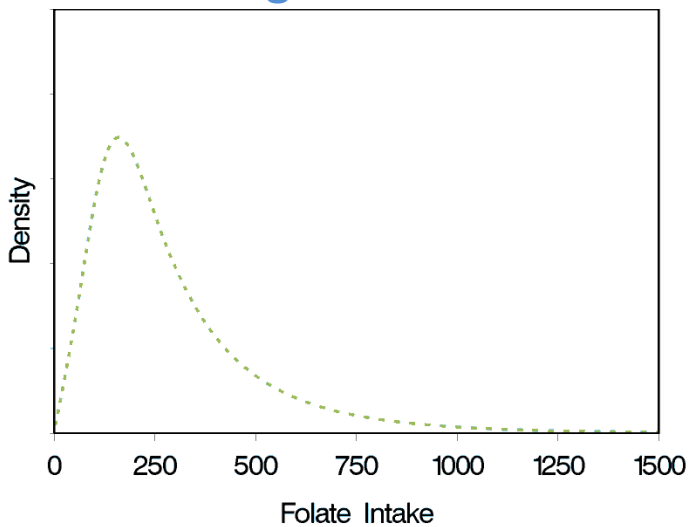
All of these methods have been built on the same framework. Data are estimated in the original scale. We see in the upper left-hand panel—this is the distribution in the normal scale in which your parameter of interest is measured. Some sort of transformation is then applied to the data to make the distribution reflective of a normal distribution. In this transformed scale, the within-person variability is then removed. We'll refer to this as "adjust" or "shrink" throughout the talk; I'll try to be consistent about it. Please keep that in mind—that I may use these terms interchangeably.

Finally, some sort of backtransformation is applied so that the data can be used in the scale in which they were collected in order to make meaningful comparisons and meaningful descriptions.

Objectives

- Provide background information on dietary supplement use in the U.S. using the National Health and Nutrition Examination Survey (NHANES)

- Identify key challenges and considerations in combining dietary and supplement intake data

- Explain statistical approaches to estimating total nutrient intakes

- Describe assumptions and caveats of current techniques of estimating total nutrient intakes

So, with that background in mind, I would like to discuss the objectives for my talk today. First, I would like to provide some background information on supplement use in the United States using the National Health and Nutrition Examination Survey, or NHANES. We will then move on to identify some of the key challenges and considerations in combining dietary and supplement intake data. Then, we will explain statistical approaches for estimating total nutrient intake and, finally, describe some assumptions and caveats of the current techniques for estimating total usual intake as well.
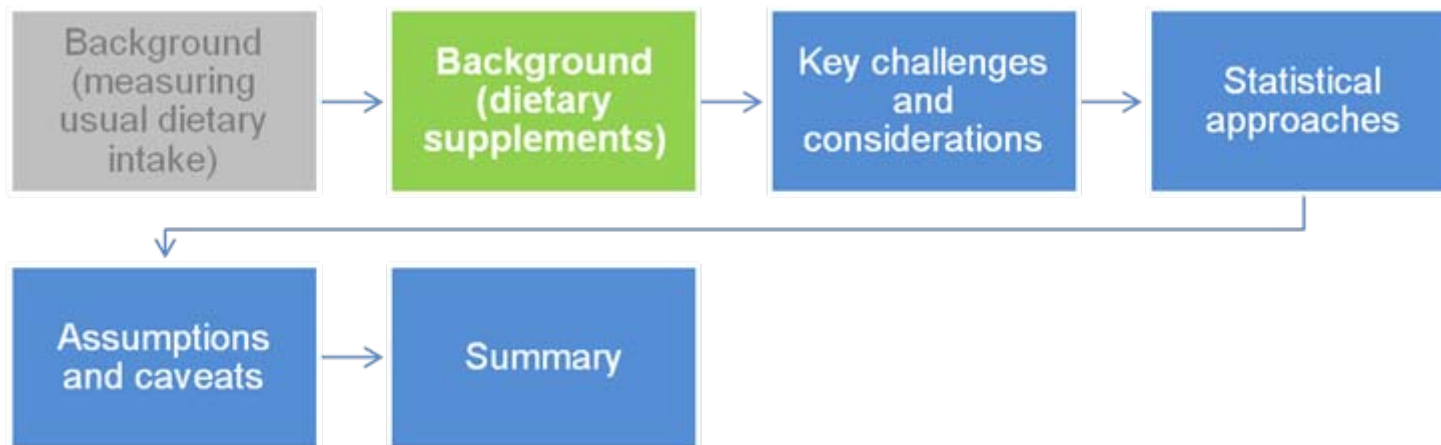
BACKGROUND: DIETARY SUPPLEMENTS

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Before we go down that road, let's talk about the background of dietary supplements.

Use of any dietary supplement

Source: NHANES, 2003-2006

Bailey et al. Journal of Nutrition, 2011; 141: 261-266
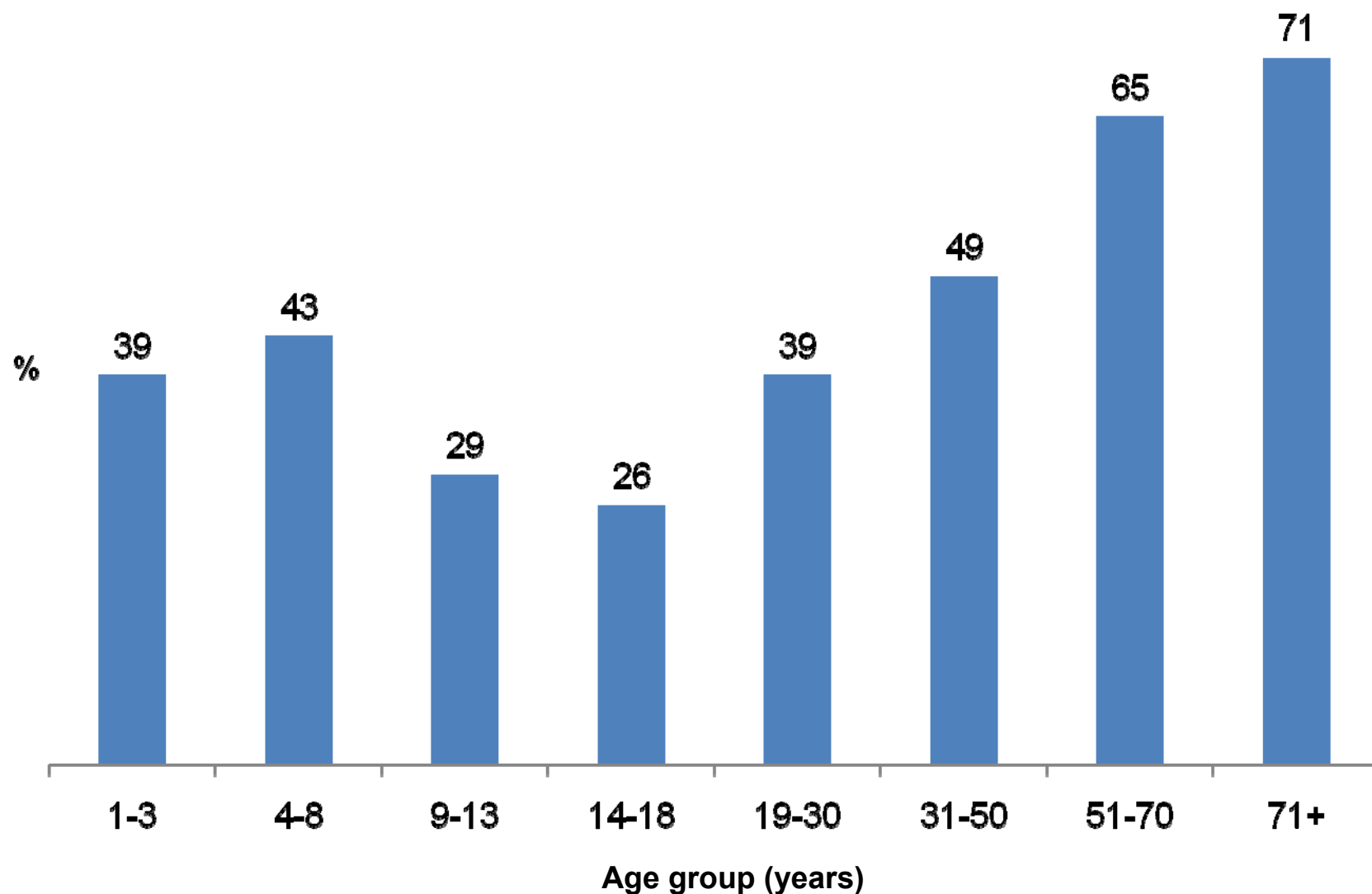
In this graph, I have the age groups of U.S. citizens along the x-axis, and this is the percent of people who report [using] any dietary supplements. As you can see, in the younger age group, 1-8, we have about 40 percent of the population reporting use. It dips slightly in use in adolescence, and through adult years tends to increase.

Use of multivitamin/multimineral supplements

Source: NHANES, 2003-2006

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Estimating total usual nutrient intake distributions from diet and supplements
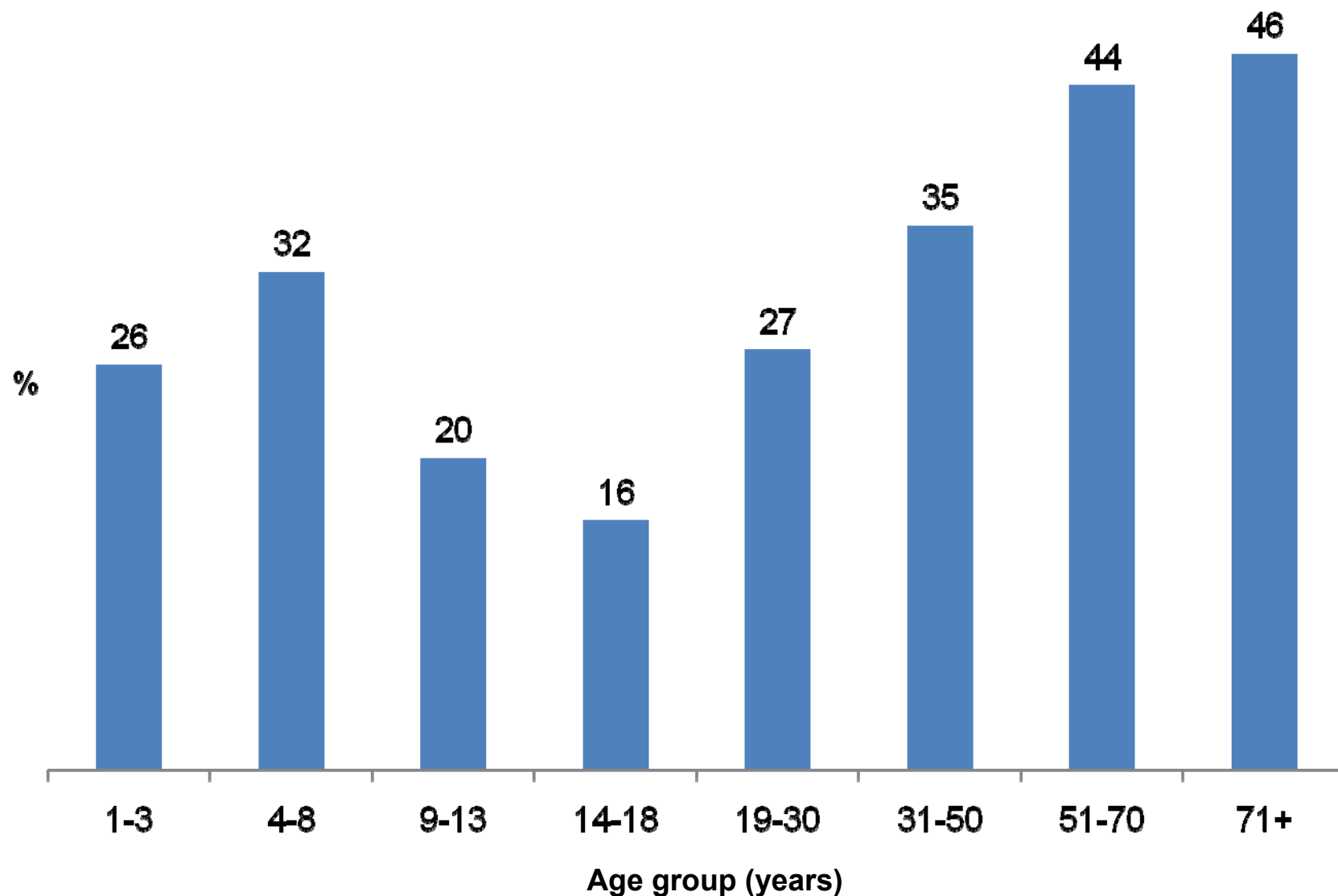
By and large, the most commonly consumed dietary supplement is a multivitamin/multimineral, and the prevalence of use of this type of supple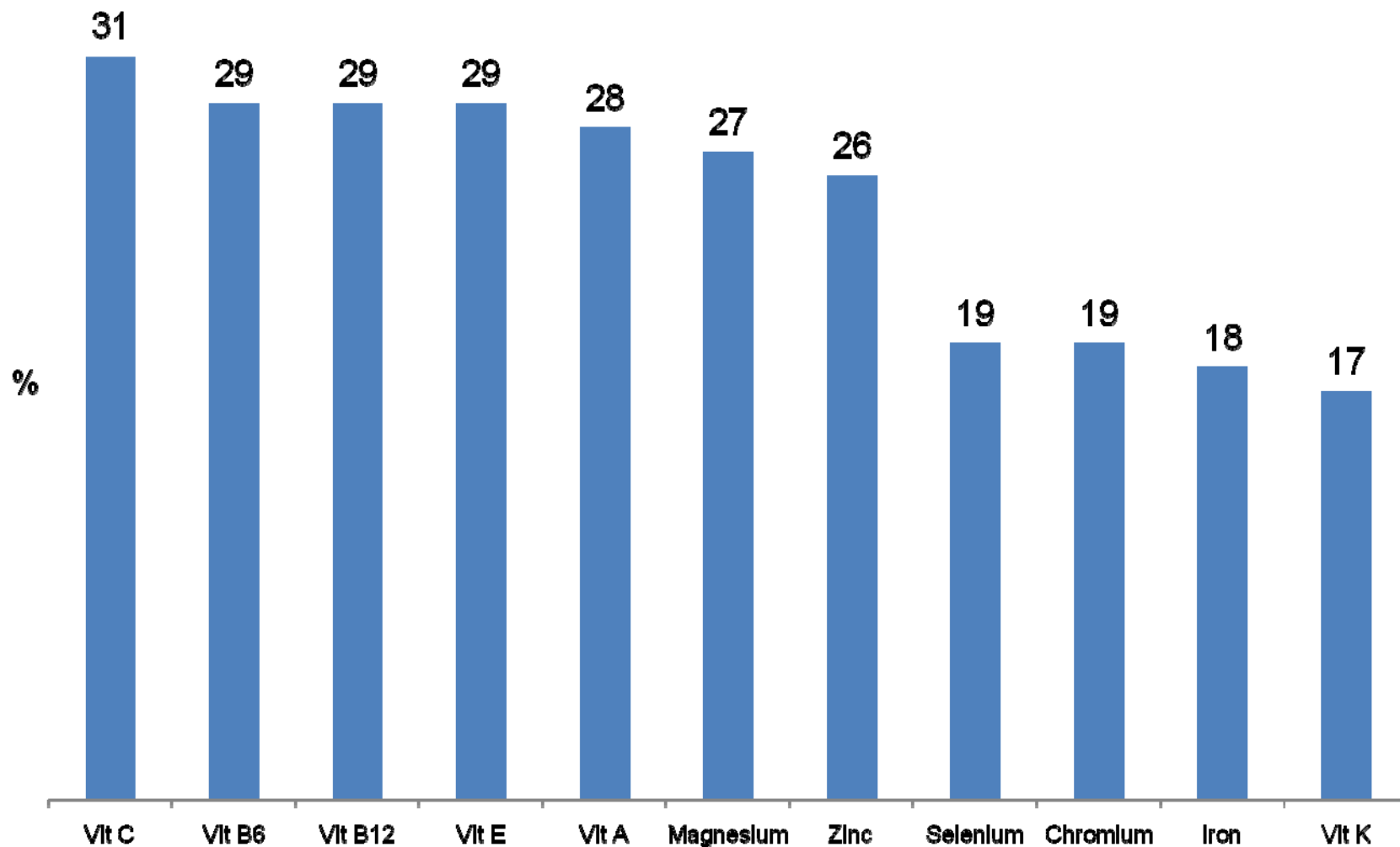ment follows that of any type of supplement—that use is about a third to 40 percent in younger groups, dips down, and then increases throughout adulthood.

Use of vitamins and minerals (adults)

Source: NHANES, 2003-2006

Bailey et al. Journal of Nutrition, 2011; 141: 261-266

Along the x-axis, here, we have the specific vitamins and minerals. This is just to give you an estimate of some of the prevalences—if this is a nutrient of interest, whether or not you may want to consider examining this. So we see about 30 percent of people in the U.S. take some sort of supplement with vitamin C, B6, B12, and vitamin E, and then it decreases with some of your minerals, and vitamin K coming in at 17 percent.

Number of supplements reported by users (adults)

Source: NHANES, 2003-2006

Bailey et al. Journal of Nutrition, 2011; 141: 261-266

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In this graph, I switched the x-axis on you again, in that along the bottom is the actual number of dietary supplements that people are reporting. So we see that about half of people report taking one supplement, but that means the other half take more than one supplement. And you will see as we go through some of the examples that this poses challenges, with about 10 percent of adults reporting that they take five or more different types of dietary supplements.

Use of supplements by BMI (adults)

Source: NHANES, 2003-2006

Bailey et al. Journal of Nutrition, 2011; 141: 261-266

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Estimating total usual nutrient intake distributions from diet and supplements
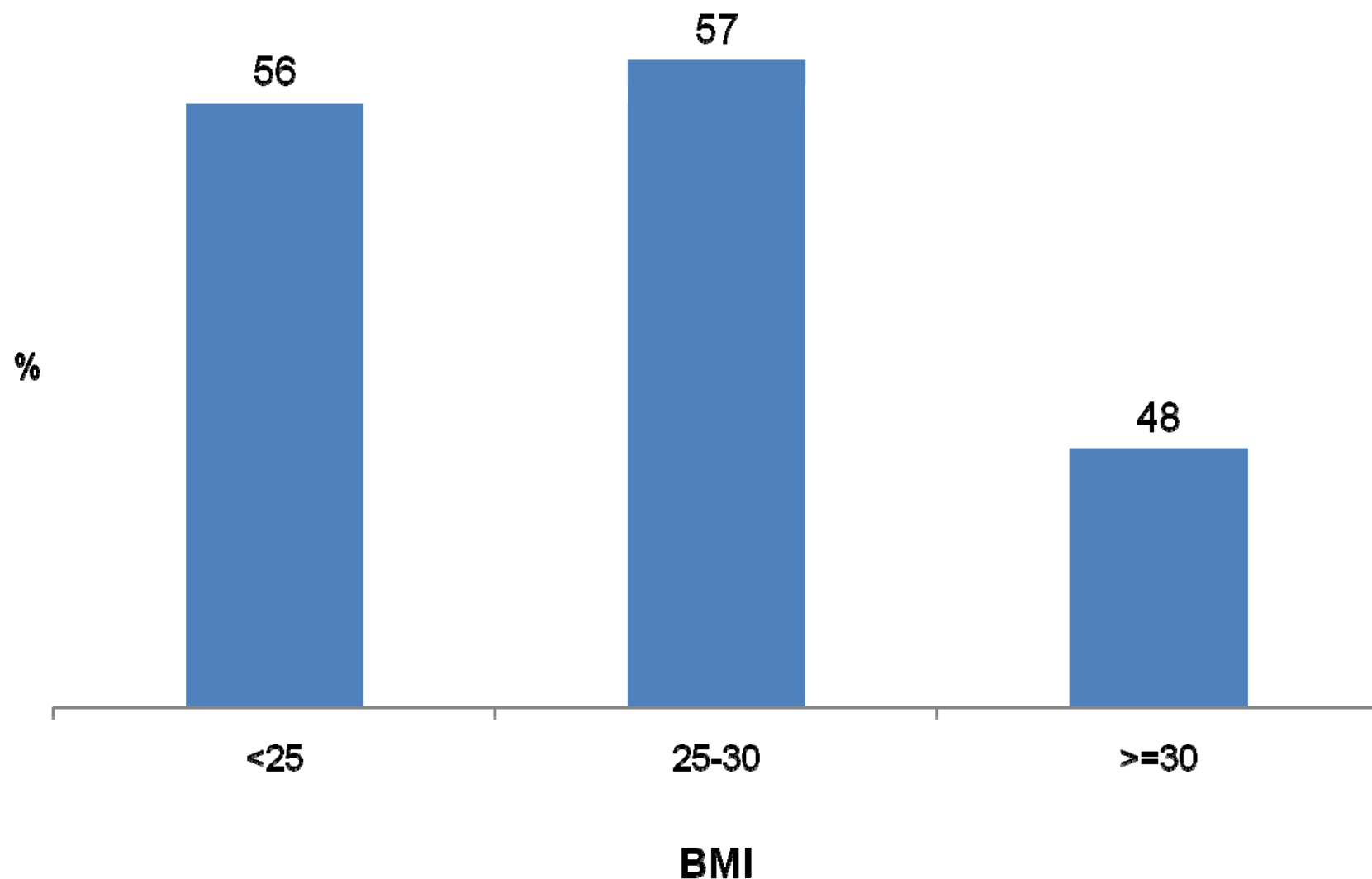
Slide 21

Just a little bit of background on some of the characteristics of supplement users: We know that they tend to be leaner in that those who are not obese tend to report more supplement use than those who are obese.

Use of supplements by education (adults)

Source: NHANES, 2003-2006

Bailey et al. Journal of Nutrition, 2011; 141: 261-266
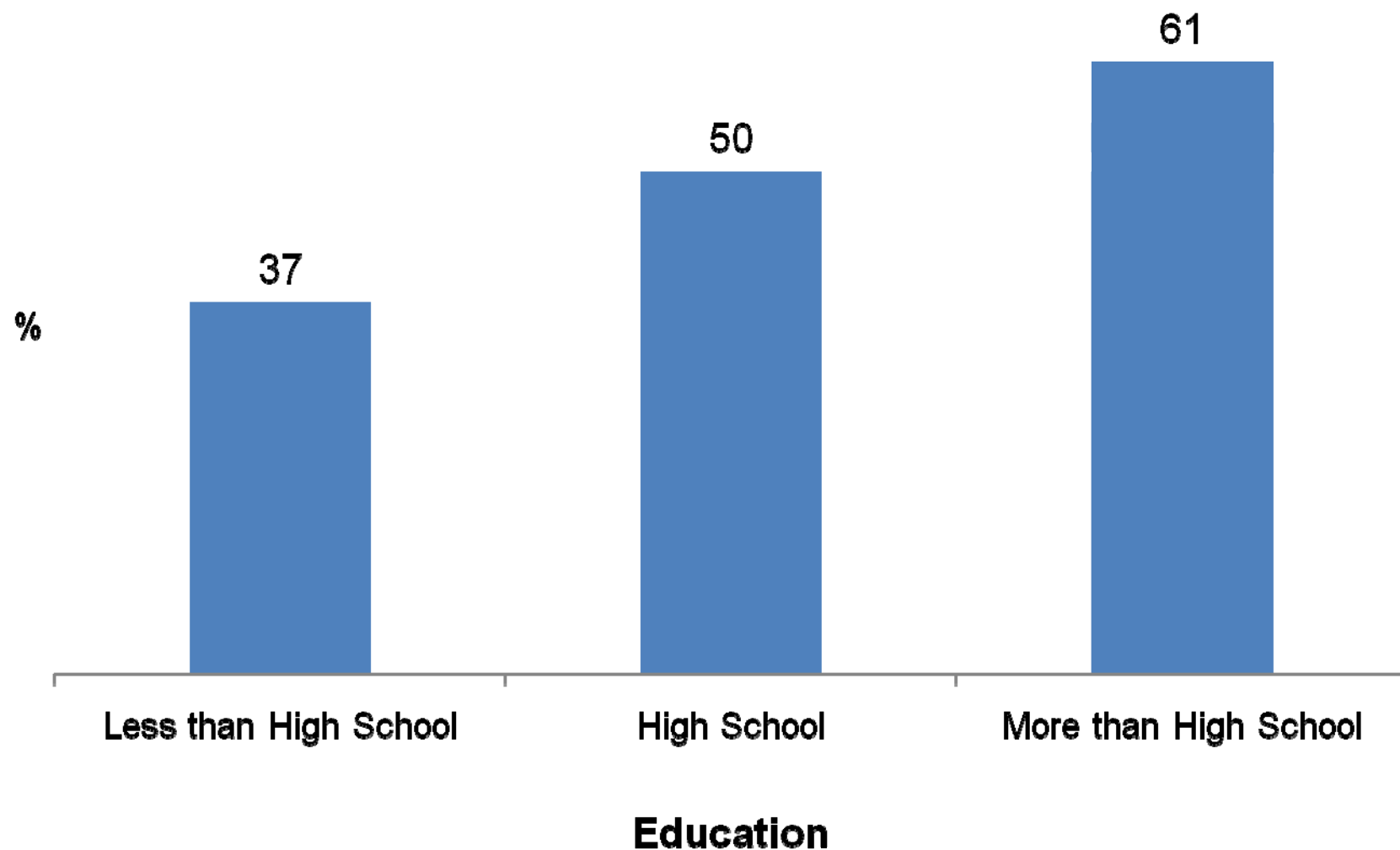
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Supplement use is also related to education in that those with higher educational attainment tend to use supplements more frequently than those who have a lower educational attainment.

Use of supplements over time, by gender (adults)

Source: NHANES III (1988-1994), NHANES (2003-2006)
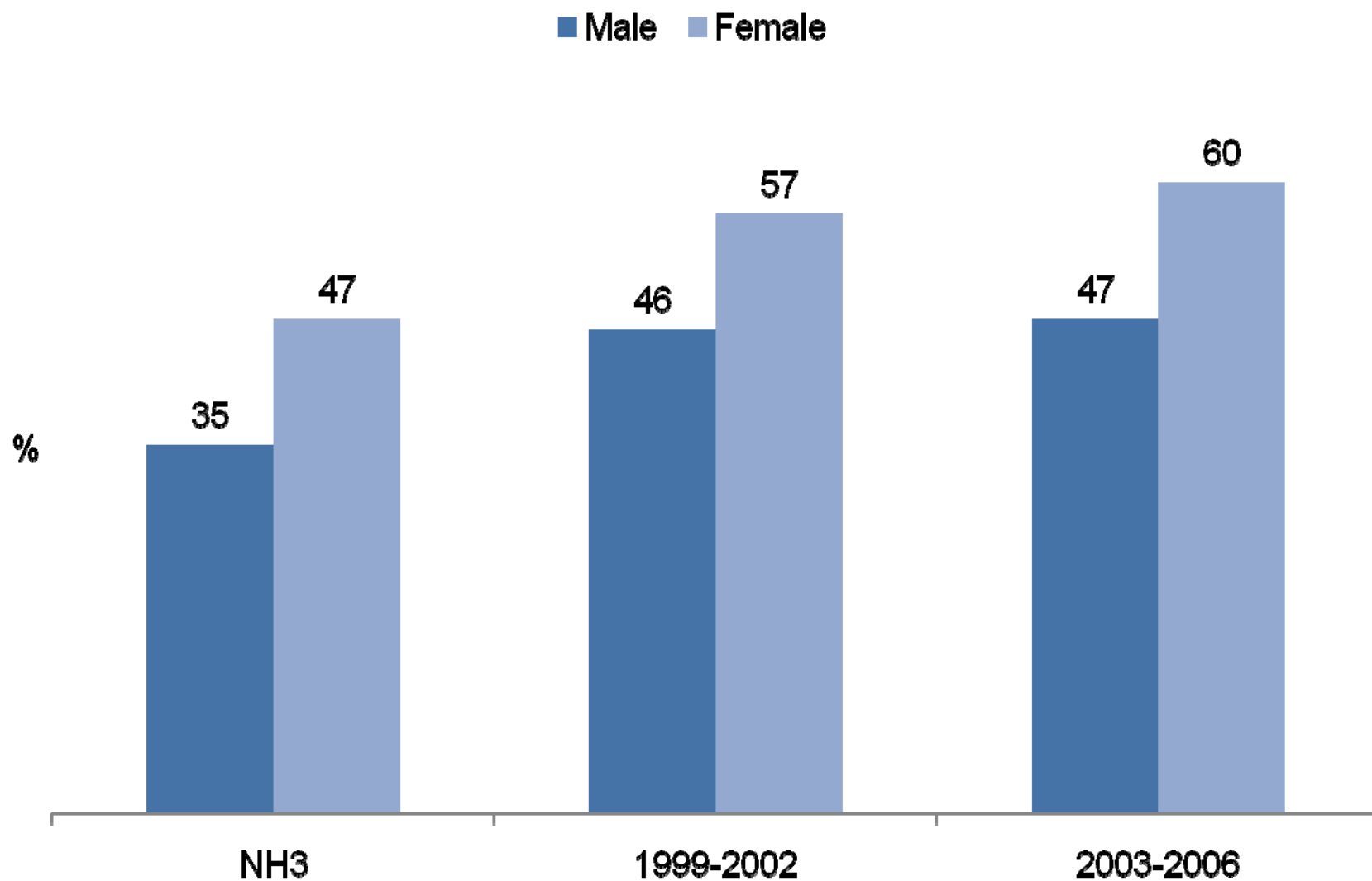
I wanted to show you some of these time trends, some of these trends over time, in that they are consistent. In the first panel, we see NH3; that means NHANES3, and that was collected in 1988 through 1994. And then you'll see the other years from NHANES across the bottom. So one clear trend we see across time is that females tend to use dietary supplements more than males do.

Use of supplements over time, by age (adults)

Source: NHANES III (1988-1994), NHANES (2003-2006)

Legend: ■ 20-39 ■ 40-59 ■ 60+

Data:
- NH3: 37, 43, 47
- 1999-2002: 42, 55, 64
- 2003-2006: 41, 55, 70

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Estimating total usual nutrient intake distributions from diet and supplements
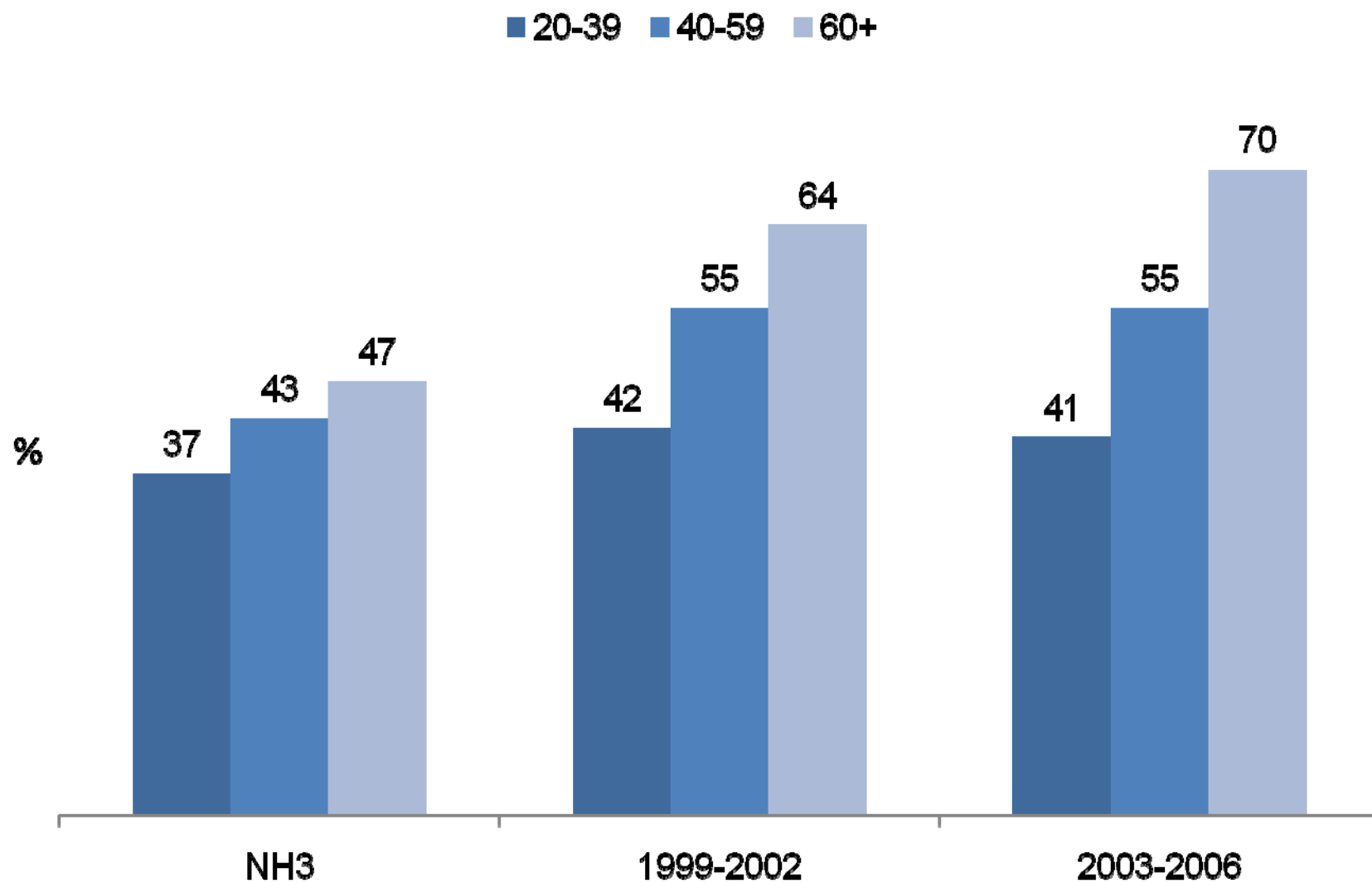
Slide 24

The x-axis is the same here, looking at trends across time with age. As we saw in the first slide, we know that supplement use is tied to age and that those who are older tend to use more dietary supplements.

Use of supplements over time, by race/ethnicity (adults)

Source: NHANES III (1988-1994), NHANES (2003-2006)

Legend: ■ Non-Hispanic White ■ Non-Hispanic Black ■ Mexican-American

Year	Non-Hispanic White	Non-Hispanic Black	Mexican-American
NH3	44	33	29
1999-2002	58	34	32
2003-2006	60	36	34

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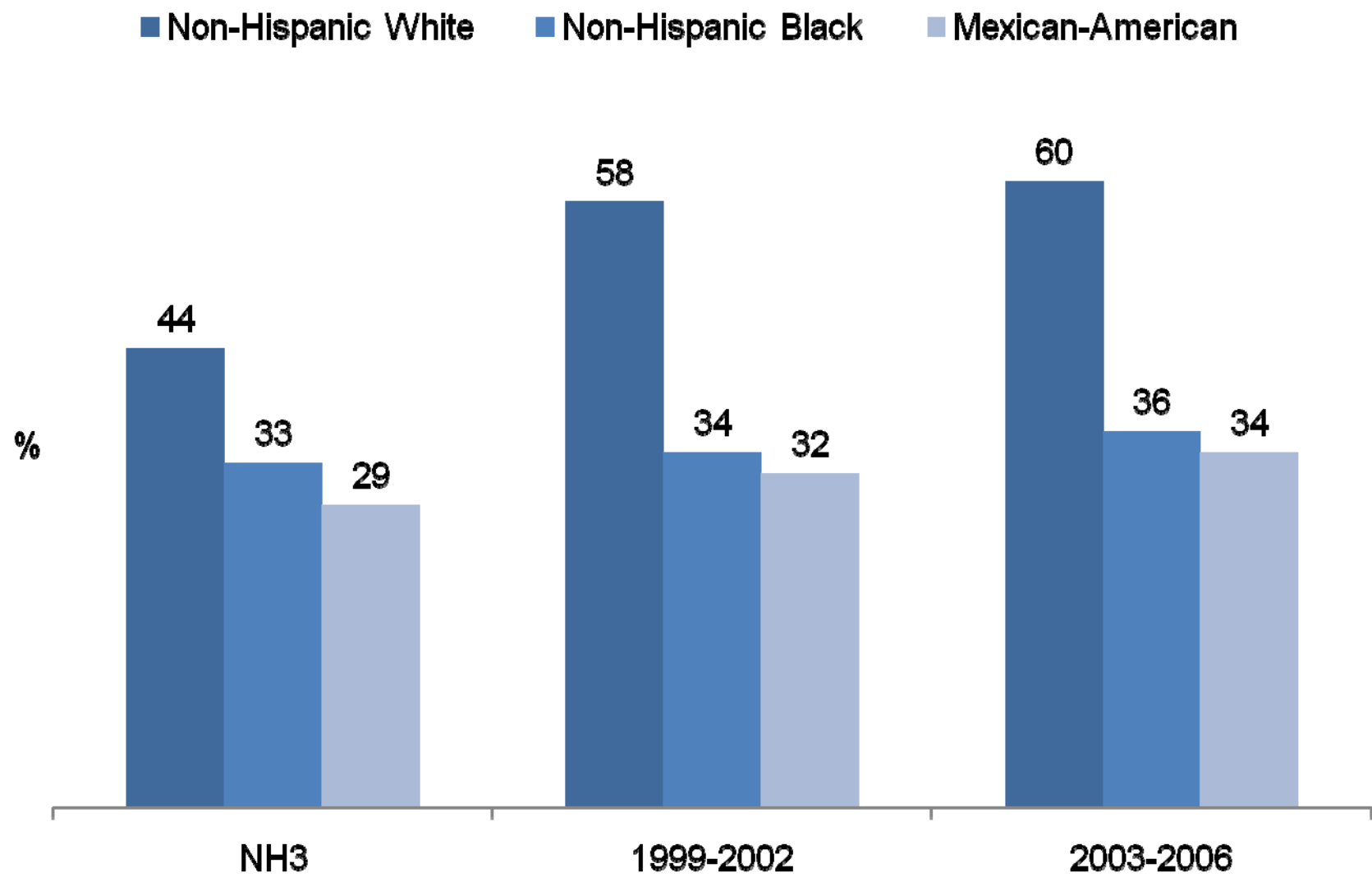
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Finally, looking at use of supplements by race and ethnicity, we know that non-Hispanic whites are much more likely to report use of dietary supplements than [are] African or Mexican Americans.

Implications of supplement use

- More than half of adults (19+ years) in the U.S. use dietary supplements

- Estimated 35% of children (1 -13 years) report use of supplements

- The contribution that dietary supplements make to nutrient intakes cannot be ignored!

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So to summarize what I've presented thus far, we know that more than half of adults and about a third of children report use of supplements, and it is my opinion that the contribution that dietary supplements make toward nutrient intake cannot be ignored.

Special considerations with dietary supplements

- For some nutrients, portion of intake from supplements may be large (e.g., vitamin D)

- Some supplements have large doses of nutrients

- Adequacy and excess are underestimated if only food sources are considered

  – Adequacy typically assessed using the Estimated Average Requirement (EAR)

- Some Tolerable Upper Intake Levels (ULs) defined only for supplement-derived nutrient intake (e.g., magnesium, folic acid)

There are some special considerations with dietary supplements. For some nutrients, the proportion of intake from supplements may be quite large. The example I have here is vitamin D. Very few reliable food sources provide vitamin D, with the exception of milk, but people could get a large amount of vitamin D from supplements.

Comparing that to my next example, where I say some supplements have large doses of nutrients—someone may be getting a large amount of a nutrient from their diet and a large amount of nutrients from their supplements, compared to vitamin D, where you don't get a lot from food but may get a lot from a supplement.

If you don't think about dietary supplements and incorporate them in your estimates, you are underestimating adequacy and excess. And at this point I would like to introduce two terms that are in the glossary for the webinar series that I'll be using today. The first is the "estimated average requirement," or "EAR." This is the lower end of the distribution that we use as a cutpoint to determine nutrient adequacy, and the other end of the distribution, the "tolerable upper intake levels," are typically used to define intakes that are excessive. For some supplements, the UL is defined exclusively from supplement-derived nutrient intake; for example, magnesium. One cannot exceed the UL for magnesium in the diet, only from supplemental magnesium.

I have folic acid here as an example, and I'm going to walk you through an example of that later in the talk, so we'll move on.

Total nutrient intake

- Food

- Beverages (including water)

- Fortified foods

- Dietary supplements

- Some medications

  – Both prescription and over-the-counter

When I use the term total nutrient intake, I mean nutrients from everywhere, and some are very intuitive; obviously, foods and beverages, including water. About 5 percent of calcium intake in the United States comes from tap water, so this isn't necessarily someone trying to increase his/her calcium intake. It's just a function of consuming water. So while there are intuitive [sources], there are also other things that aren't as intuitive: fortified foods, both mandatory fortified foods, like folic acid, but there's also voluntary fortification, and super foods [are] being introduced into the market. Obviously, [there are] dietary supplements, what we're talking about today, and also some medications. You may not think about it, but some prescription medications and over-the-counter medications contain nutrients. If you don't assess nutrients from all of these sources, you are not accurately characterizing total nutrient intake.

Usual total nutrient intakes

- Limited research exists contribution of dietary supplements to total nutrient intakes

- Perception that handling supplement data is challenging

Total nutrient intake is different than usual nutrient intake. Usual total nutrient intakes are the long-term average intakes from all of these sources. So not only do you have the problem of getting total intake from all of these sources; we also want to make it usual, or reflective of habitual and long-term intake. Limited research exists on the contributions dietary supplements make toward total usual nutrient intake. And that may or may not be because there is this perception that handling dietary supplement data is challenging.

KEY CHALLENGES AND CONSIDERATIONS

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That moves us on to our next section. While it is challenging, I don't want to discourage you from using dietary supplement information because, as we'll be able to see today, there are many strategies that we can use.

Most common ways to assess supplements

- Frequency questionnaire

  – Supplements have the potential to be episodically consumed

  – Length of use may be important

  – Supplement use is aggregated

  – Used most often

- 24-hour recall (24HR)

  – Administered with food recall

  – Emerging

So how are dietary supplements assessed? Very much in the same way that we assess foods, you have two options—short-term and long-term measurement. Longer-term measurement, i.e., a frequency questionnaire—this is important in the context of supplements because, as I mentioned, they have the potential to be episodically consumed. Another bonus of using a frequency questionnaire is that you may be interested in the length of time someone is using a supplement and relating that to some sort of outcome.

Supplement use is often aggregated, and as I mentioned, if people are taking multiple supplements, when you use a frequency questionnaire you typically get the results as one line item. So someone may take five different supplements that contain calcium and when your data are analyzed and handed to you, you have one estimate of average calcium intake. And this is the most often used approach to assessing dietary supplements. However, supplements can be assessed using 24 hour recalls, typically administered when you're using 24 hour recalls for food.

Most common ways to assess supplements

- Frequency questionnaire

  – Supplements have the potential to be episodically consumed

  – Length of use may be important

  – Supplement use is aggregated

  – Used most often

- 24-hour recall (24HR)

  – Administered with food recall

  – Emerging

- Want average daily exposure: ideally can be obtained using both sources of information

And this is an emerging method of collection because, ideally, what we want is usual total exposure. So you can get information from both of these types of sources that are integral to your estimates.

Error structure in reporting dietary supplements

So what do we know about the error structure in reporting of dietary supplements? Unfortunately, we know very little. There is no doubly labeled water technique to which we can compare like we can for food records for energy and protein. There are just not a lot of good ways to assess the error structure. That's something that we're working on currently.

Implications of measurement

- Both 24HR and frequency methods are subject to different types of measurement error

- Data may be collected over two different periods of time

- Nutrient estimates from the two instruments may not be directly comparable, and simply adding them together may not be a satisfactory approach

We talked a little bit about the implications of your measurement tool. As we discussed earlier in the series and earlier today, both 24 hour recalls and frequency methods are subject to different types of measurement error. Specific to supplements, as well as food, data may be collected over two different time periods, so you have the last 30 days for a supplement, but the last day or 2 days for a 24 hour recall. So you have two different time periods, and simply adding up those two different time periods and those two different estimates may not be the most satisfactory approach.

Challenges and considerations with supplements

- Reports accepted as "truth"

- Altered distributions of intake

- Moving targets = reformulations

- Default values in databases and reports

- No single comprehensive database

- Bioavailability

- Analytical vs. labeled values

As I mentioned, this is a working assumption that we go through in these models that we're using with supplements—that the report from supplements on the questionnaire and the 24 hour recall—we are forced with this working assumption to accept this as truth because we have no other way to validate it at this point.

Challenges and considerations with supplements

- Reports accepted as "truth"

- **Altered distributions of intake**

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- Analytical vs. labeled values

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Estimating total usual nutrient intake distributions from diet and supplements

A key challenge with supplements, and I would say the chief problem with working with supplements, is this altered distribution of intake. And let me talk about what that means.
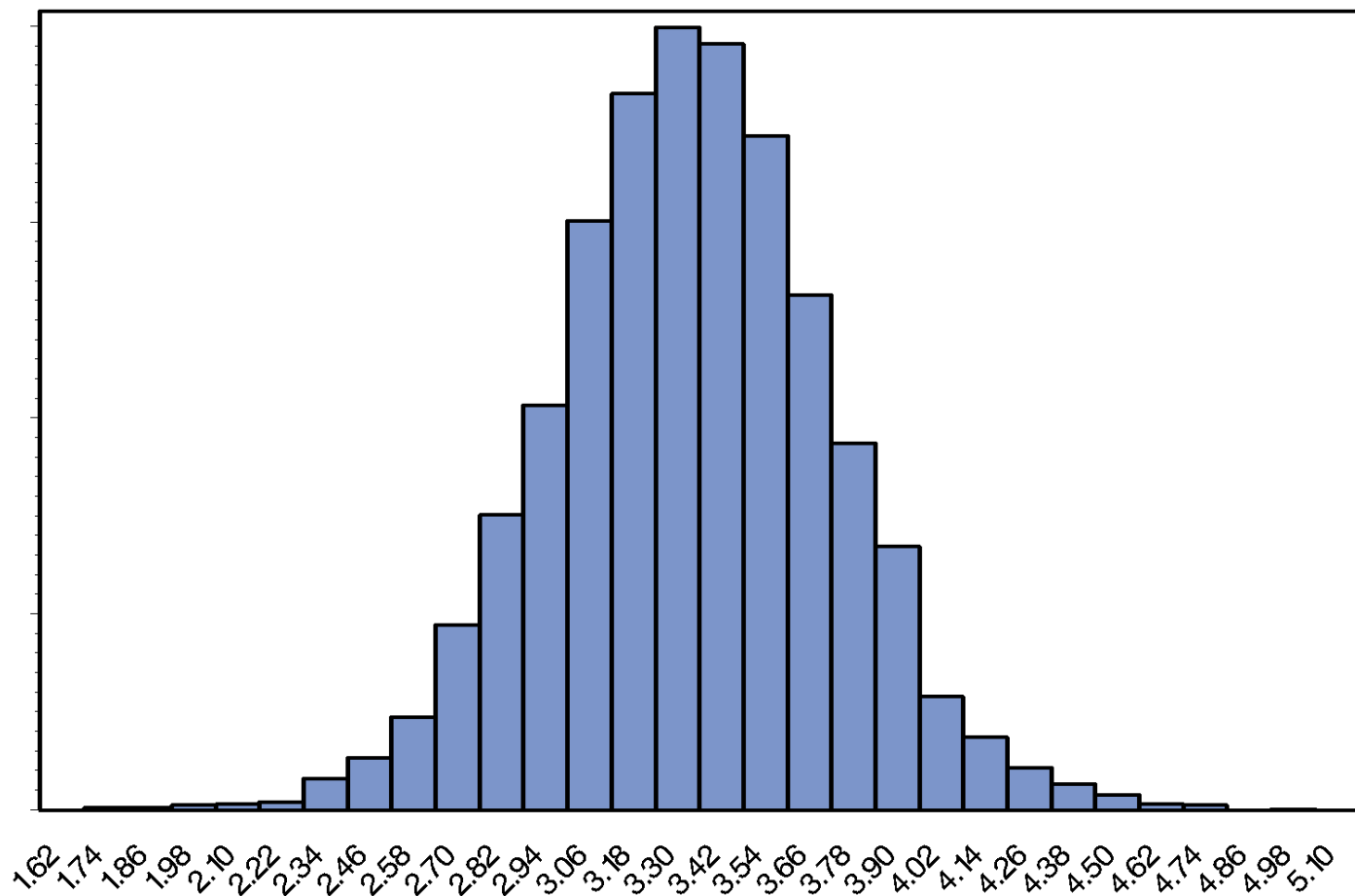
Nutrient from food sources = often skewed
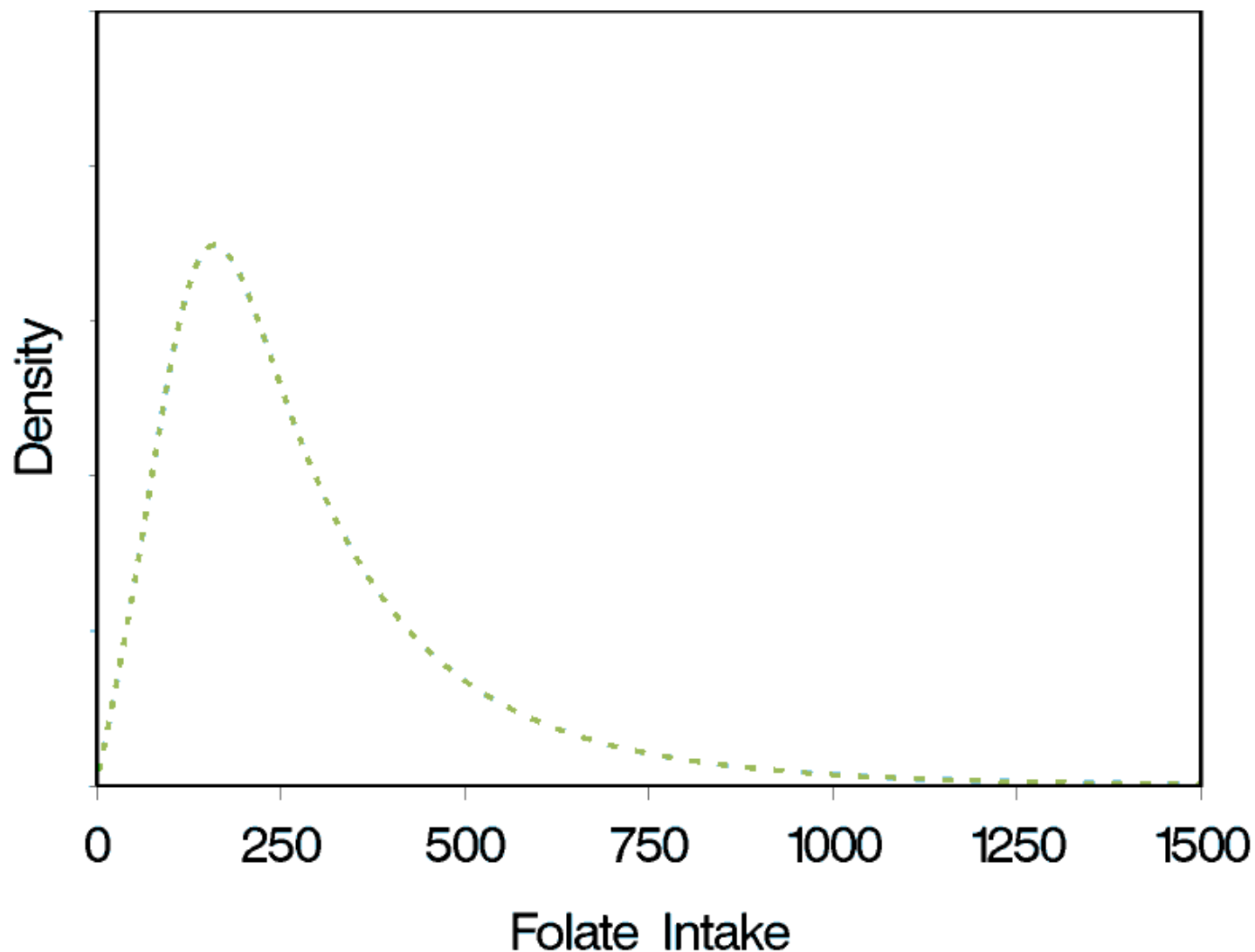
As we discussed previously, the nutrient intake distribution from food sources is often skewed, with some people consuming large amounts. Dietary supplements only compounds this.

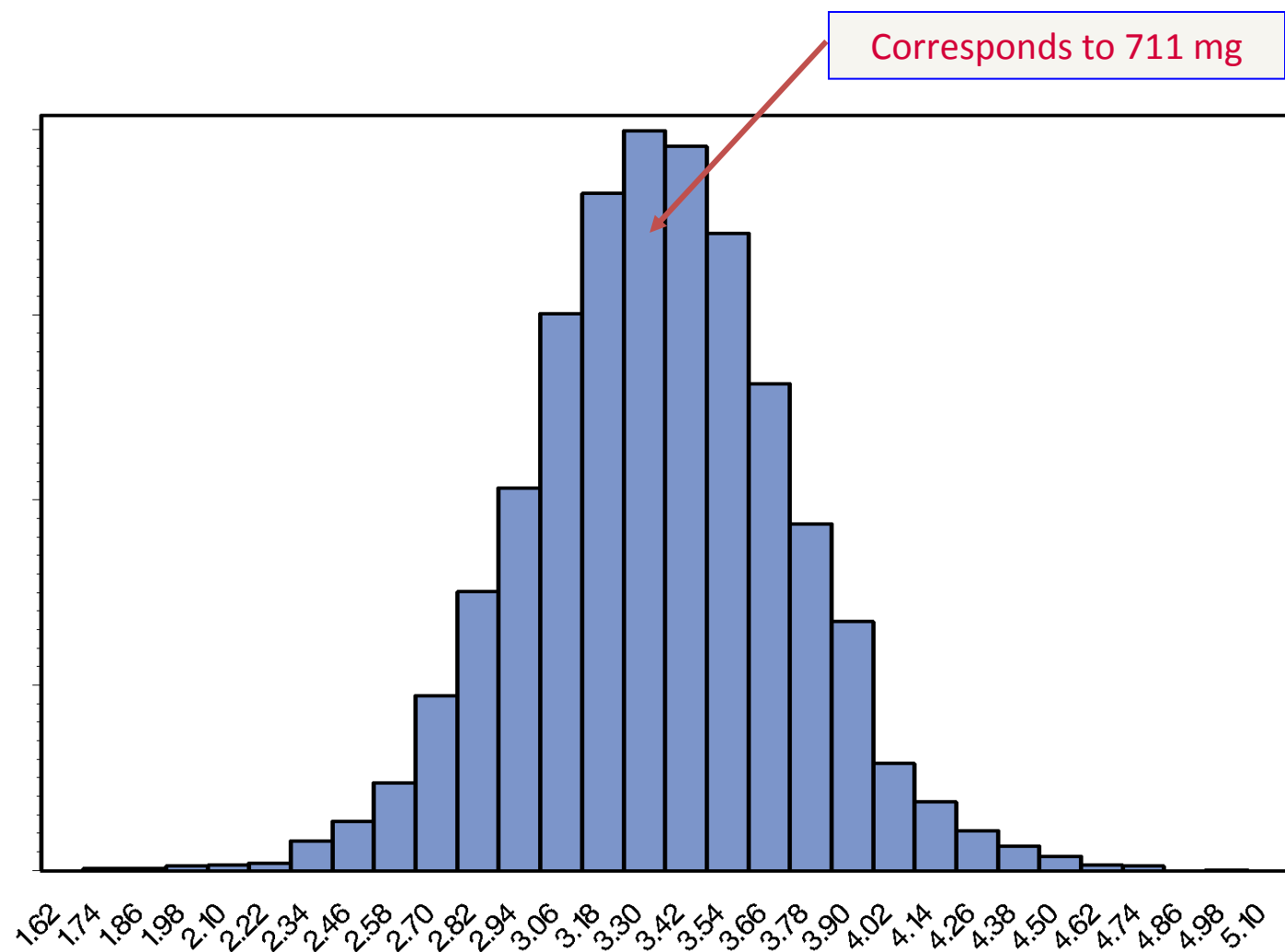# Nutrient from food sources = easy to transform

Transformed single-day calcium intake from food sources

In this example, though, we see that a skewed distribution—for example, [for] calcium—can easily be transformed to approximate normality.

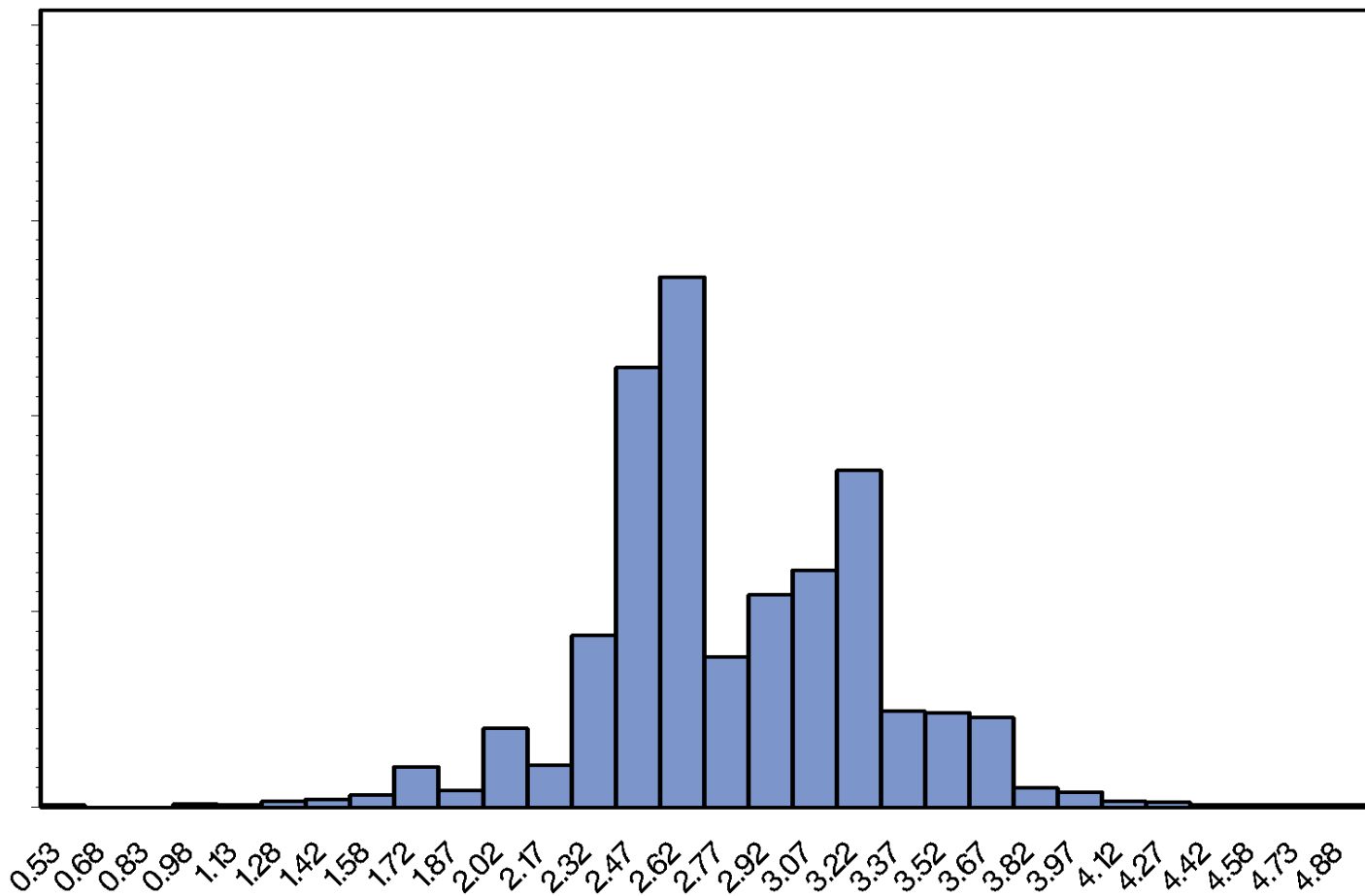# Nutrient from food sources = easy to transform

Corresponds to 711 mg

Transformed single-day calcium intake from food sources

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As you can see, the rank order is preserved, with most people consuming around 700 mg in this distribution.
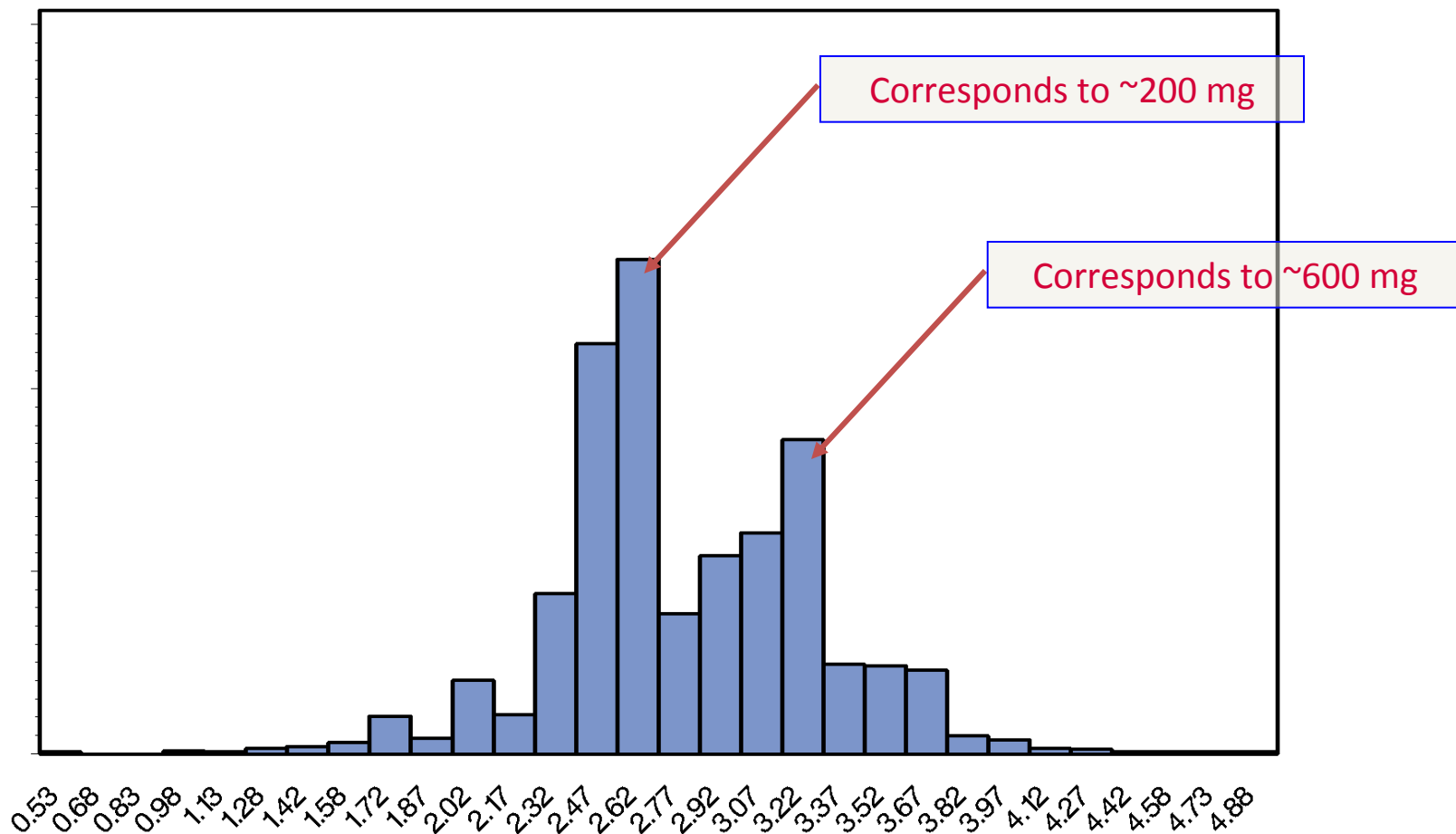
Nutrient from supplements ≠ easy to transform

Transformed calcium dosage from dietary supplements

Slide 40

However, nutrient intakes from supplements are not as easy to transform as [those from] foods.

Nutrient from supplements ≠ easy to transform

Corresponds to ~200 mg

Corresponds to ~600 mg

Transformed calcium dosage from dietary supplements

Slide 41

And these are the calcium [intakes] from supplements in this example. And we see two peaks here: one corresponding to about 200 mg and one corresponding to about 600 mg. This makes sense if you think about it. I said earlier that the most commonly reported dietary supplement is a multivitamin/multimineral. So those types of supplements frequently provide between 150 and 200 mg of calcium, so that's that first peak we're seeing. The second peak we're seeing is people who are using calcium-specific supplements. That could be calcium alone or calcium and vitamin D. These are typically bone health types of supplements.

So in this distribution, you see that we have what we'll refer to as spikes.

Nutrient from supplements ≠ easy to transform
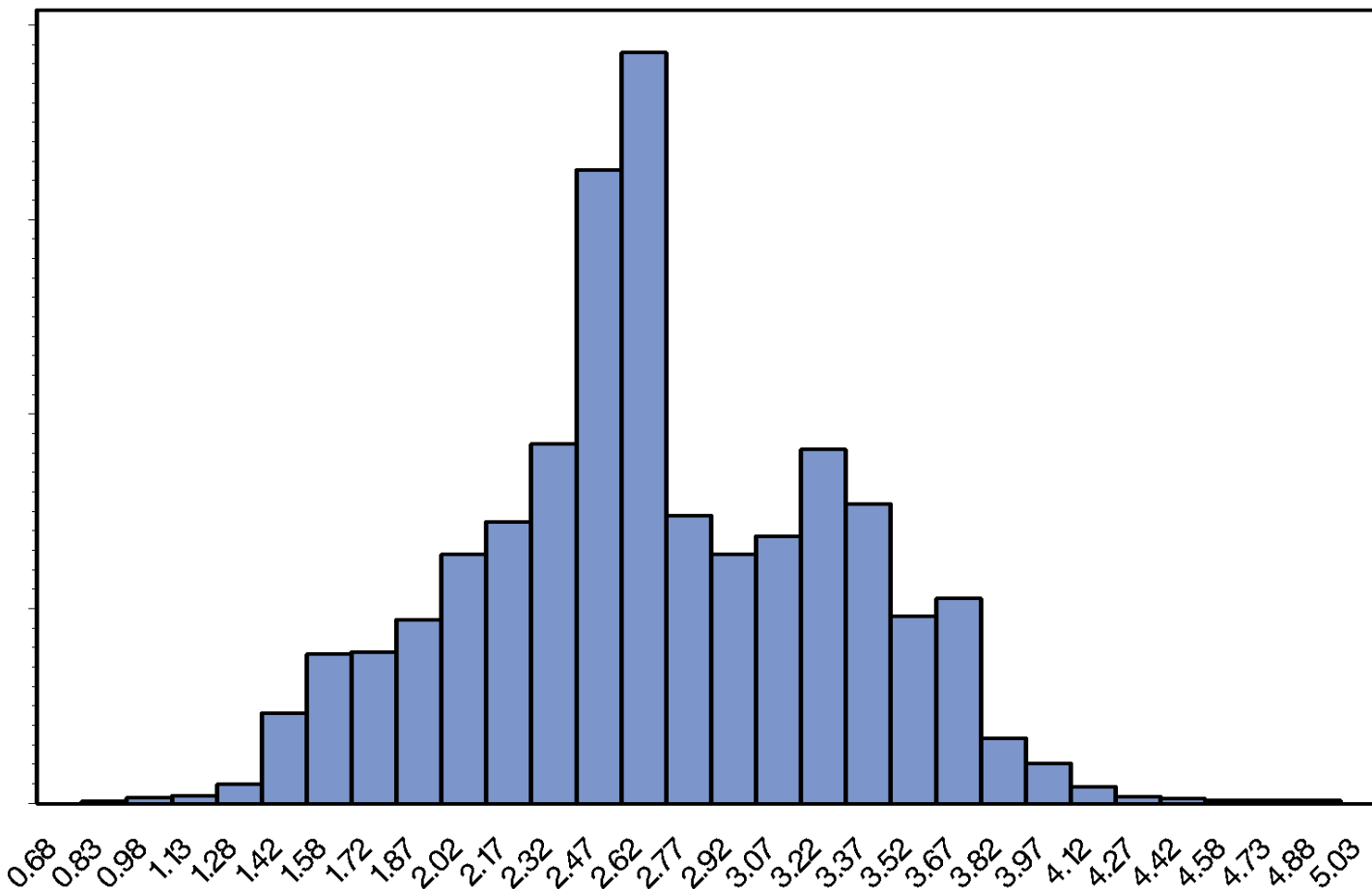
Transformed estimated usual intake of calcium from dietary supplements

This is a transformed estimated usual intake of calcium from those dietary supplements. Even with the transformation, you can see that this is not a nice, normal distribution as we would hope. In fact, it's pretty ugly, and that will help; that is something to remember as we go through these modeling exercises.

Complications of skewed distributions

- - - - Single-day intake
- · - · - 2-day mean intake
———— Usual intake

Long right tail

Density

Folate Intake
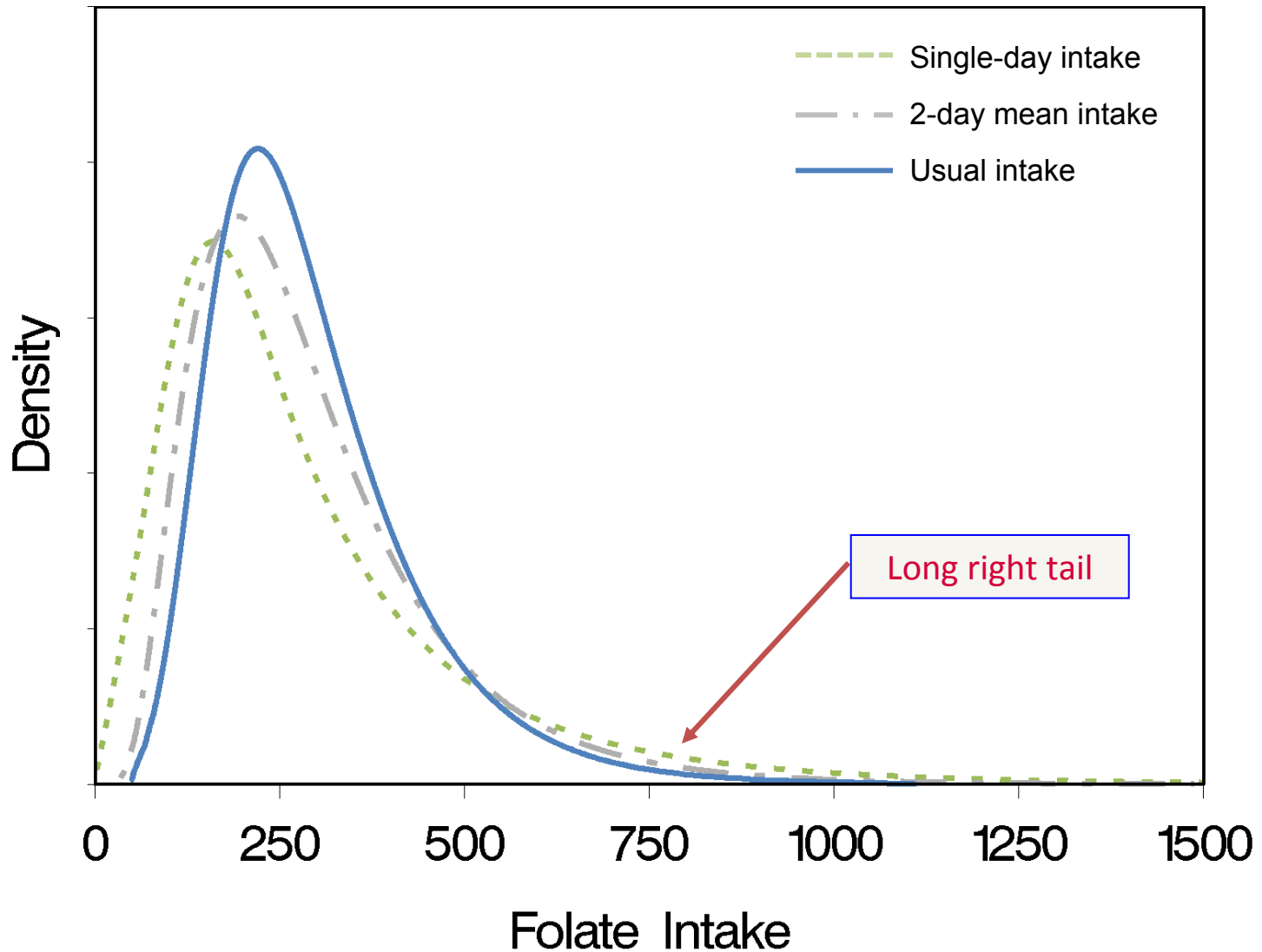
So, as I mentioned, the food intake distributions can be skewed, and we can only imagine what dietary supplements can do because these can add pharmacological doses of nutrients to people's intakes. So that tail can just keep right on going, because supplements have that potential.

# Total nutrient intake distributions

- Distributions from foods are not so spiked

  – Everyone eats, not everyone uses supplements

- Supplements can severely alter nutrient intake distributions

  – Spikes and skews

- Depending on how supplement data are collected, affects between- and within-person variation

So let's talk about why. The distributions from foods are not so spiked because everybody eats. Everybody is getting some form of calcium in this example that we're using, but not everybody is using dietary supplements. So supplements severely alter that distribution. If you have a lot of people who don't use supplements, you have a big spike at zero because they're not getting any nutrients from there. And then the skew can be because people are consuming megadoses of calcium. So this multimodal distribution is something that needs to be considered as we go through these modeling exercises.

Finally, [the way] supplement data are collected can affect the within- and between-person variability.

Between- and within-person variation
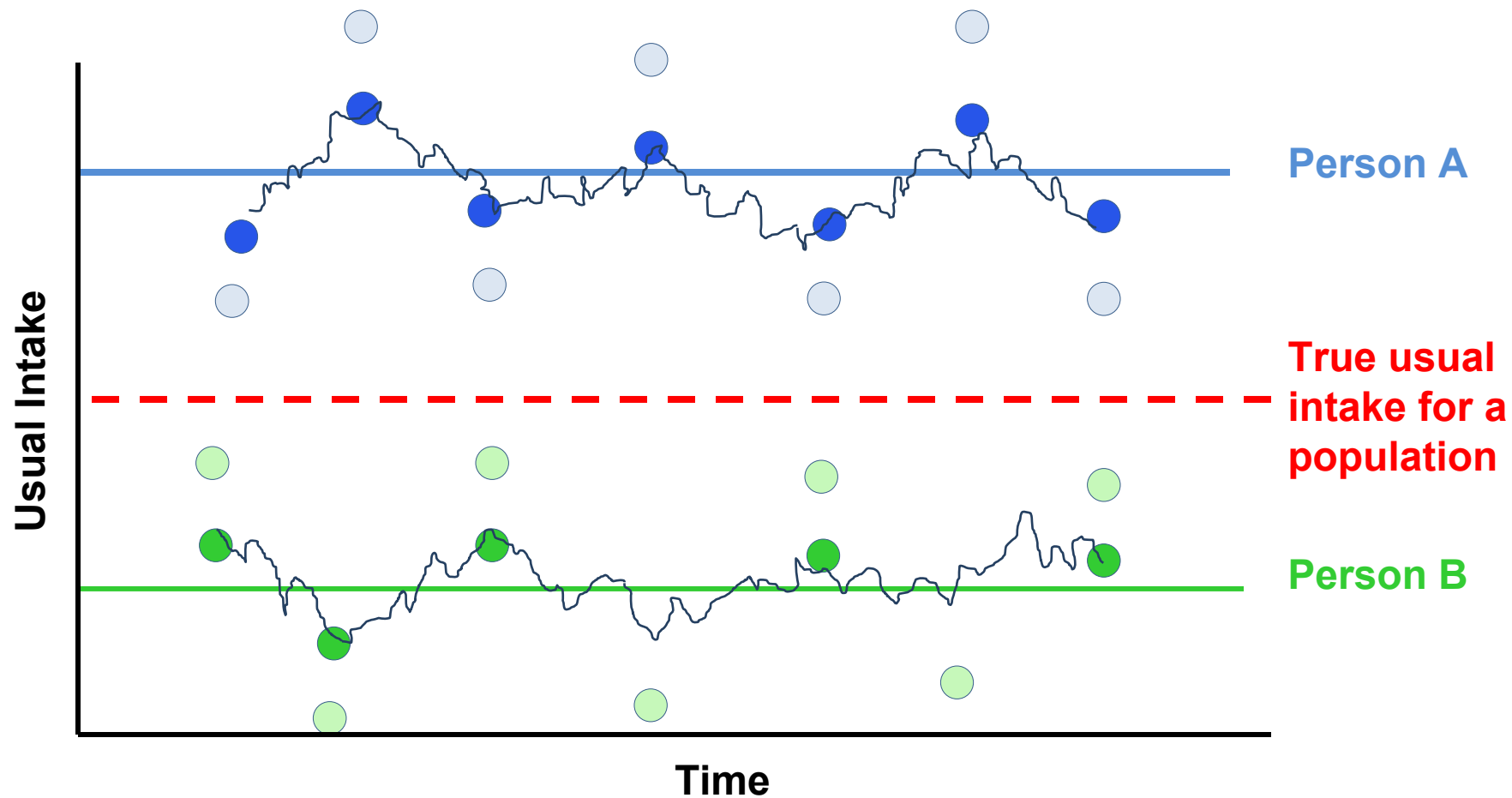
Slide 45

And let's talk about that. Remember that variation around person A's intake is within-person variability, and the difference between [the intakes of] person A and person B is the between-person variability. So if your supplement information is collected in the way you typically would [collect it] with the questionnaire, you calculate an average daily exposure, and you add that to the nutrient estimates from food. So you are adding a constant to each of your recall days. And that doesn't do anything to within-person variation. But what that does do is that increases the between-person variation—the difference [in intake] between person A and person B. And from a biological perspective, that's true. Person A has [a] higher intake than person B. But from a modeling perspective, that creates a wrench in our model that must be considered. If you're measuring supplement [intake] with a 24 hour recall, you can—you have the potential to increase both within- and between-person components of variation in your model.

Challenges and considerations with dietary supplements

- Reports accepted as "truth"

- Altered distributions of intake

- Moving targets = reformulations

- Default values in databases and reports

- No single comprehensive database

- Bioavailability

- Analytical vs. labeled values

Okay, so next I'd like to talk about these remaining challenges and considerations, and we'll go through these very briefly because these are things that we can't necessarily fix with our model. Supplements are moving targets. FDA estimates that there are 50,000 dietary supplements on the market today, and they admit that that is a conservative estimate. They also estimate 1,000 new products being added to the market each month. That is in addition to products that are already existing [or] being reformulated. So I have this listed as moving targets because you have to keep current with your databases in order to make sure that you have the right supplements that people are reporting to make your estimates most reflective of what's actually being consumed.

And that ties in with the next point about default values. If someone says they take a multivitamin but they don't know the manufacturer [and] they don't know the specific type, they are typically assigned a default value for the most commonly consumed multivitamin or multimineral in this example. So, say your research question is: What is the effect of lutein on some type of cancer? If that person is using a multivitamin/multimineral with lutein, and that is replaced in the database with the basic multivitamin that doesn't contain lutein, you're really introducing a bias there. And there is no one single comprehensive database for dietary supplements. There is work ongoing at the USDA in the Office of Dietary Supplements to help fix this problem, but as we are today, there is no one correct database to use.

I just want to talk very briefly about bioavailability. I often get this question, and people will say, "I take a supplement. Well, how much am I getting?" We can't be concerned with bioavailability because we just don't know right now, and that's beyond the scope of this webinar. What we're trying to do is model the intake. What you have to consider from your biological perspective is what bioavailability—and we won't be talking about that today.

Finally, we have this last point about analytical versus labeled levels.

Mean % difference from label for 18 nutrients in adult MVMM

Percent Difference from Label
(Error Bars represent SEM)
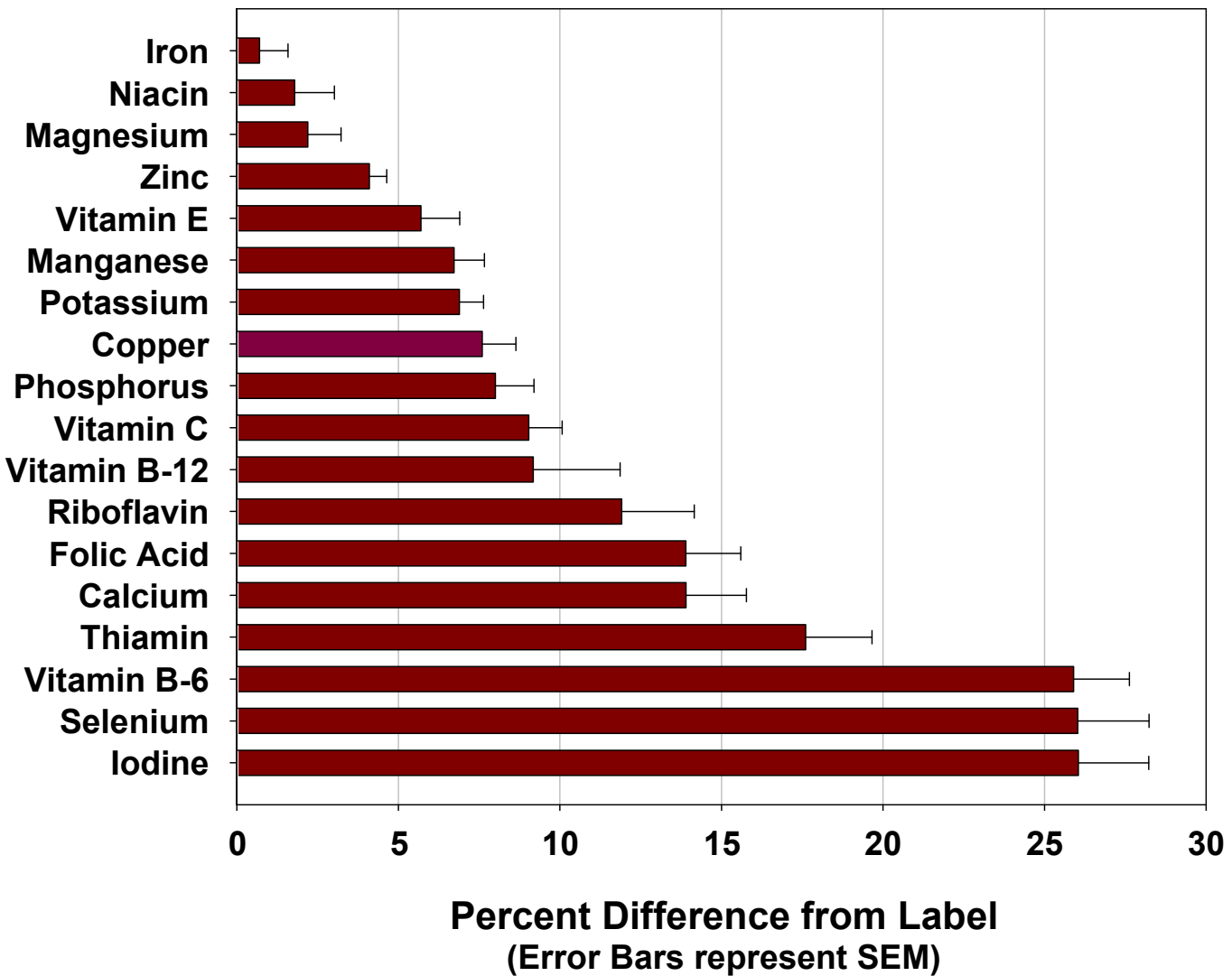
Slide 47

Moving on to this slide, this is the percent deviation between what is on the label and what is actually in the bottle, determined by chemical analysis. So we can see that for some supplements, what's on the bottle is very close to what's on the label; for example, for iron. But for vitamin B6, selenium, and iodine, there's upwards of 25 percent more in the bottle than is on the label. And I have a link on the bottom left of this slide if you want more information about this project, and they actually have a calculator that you can use for research purposes if you want to incorporate these estimates into your total usual nutrient intake estimates.

STATISTICAL APPROACHES

Slide 48

Okay, so let's move on to our statistical approaches.

Reminder

- The choice of methods of analysis should be based on your research question

  – Do you want the mean of the group?

  – Do you want the prevalence below or above a cut-point?

  – Do you want to describe the entire population?

  – Do you want to describe users and non-users of supplements?

[I'd like to] remind everyone before we go down this road that whatever method you choose should be based on your research question. And this sounds so simplistic but it's so important. You really need to know what you want, what information you want from dietary supplements, before you choose your model. Do you want the mean of the group? Do you want the tail of the distribution, the prevalence above or below a certain cutpoint? Do you want to describe your entire population, or do you choose to describe people as users and nonusers.
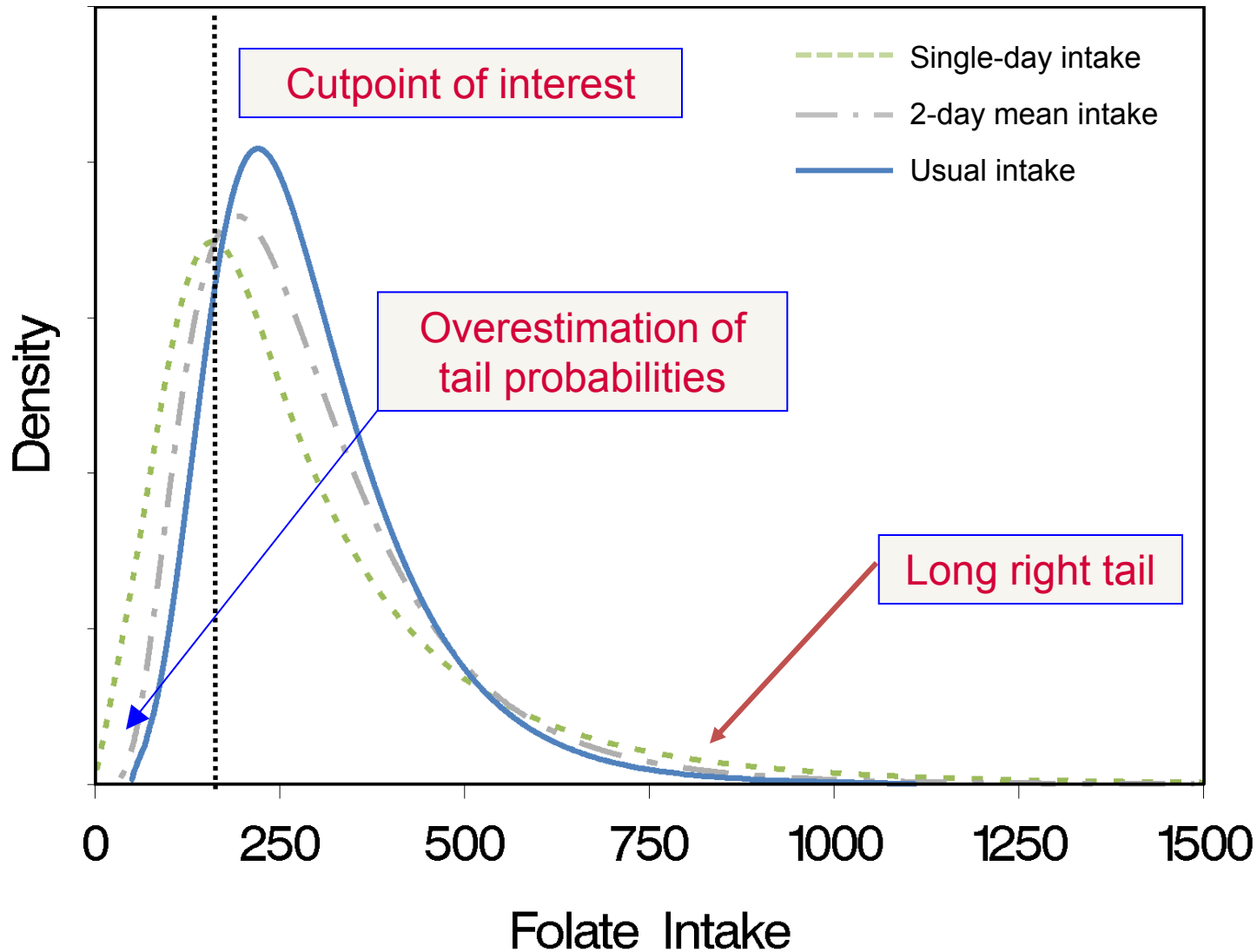
How do we combine supplements and foods?

- Basic

  - Simply add nutrient intakes from food and dietary supplements

  - This strategy works if you want to describe the mean

  - Can be used with frequency questionnaire or 24HR

  - **<u>Cannot</u>** be used to assess the population distribution (i.e., <EAR or >UL)

So how do we combine supplements and food? I'm going to be talking about two approaches today. The first is what I'm calling a basic approach—simply adding nutrient intakes from food and nutrient intakes from supplements. And this strategy works if you want to just describe the mean of your population. It can be used with a frequency questionnaire or with 24 hour recall data; however, it can't be used if you want to assess the population distribution.

Within-individual variability in 24HR

Cutpoint of interest

Overestimation of tail probabilities

Long right tail

Single-day intake

2-day mean intake

Usual intake

Density

0   250   500   750   1000   1250   1500

Folate Intake

You'll remember from the previous webinar series that without adjustment or shrinking, we have overestimation of the tail probability, so we would lead to incorrect inferences about the proportion above or below a certain cutpoint unless we apply an adjustment procedure.

How do we combine supplements and foods?

- Adjusted

  – Estimate distribution of usual intake by removing within-person variation using statistical modeling

    • Can incorporate covariates

      – Allows different means for subpopulations, while pooling information about variance components

  – **<u>Can</u>** be used to assess the population distribution

Slide 52

That brings us to our second choice, adjusted. So what I'm talking about here—I'll say adjust or shrink—we estimate the distribution of usual intake by removing the within-person variability component using modeling. Remember, I placed the slide up with all the different types of models that are currently available. The model that I will be discussing today is the NCI method because it has the advantage of incorporating covariates. Covariates allow for different means of subpopulations while pooling information about the variance components. And Dr. Kevin Dodd talked about the importance of covariates in his webinar, which was the last webinar. And if you're interested in that, you can go to the URL and listen to that.

When do you add supplements?

■ Before or after you adjust?
  – Before
    • Add the nutrient intakes from dietary supplements and then apply an adjustment procedure

      – "Add, then shrink"

  – After
    • Adjust the dietary nutrient intakes with an adjustment procedure and then add the nutrient intakes from supplements
      – "Shrink, then add"

Slide 53[1]

So, when do you add supplements? And before we talk about this, of all the times in my life to make a typo, I made one here. So if you are sleeping, wake up, because I have these labeled incorrectly. So when do you add supplements—before you adjust the nutrient distributions? We will refer to this as "add, then shrink." Or do you add them after, so you adjust the dietary nutrient intake and then you add supplements? That is called "shrink, then add."

So if you have the slides from yesterday, this will be incorrect in your slides, and please just make a little arrow to turn those around.

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[1] The original slide contained a typographical error and has since been corrected. Adding supplements before adjusting nutrient distributions is referred to as the "add, then shrink" method, while adding them after adjusting is referred to the "shrink, then add" method.

When do you add supplements?

■ **Before you adjust***

- – Users and non-users have same mean total intake

- – Ignores a measured covariate

  - • Potential bias

- – Multi-modal distribution

*Possible to do with users and non-users separately

So if you add supplements before you adjust, you assume that users and nonusers have the same mean total intake. And this may be flawed because it ignores a measured covariate, which can, as we discussed earlier—has the potential to introduce a bias. As we also discussed, remember that multimodal distribution. There is no good transformation that can make that spike and skew look like a nice, normal curve. I have a little asterisk here because it is possible to use this strategy if you're going to look at users and nonusers separately. And in the recommended readings for today's webinar, there is a lovely paper by Didier Garriguet that explains how to do this. [In the interest of] time today, this is one of the methods that we won't be describing because he does such a great job of describing that technique in that paper.

When do you add supplements?

- **After you adjust**

  - Users and non-users have different mean from foods and for total

  - Less complicated transformations

If you add supplements after you adjust the nutrient intake distribution from foods, you allow users and nonusers to have different means. And as we discussed earlier, this allows for less-complicated transformations.

Using NHANES to calculate usual total nutrient intake

- Calcium Example: NHANES 2007-2008

  - Food and beverages

    - Two 24HR

  - Dietary supplements

    - 30-day frequency questionnaire (DSQ)

    - Two 24HR

  - Some medications

    - Antacids
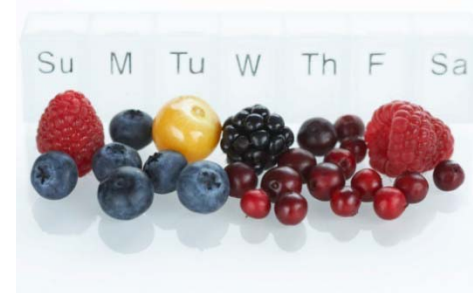
So I'm going to show you an example right now using data from the National Health and Nutrition Examination Survey in the years 2007 and 2008. This is the first time that NHANES had collected dietary information with both a 24 hour recall and a dietary supplement questionnaire. So we'll be looking at how to use the data if you have both types of data. And we're also including medications from antacids because they are an important source of calcium.

Analysis strategy: calcium

- Basic

- Adjusted – NCI method

  – Add then adjust (Add, then shrink)

  – Adjust then add (Shrink, then add)

    • Covariates

      – Day of the week

      – Sequence of 24HR

   – Supplement user – from questionnaire (DSQ)

      – Amount of calcium from the 24HR

So we're going to go through this example using the 2007-2008 data, and we're going to look at the data if we simply add them up—the basic approach—or if we adjust. And by adjusting, I mean shrinking. And we're going to use this with the NCI method. And within this method you can have two choices. You can add, then adjust—remember, as we described, add, then shrink. Or you can adjust, then add, which we refer to as shrink, then add.

The covariates we used in the shrink, then add model are the day of the week, the sequence of a 24 hour recall, whether or not someone is a supplement user based on the frequency questionnaire, and the amount from the 24 hour recall.

Agreement between methods: % use
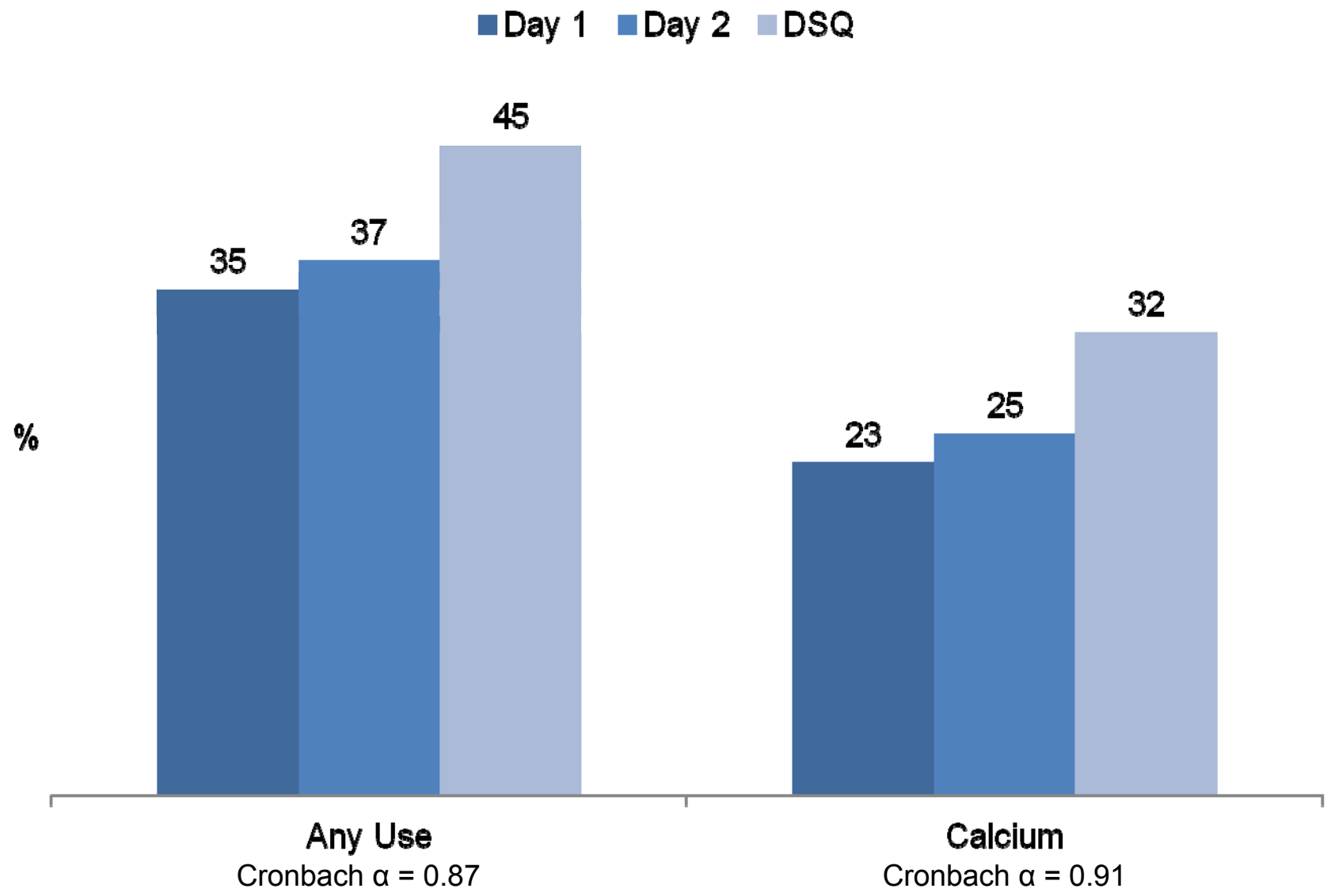
Slide 58

So in this slide, I show you the agreement between these methods. And this makes sense. In the darkest panel we have day 1 of the 24 hour recall; the lighter blue panel is day 2; and the lightest blue [panel] is from the dietary supplement questionnaire. And it makes sense that we have a higher prevalence of use from the questionnaire because someone can report using a supplement over the last 30 days. So as we said, it's important to use questionnaire information for the frequency of use for those episodic consumers, and this difference could be reflected in them.

The second prevalence estimates I'm showing [are] for calcium, so 23 percent were users on the first day; 25 percent, on the second day, and 32 percent, from the frequency questionnaire.

Agreement: calcium amount (mg) from supplements
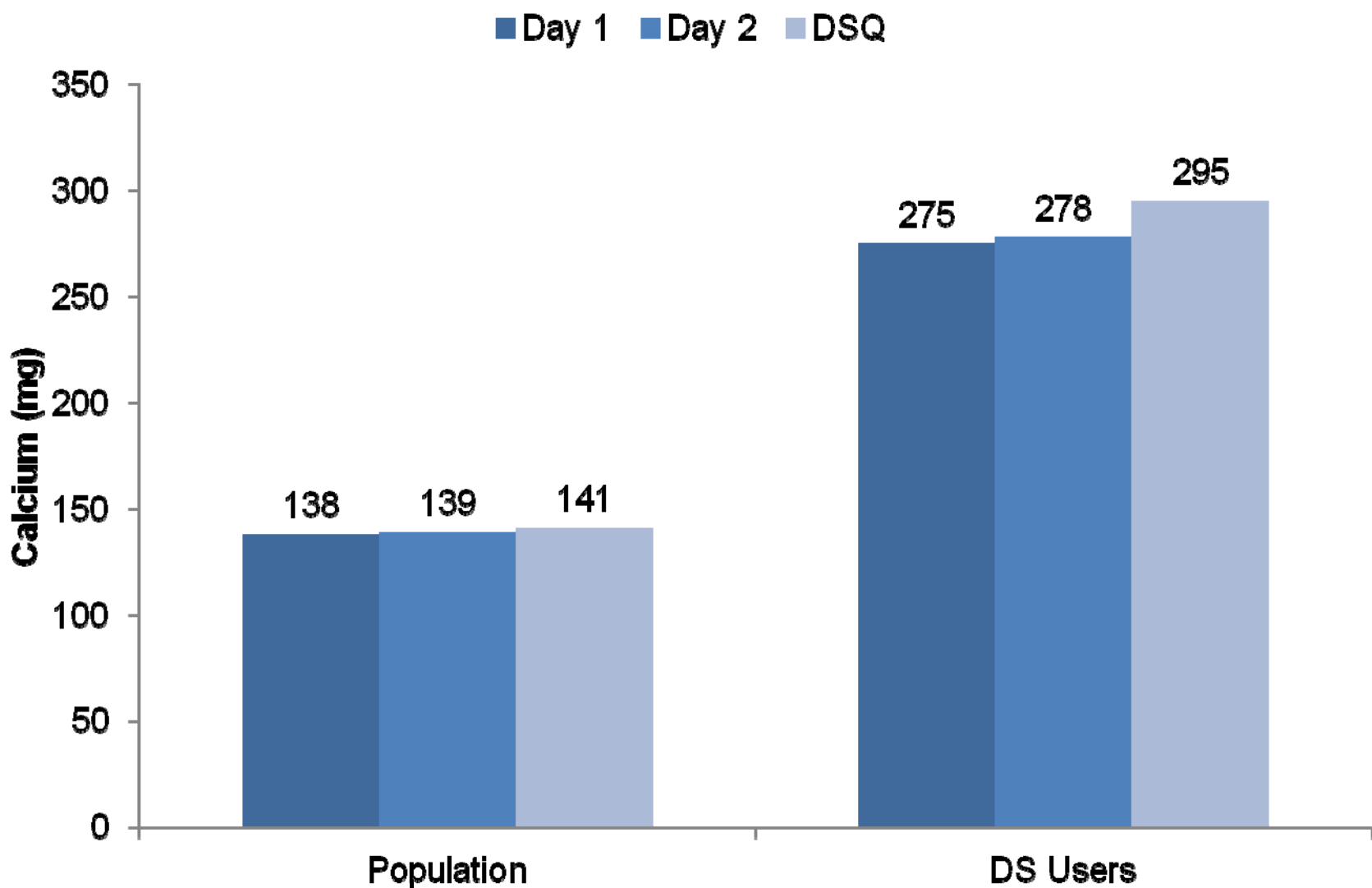
This is the mean amount of calcium from supplements. Again, going back to that research question, do you want to know what is the average amount of calcium that is used by the U.S. population? We see that the [intakes] are strikingly similar, whether it's measured from a recall or the questionnaire, at about 140 mg. However, if you want to know the mean calcium amount from users, we see that that's about 275 to 300 mg per day.

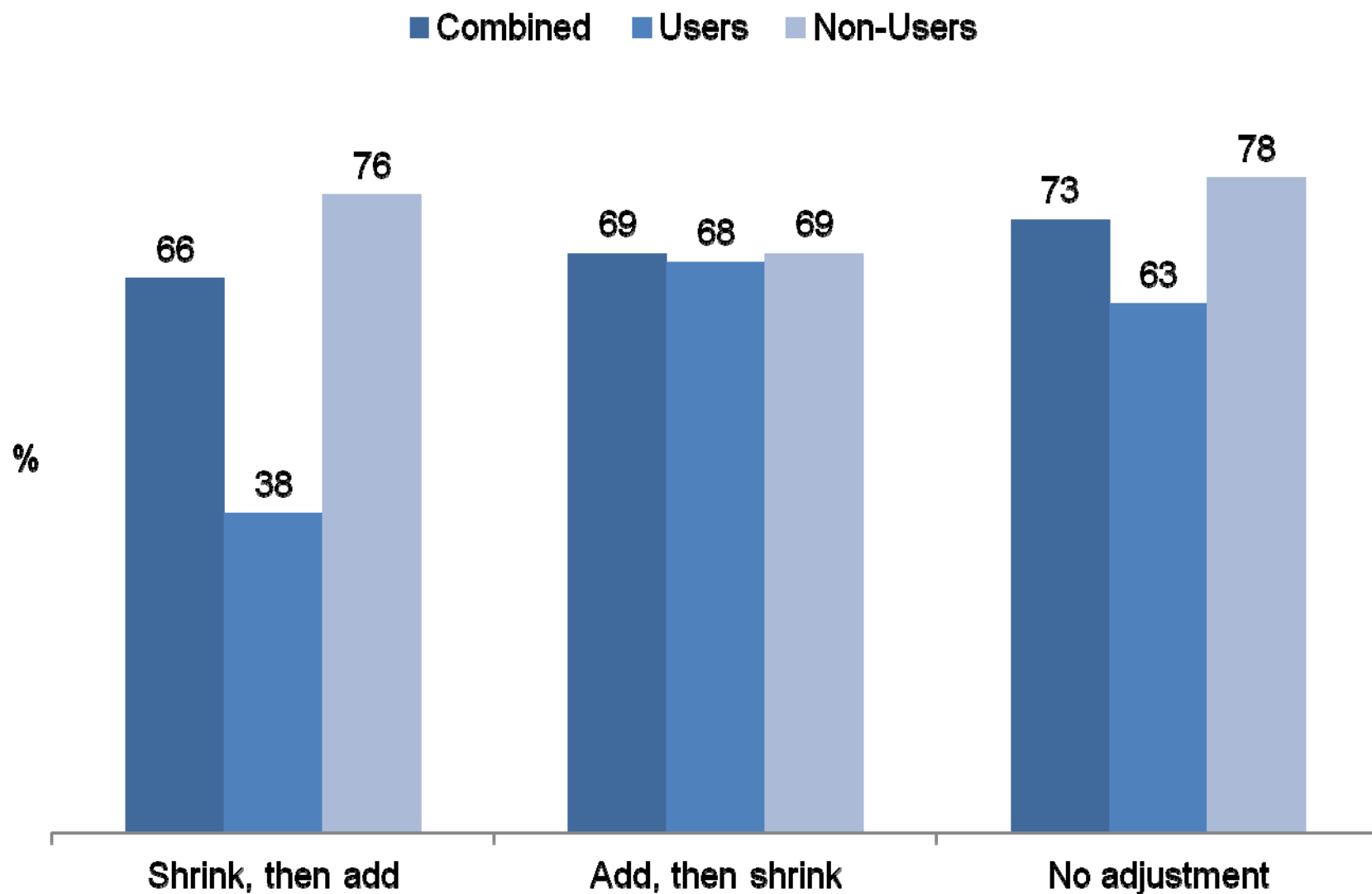# Total calcium intake: Girls, 14-18 years old
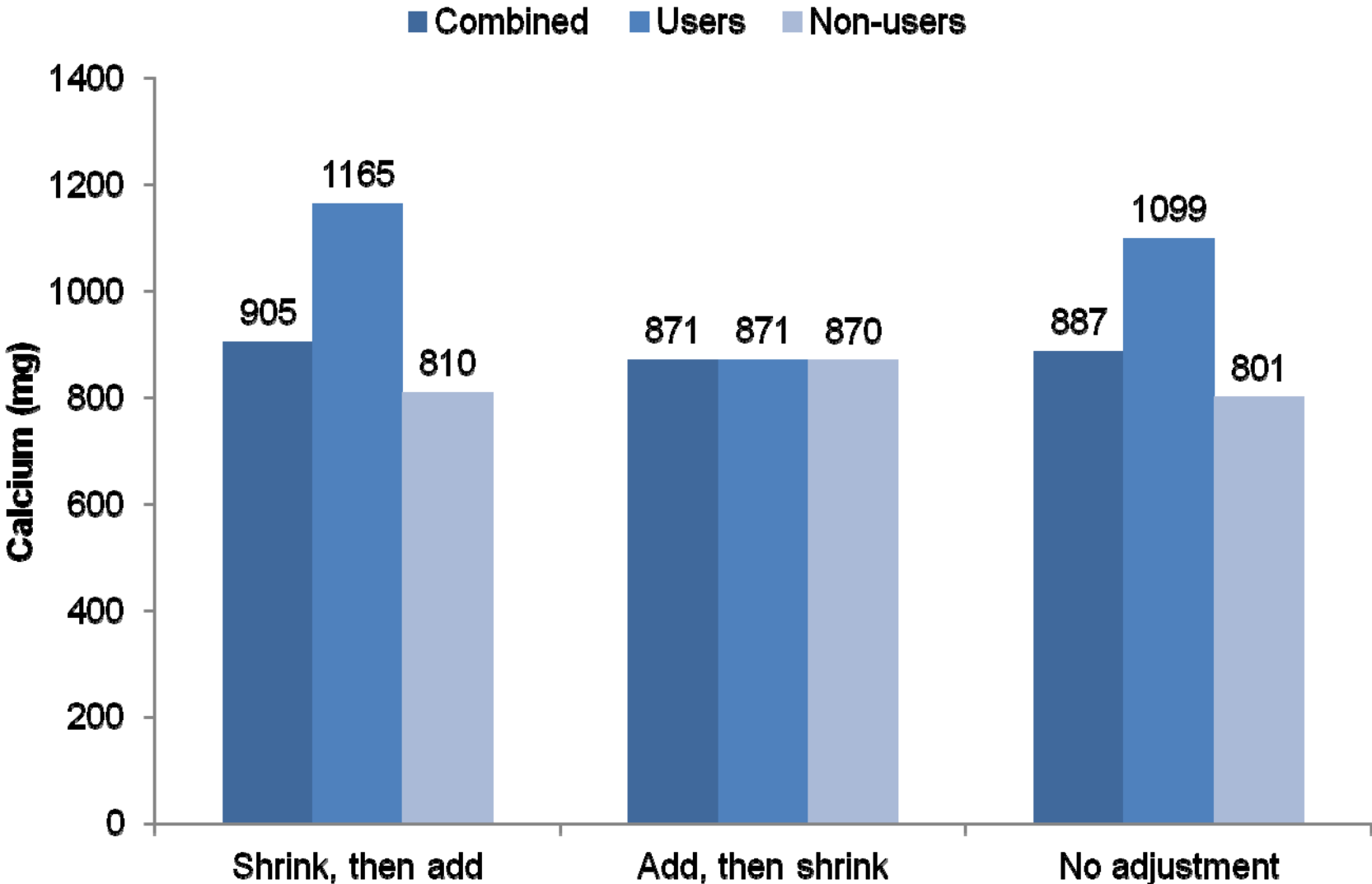
Slide 60

Okay, so this is where we compare the three types of methods for analysis. And in this example, I'm looking exclusively at girls 14 to 18 years of age, and this is an important group who needs calcium. I'll show you in the first example shrink, then add. If we have users and nonusers combined, the mean is about 900; that's very similar to if we use the add, then shrink approach, and very similar to no adjustment. So the means are pretty similar. If we look at users versus nonusers, we see the shrink, then add has a much higher mean for users when compared to the add, then shrink method. And remember, one of the limitations of add, then shrink using users and nonusers together is that we assume that they have one mean. Finally, the mean for nonusers, in the lightest bar, is presented for each of the methods.

Remember, there are different research questions. Where we really see the impact of these choices is when we look at the percent below the EAR.

Prevalence of inadequacy (% < EAR)

Estimating total usual nutrient intake distributions from diet and supplements

measurementERRORwebinar series

Slide 61

If we have users and nonusers combined, we see that with shrink, then add, we have 66 percent of people who are below the recommendation. If we look at users and nonusers separately, this is really where we see the difference in these modeling procedures, in that with the add, then shrink method, there is no difference between users and nonusers, and that simply does not make sense from a biological perspective. And that's why this model is inferior to our shrink, then add model for the research question that we have pose.

Take-home messages

- Mean intakes for the total population are relatively similar regardless of analysis strategy

- Distributions are most affected by methods

  - Do not present <EAR or >UL using unadjusted intake data

  - Suggest <u>modeling diet first</u>, then add supplements

measurement ERROR webinar series

So to summarize, if you're interested in the mean intake for the population, this is relatively similar regardless of the analysis strategy, but the distributions are most affected by the method of analysis. I would recommend that you do not present intakes below the EAR or above [the] UL on adjusted intake data from the simulations and the data that we've presented. We also suggest that you first model the dietary intake using those procedures that we described, and then add supplement [intake] to that.

NHANES calcium example, 2003-2006
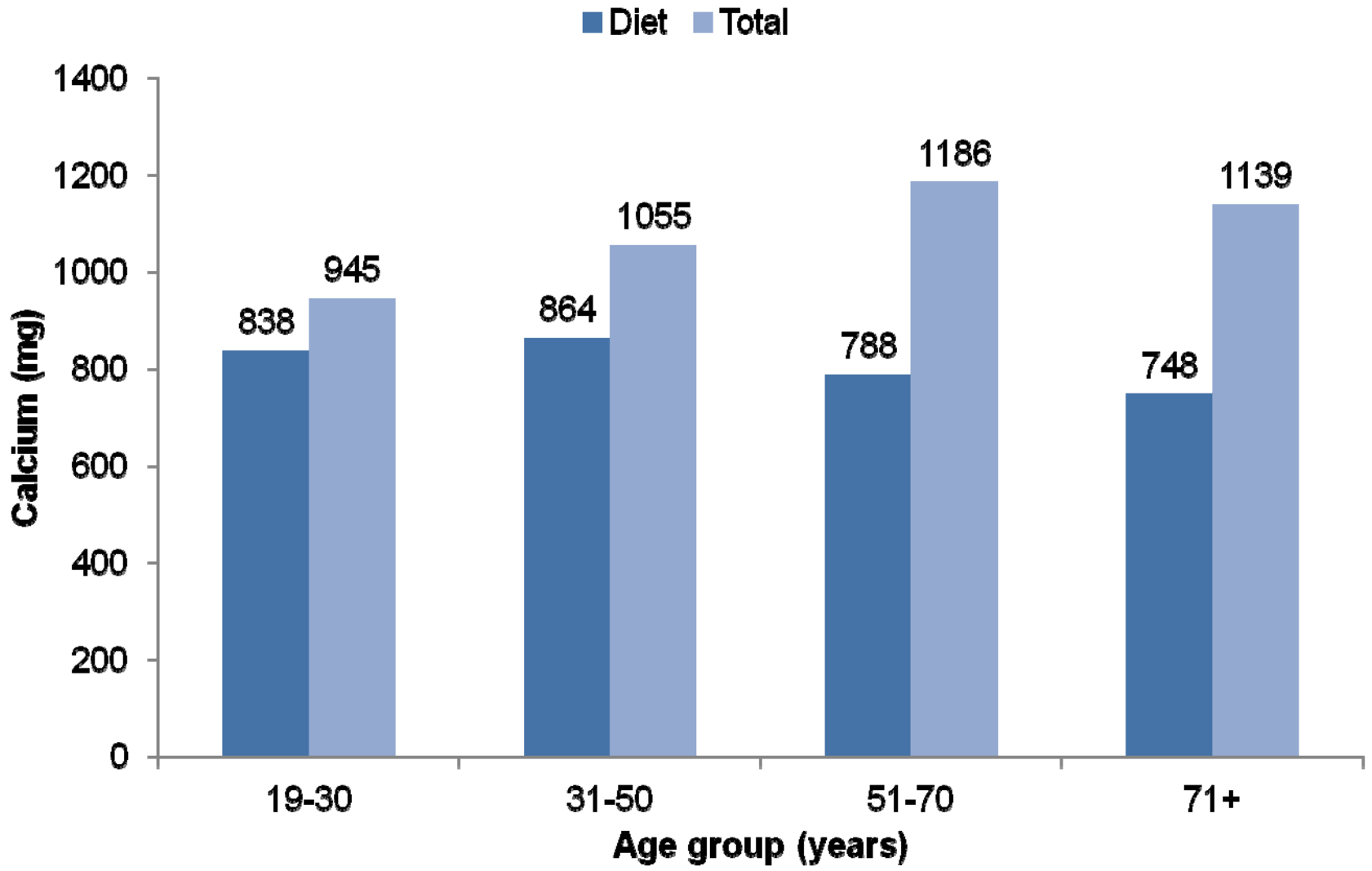
- Calcium intakes

  – Diet from two 24HR

  – Supplement information <u>only</u> from a questionnaire

- Adjust dietary intake distributions

- Add average daily supplement exposure to the adjusted dietary intakes

  – "Shrink, then add"

In the next example, I'm going to continue with calcium but move to a different time period—2003 to 2006. In this time period, we did not have dietary supplement use from the 24 hour recall. We simply had it from a questionnaire. And this may be the way that you have data, and that's why we've constructed this example. As we go through the data, we're going to examine what different types of research questions you may have, knowing that throughout these examples what we've done is we've added the average daily supplement exposure from the questionnaire to the adjusted dietary intake from the 24 hour recall, so using that shrink, then add approach that we described in the previous example.

Mean calcium intakes, women
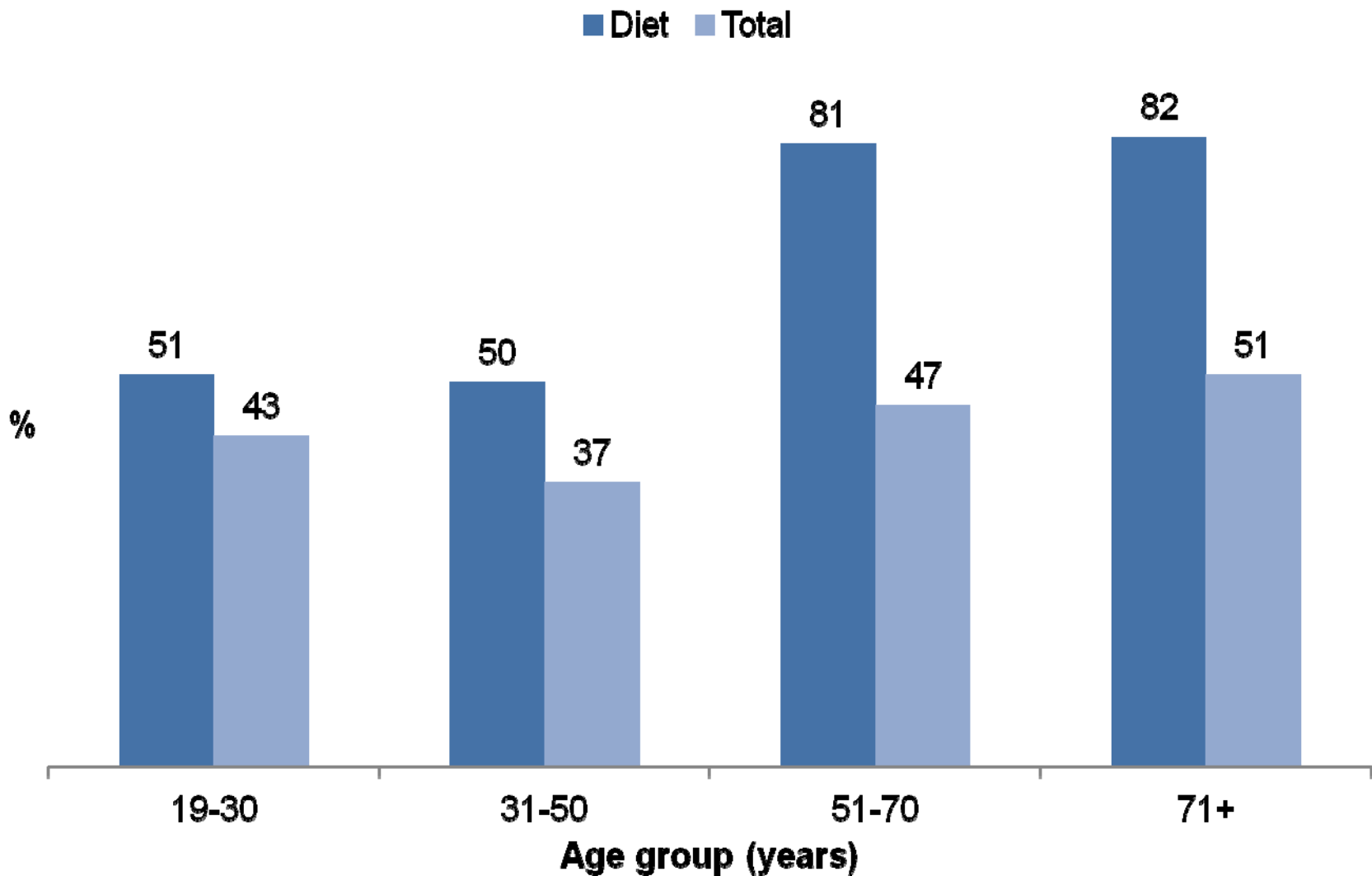
Source: NHANES, 2003-2006

This is looking at mean calcium intakes of females, and it seeks to address the research question at the top of the screen: What is the mean calcium intake of women in the U.S.? Mean intakes of food are in the darker blue, and total intakes, in the lighter blue.

Prevalence of inadequate intakes (% <EAR), women

Source: NHANES, 2003-2006

Slide 65

If your research question is: What is the prevalence of inadequate calcium intake among women, regardless of dietary supplement use? You have users and nonusers combined and you've produced your estimates, noting here the oldest age group, which may be important because of bone health issues. If we look, we see 51 percent of women over the age of 71 have inadequate calcium intake. That's what we would say about the group of U.S. women.

Implications of modeling decisions

- Several studies indicate the users of supplements actually have higher nutrient intakes from foods than non-users

  – Consider modeling separately

  – Potentially include other covariates
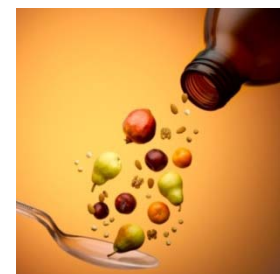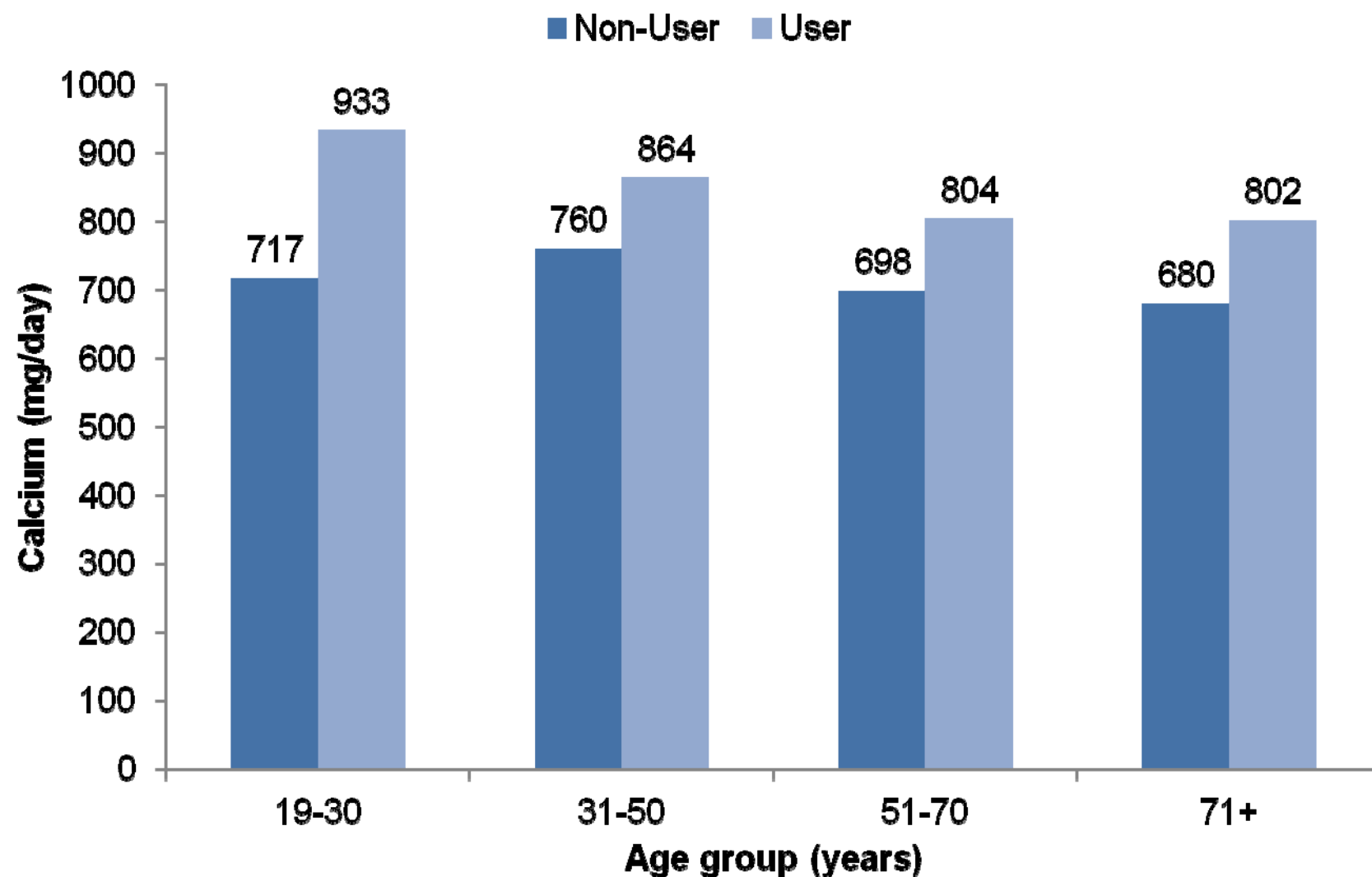
However, that may be simplistic because several studies have indicated that users of supplements actually have higher nutrient intakes from food sources than [do] nonusers. So you need to consider modeling them separately and potentially including other covariates of interest.

Mean calcium intakes from food sources alone, by supplement use

Source: NHANES, 2003-2006

Project sponsored by Fortification Committee of the
International Life Sciences Institute, North American Branch

In this slide, we're using the same data to answer a slightly different research question: What is the mean calcium intake of women by dietary supplement use? This is from food sources only, so as I alluded to earlier, you can see that women who choose calcium supplements also have dietary intakes of about 100-200 mg of calcium higher than those who don't. So they already have different intakes before considering supplement use.

Mean calcium intakes from all sources, by supplement use

Source: NHANES, 2003-2006

Project sponsored by Fortification Committee of the
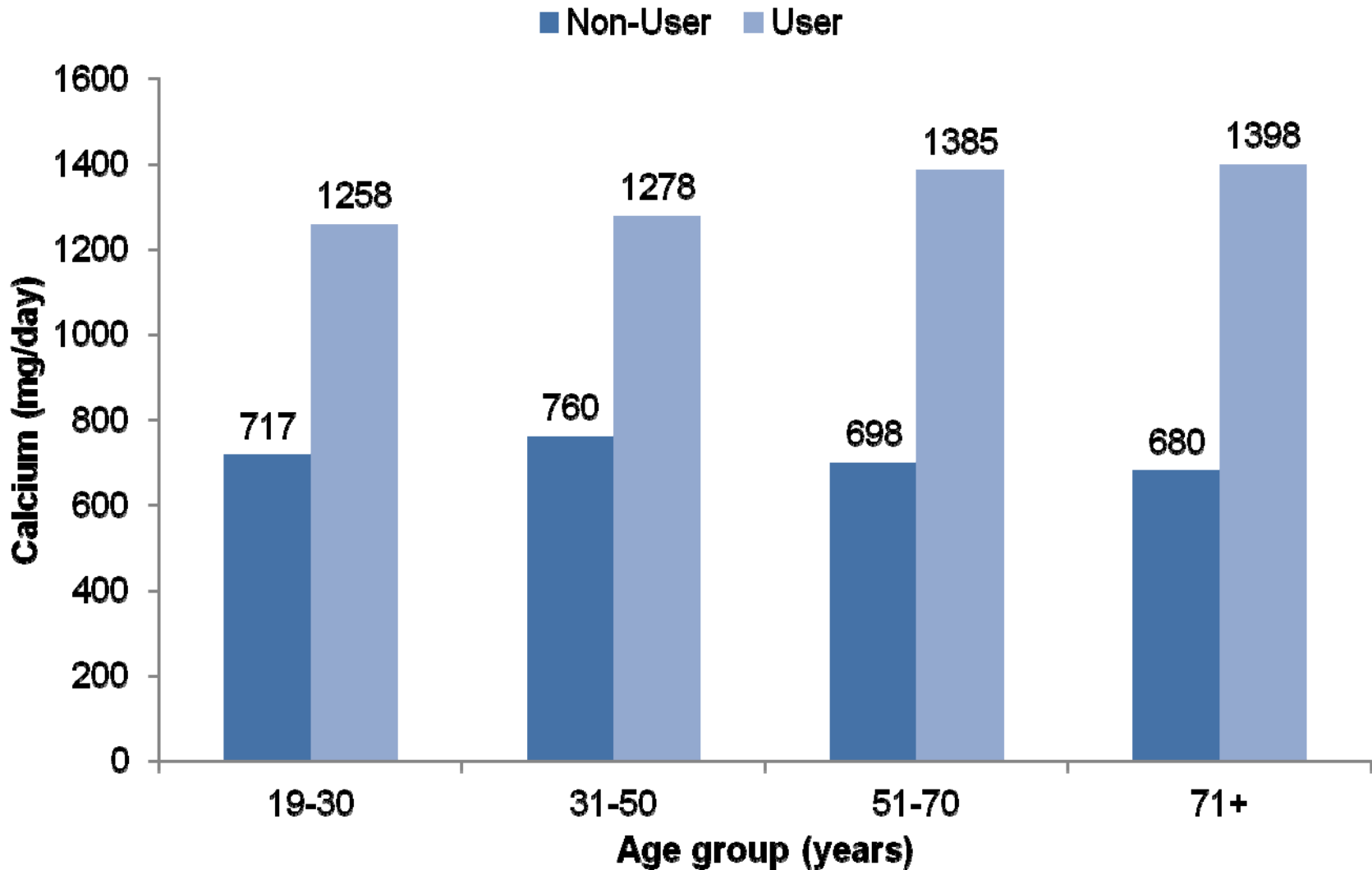International Life Sciences Institute, North American Branch

Look at the impact when we do consider supplement use. For some age groups, the intake almost doubles. Now, as you can imagine, this really comes out when we look at those tails of the distribution—the people who we are worried about not getting enough. So looking at that age 71 category again, 90 percent of nonusers don't get enough calcium compared to about a quarter of those who do use supplements.

Prevalence of inadequate intakes of calcium (%<EAR) among women

Source: NHANES, 2003-2006
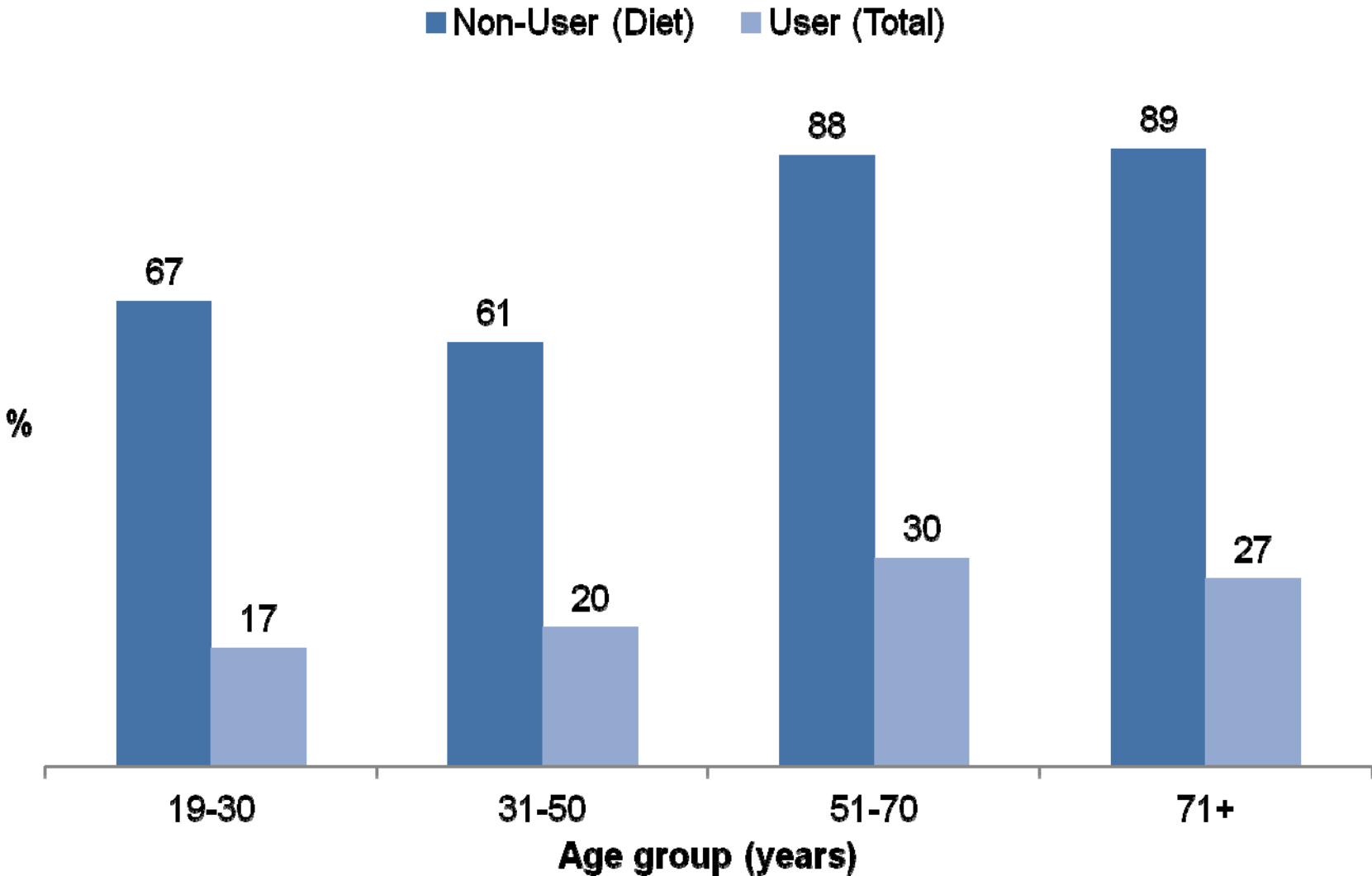
Slide 69

[No notes]

Data summary (e.g., women 71+ y)

- What is the prevalence of inadequate intakes of calcium among women in the U.S.?

  – Slide 65 – 51%

- What is the prevalence of inadequate intakes of calcium among women in the U.S., by supplement use?

  – Slide 69 – 89% among non-users and 27% among users

So to summarize those older females—if your research question is, "What is the prevalence of inadequate intakes among older women in the U.S.?" the answer is 51 percent. If you want to know the prevalence of inadequate intake of calcium by supplement use, the answer is quite different—about 90 percent of nonusers and 27 percent of users. And you may be sitting there saying, "So what?" Well, if you're somebody who needs this information to tailor a public health message, this information is really important. And so you really need to know what you want to answer before you choose a method of analysis.

Food folate vs. folic acid

- Fortificant in food supply

  – Shifts the entire distribution curve

- Folate bioequivalence

  – 1 DFE = 1 µg food folate = 0.6 µg folic acid from supplements and fortified foods

  – EAR is in terms of DFE, but UL is ONLY for folic acid

 – 39% of the U.S. population uses a dietary supplement with folic acid

I'm going to use folate as my final data example, for two reasons. Folate is a fortificant that's added to our food supply because of the known role of folic acid in the prevention of neural tube defects. So when a fortificant is added to the distribution, it shifts the entire distribution curve—everybody is getting more. So that's something that's unique and interesting about folic acid.

The second important thing that this example illustrates is bioequivalence. And what I mean by that is that folate from food is not nearly as bioavailable as folate that is used as a fortificant or from dietary supplements. So for that reason, the dietary folate equivalent metric was developed to account for this differential bioavailability. And this is important in terms of estimating our distributions because the EAR, or that lower cutpoint, is in terms of the dietary folate equivalent; that is, food folate, fortified folic acid, and supplements can all be used to help you meet your lower requirement, but the upper level is only for folic acid. So one cannot exceed the upper level from food folate alone. So you have to analyze this—you have to analyze each of these separately if you want to look at the EAR versus the upper level.
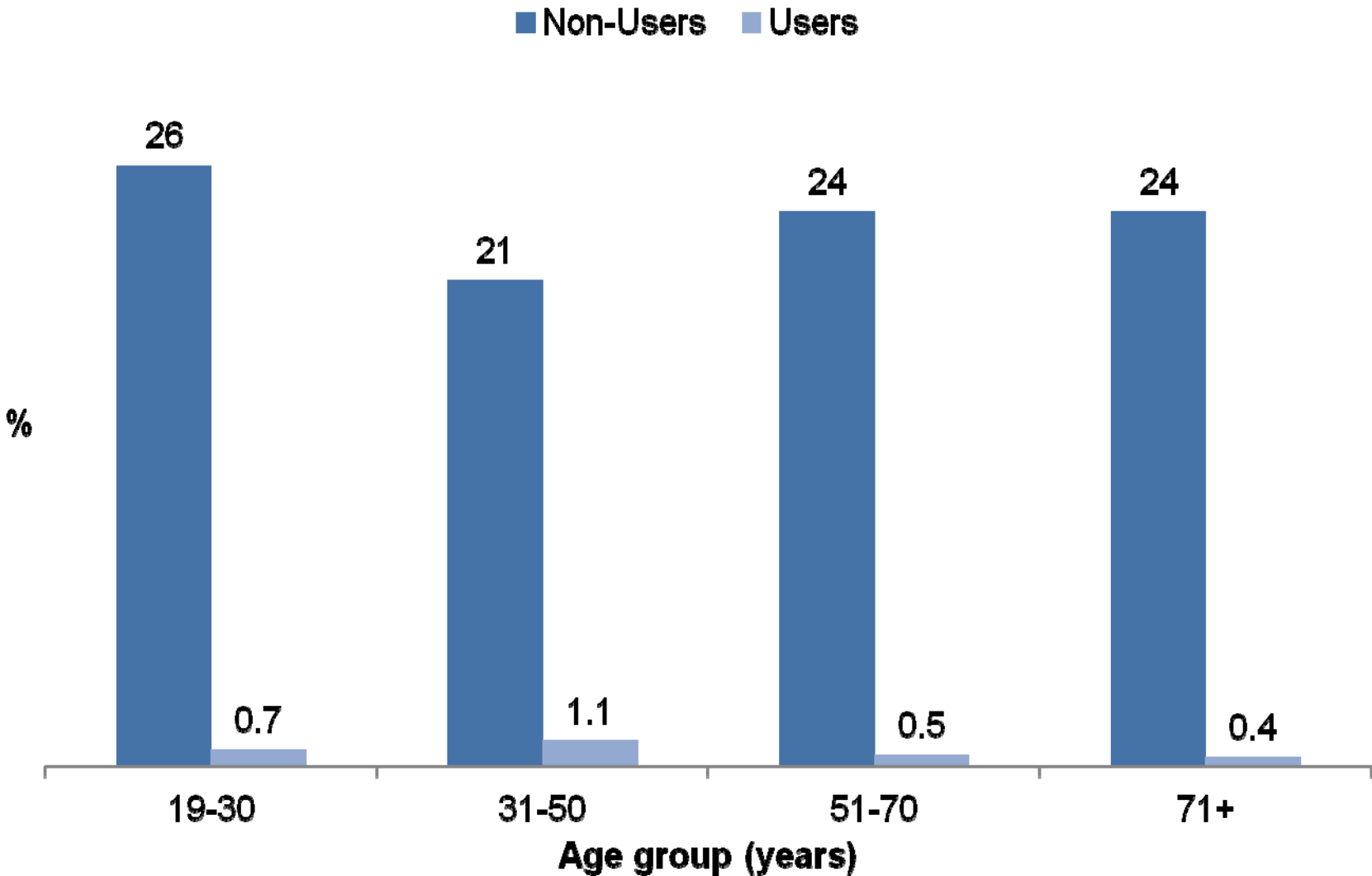
Prevalence of inadequate intakes (%<EAR), women

■ Dietary Folate   ■ Total Folate (Diet + DS)

Age group (years)
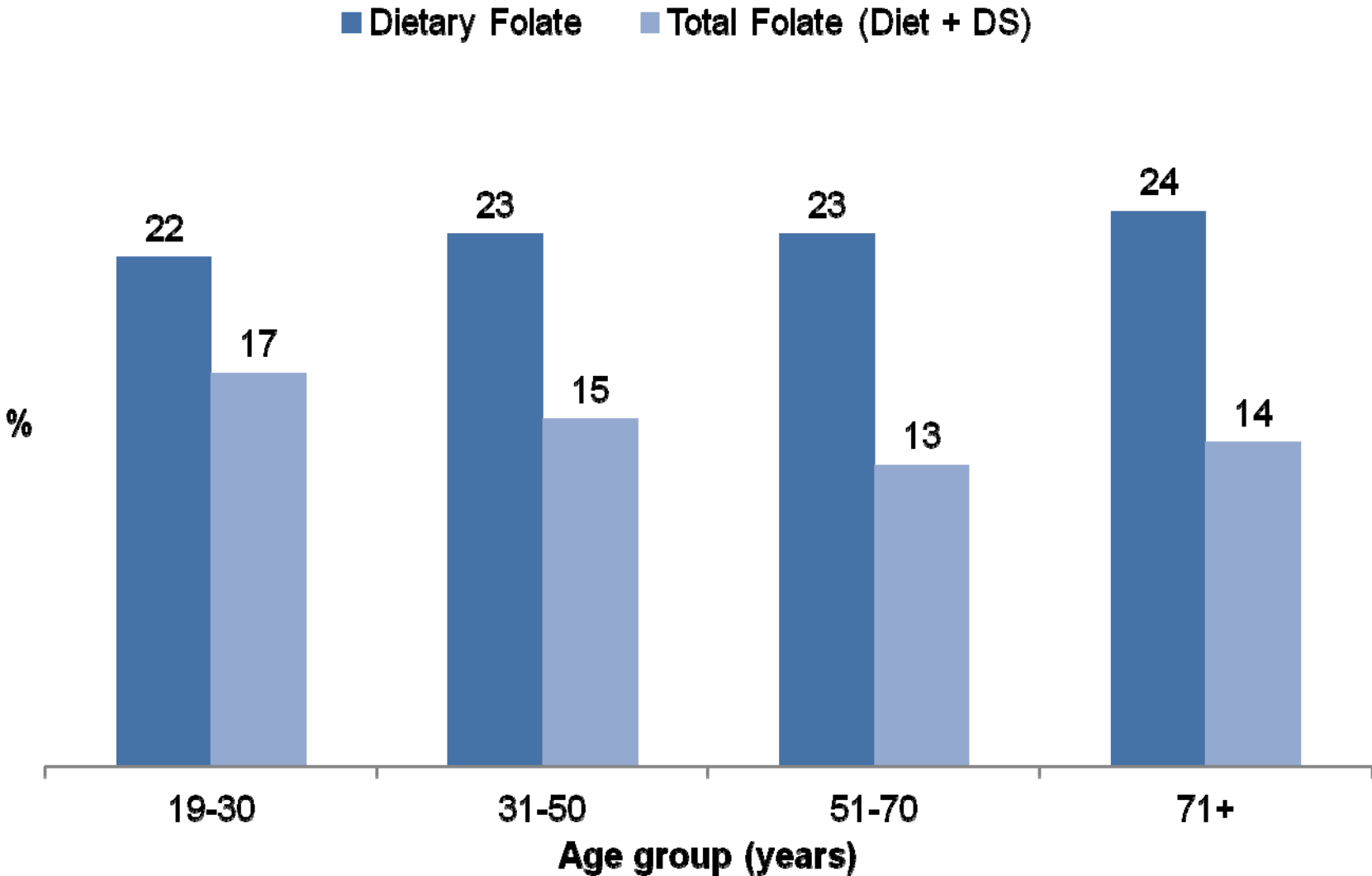
And in this slide, we're answering the research question, "What is the prevalence of inadequate intakes among females in the U.S.?" Because I mentioned that folic acid is important for reproductive-age females, let's focus here on the 19 to 30 age group. That isn't to say that you can't have a baby if you're older than 30, because I just had a baby and I'm well older than 30, but for illustration purposes, indulge me. We would say that 22 percent of reproductive-age females don't get enough folate from the diet if you only consider food sources. If you consider supplements, that's lowered to about 17 percent, and that's because not that many people in this age group use the folic acid supplement.

Prevalence of inadequate intakes (%<EAR), women

However, if your research question is, "What is the prevalence of inadequate intake by dietary supplement use?" we see quite a different picture where virtually no one who uses a supplement is at risk for inadequate intake, but about one in four, about 25 percent, would be at risk if they don't use dietary supplements. So supplements help to meet the nutrient recommendations for the lower end of the tail…

Prevalence of excess intakes (%>UL), women
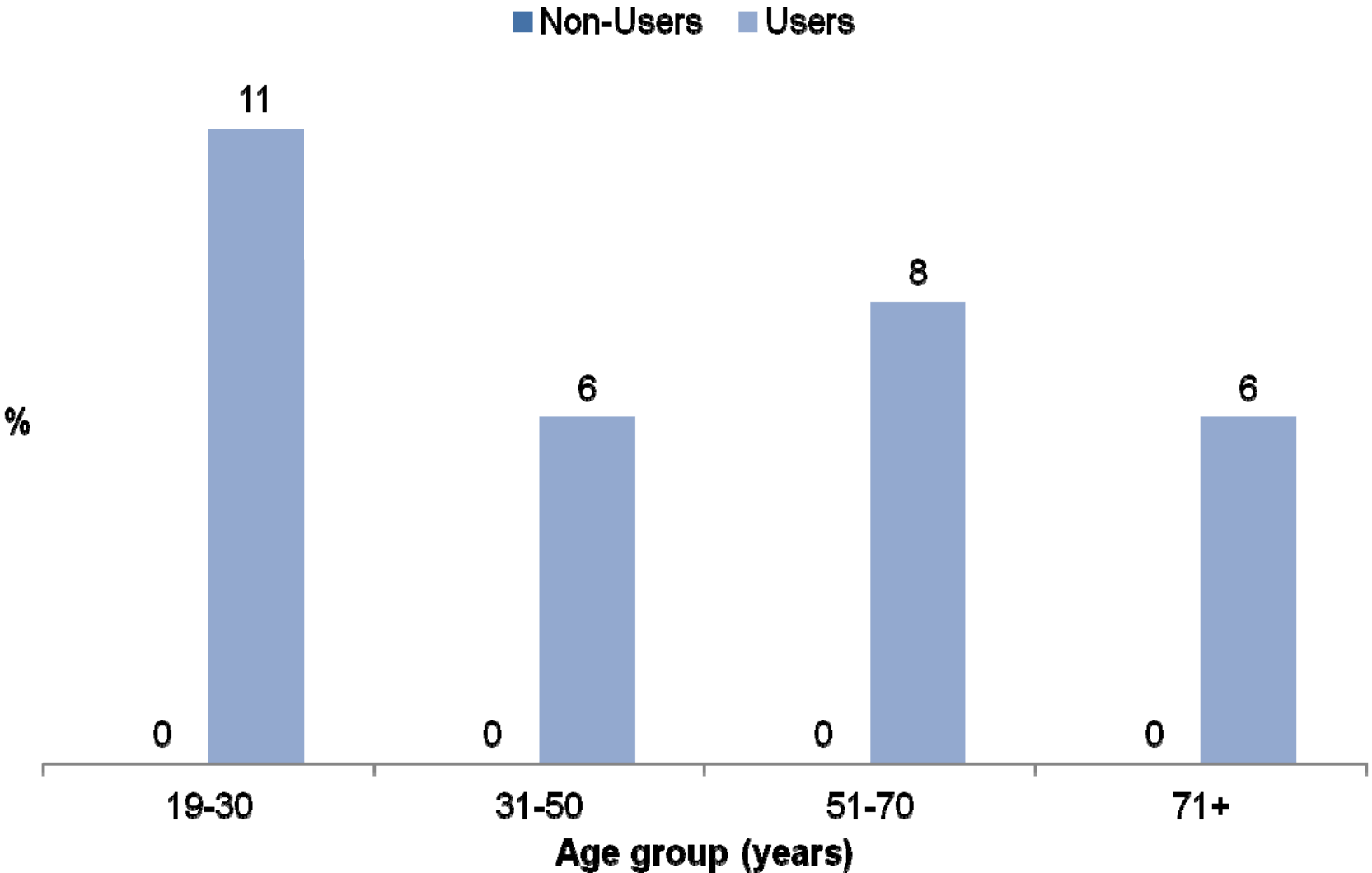
Slide 74

… but that has implications for the other side of the distribution as well, because supplements have the potential to push the distribution above the upper limit recommendation.

So in this slide, you can see that among nonusers, zero percent exceeded the upper limit for folic acid, whereas in our example, 11 percent of reproductive-age females exceeded the upper tolerable intake level.

Data summary (E.g., women 19-30 y)

- What is the prevalence of inadequate intakes of folate among reproductive-age females 19-30 y in the U.S.?

  – Slide 72 – 17%

- What is the prevalence of inadequate intakes of folate among reproductive-age females 19-30 y in the U.S., by supplement use?

  – Slide 73 – 26% for non-users, 0.7% for non-users

  – Remember 11% of users were above the UL compared to 0% of non-users

Slide 75

So again, it goes back to your research question. If you want the prevalence of inadequate intakes of folate in reproductive-age females 19 to 30, our estimate is 17 percent. But when we look at that by users and nonusers separately, we see a much different picture. And remember that supplements always increase intakes and have the potential to push that skew over the upper level recommendation.

ASSUMPTIONS AND CAVEATS

Slide 76

Let's talk about some of the assumptions and caveats in these models.

Assumptions and caveats

- Reported nutrient intake from food sources from 24HR are unbiased

- Self-reported dietary supplement intake reflects true long-term supplement intake

- Label declarations are accurate, or incorporate analytical values from the Dietary Supplement Ingredient Database project (slide 47)

Slide 77

They operate under this assumption that reported nutrient intakes from food sources from 24 hour recalls are unbiased. As I mentioned earlier, we also rely on the assumption that self-reported dietary intake reflects true long-term supplement intake. We also rely on the fact that label declarations are accurate. If you want to incorporate those analytical values that I showed you in slide 47, please visit the Web site there for the dietary supplement ingredient database project. Information is provided there on how to incorporate those data.

Caveats

- **There is no one right way to handle dietary supplements**

- **Know your research question**

- **Know your sample**

- **Know your nutrient**

Slide 78

I want to take a minute to just say there is no one right way to do this. We've presented here some of the strategies that we have used and others are using in the field. Whatever method you choose will be dependent on your research question [and], as we saw today, will be dependent on your sample. If you have a sample with very few dietary supplement users, you may not have to go into all of these exercises. But if you had a sample with many users, you would. You also need to know your nutrient. I showed you the example of folic acid and how the different forms of the vitamins make a difference in answering your research question. This is true for vitamin A, vitamin E, magnesium, and probably many others that I'm neglecting to mention now.
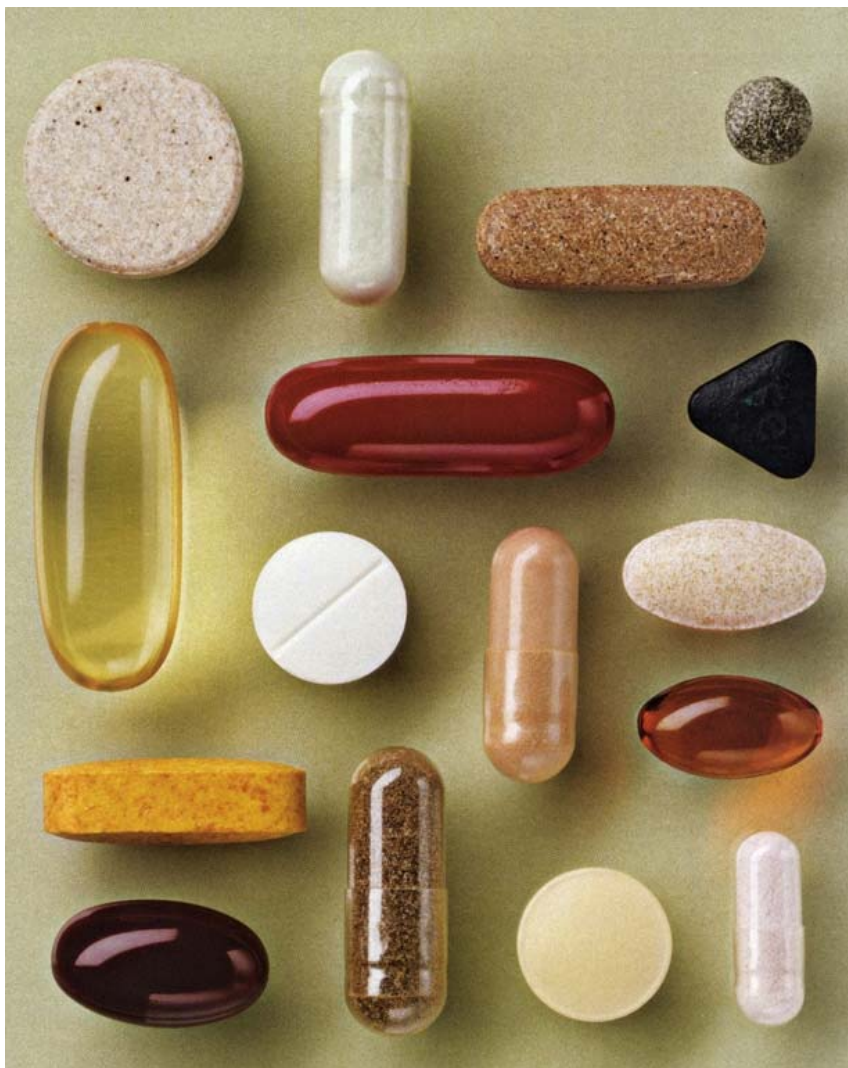
SUMMARY

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So I would like to summarize now what I've presented today.

Bottom line – accounting for supplements

- More than half the U.S. population uses dietary supplements

- Must be included in nutrient intake estimates

- Must be accounted for when calculating prevalence of inadequate and excessive intakes of nutrients in a group

More than half of adults and a third of U.S. children use supplements. They have to be included in your nutrient intake estimate, particularly when you're calculating the prevalence of inadequate or excessive nutrient intake of a group.

Bottom line – methods

- If you want the population mean – most strategies will work

- If you want total usual nutrient intake distributions

  - Adjust dietary estimates

  - Add dietary supplements

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If you want the population mean, most strategies will work. If that's all you want, all of the three analysis strategies we showed you will get you your answer. But if you want the usual total nutrient intake distribution, we recommend that you first adjust your dietary intake estimate and then add your dietary supplement estimate.

Thank you!

- **Webinar**
  - Kevin Dodd
  - Sharon Kirkpatrick

- **Researchers**
  - Alicia Carriquiry
  - Didier Garriguet
  - Janneke Verkaik-Kloosterman

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I'd like to take a moment to thank Kevin Dodd, who is instrumental in all of the methods we've presented here today. As I said earlier, I come at this from the perspective of the user. I'm not a statistician. I don't even play one on TV. I'd also like to thank Sharon Kirkpatrick. As I mentioned earlier, she has really poured her heart into making this webinar series possible for all of you, and I implore you to take a moment to send her a quick thank you email for all of the work that she's done.

I'd like to also acknowledge the researchers whose work these models have been built upon. I am not responsible for the methodology or the statistics that were seen here today. Kevin and these other researchers, and likely others that I'm neglecting to mention, should be acknowledged.

QUESTIONS & ANSWERS

Moderator: Susan Krebs-Smith

Please submit questions using the *Chat* function

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Thank you, Regan. We'll now move on to the question and answer portion. Kevin will be here to help answer questions if they are more methodological, and I'm here for practical and biological questions. Thank you very much for your time and for your interest in this series.

Question: **You mentioned the 24 hour recall and supplement intake cannot be adjusted for within-person variability because they do not transform well in normality. Does this mean that frequency questionnaires are better than 24 hour recalls for assessing supplement intake, would you say?**

I wouldn't say that one is better than the other, because we simply don't have enough information. As I mentioned, ideally, we would want to capitalize on the strength and minimize the weaknesses of both frequency methods and 24 hour recalls. *(R. Bailey)*

Does the use of NHANES data to estimate total intakes account for all of the sources of nutrients that you mentioned; specifically, does it account for the nutrients in water and how would you account for the nutrients in water?

Yes, and that's one of the beauties of NHANES, is it captures the totality of exposures that are relevant to total nutrient intakes. There are prescription drug questionnaires that we can get antacid use from. There are other nutrients in prescription medications that can be obtained that way. The estimates are provided for water, for all beverages, and all foods. So NHANES is just a wonderful resource and we're all so fortunate to have it. *(R. Bailey)*

Does NHANES—when using NHANES data to examine usual intakes, how do you account for the use of multiple cycles of data; for example, pooling of the 2003-04 and '05-'06 cycles? Specifically, does the code for the NCI method need to be modified to handle multiple cycles?

Actually, the code for doing the analysis doesn't actually need to be changed. The construction of the data set generally needs to be changed and the NHANES dietary Web tutorial and also the continuous NHANES tutorial give you examples of how you have to go through and adjust the sampling weights to make sure that what you're getting is going to work well for it when you combine multiple NHANES surveys. *(K. Dodd)*

Does the NCI macro incorporate shrink, then add or is it something we need to do ourselves afterward? If the latter, is there an example available?

I believe, and, Sue, you correct me if I'm wrong, that in the advanced section of the dietary Web tutorial, Janet did go through an example using at least a primitive version of the NCI method macros for doing exactly

that. So there is an example there on how to use it. As Regan has said, these methods are currently evolving and we don't have necessarily the final say in exactly how we might approach the estimation of total nutrient intakes, so we don't have a do-it-all-in-one macro right now that incorporates everything that Regan's talked about today. But Janet did go through an example on the Web tutorial using one aspect of the add, then shrink method … or shrink, then add … sorry. *(K. Dodd)*

How does the appropriate handling of the analysis differ for nutrients that have an AI rather than an EAR? And maybe you want to explain a little bit what an AI is.

Okay, for some nutrients, we don't have an RDA or an EAR established because there was not enough research to make a definitive recommendation for these levels. So just very briefly, the RDA is two standard deviations above the EAR. And assuming that we have standard deviations, we're assuming that we have a normal curve. When we don't have enough information to make that curve, what has been proposed is an adequate intake, or an AI. And, really, we can't use an AI in population-based research because we can only say that intakes above the AI are okay, but we can't say anything of intakes below the AI, so it's really not useful in population monitoring and surveillance. *(R. Bailey)*

And since folic acid fortification was mandated, has the folate database in the U.S. been updated?

Well, the USDA database provides information as naturally occurring folate and folate that is added as a fortificant; so they have those two variables separate. Then, they also have those combined using the DFE metric, and that's invaluable, as I showed in the example, because if you want the information to describe the EAR, you need both food folate and folic acid. If you want the upper limit, you only have folic acid. So it's wonderful that we have the data in all of those various ways from the USDA database. *(R. Bailey)*

Along similar lines: Are foods and beverages like Total cereal and Vitamin Water handled as foods or supplements?

Those are currently handled as foods. A supplement is defined as something taken by mouth to supplement the diet. Right now, though those may be used by people as a supplement, they are currently being treated as foods because that's the typical vehicle they come in. *(R. Bailey)*

And then the fortification levels might make those foods have—act sort of like supplements in terms of the analysis.

Yes. *(R. Bailey)*

Would you comment on the extent to which issues of bioavailability might introduce error into usual total intake estimates?

Well, sort of tongue in cheek, it's not going to introduce any error in your estimates of intake because you're only worried about bioavailability after it gets into your mouth. What we're talking about is before it gets into and while it's in your mouth. We really can't address bioavailability at this time. There is some work being done on it, but we're not ready for prime time on how to address bioavailability in these models. *(R. Bailey)*

DFE that you mentioned was developed based on a very small study a while ago and has not been updated since then. Is DFE reliable in terms of considering bioavailability of folate? What are your thoughts on that?

My thoughts on that are that this is something that was developed by the Food and Nutrition Board at the Institute of Medicine. While we all may have our thoughts and suspicions and bias about what those should or should not be, they are. And we have to use them as they are given to us by the dietary reference intakes, not as we think they should be. So we analyze data based on the recommendations, not based on what we think they should be. *(R. Bailey)*

Slide 23 described supplement use over time. Have you examined the supplement use over time by individuals, i.e., what proportion of users use supplements for multiple years?

I haven't really addressed any of that in my research to date. Kevin, have you ever? *(R. Bailey)*

Well, the total—well, the separate use over time question—you're not going back to the same people year after year, so in NHANES you can't say, "You said you took it for … you've been taking it for five years two years ago. Have you now been taking it for seven years?" That sort of stuff you can't do because of the—it's a cross-sectional study, not a longitudinal one. And as far as the point estimates for the population, have those numbers been stable over the years? I think what Regan showed in that slide, was that the prevalence of use has been going up, I guess slightly, overall. And non-Hispanic whites in particular have had a great increase over time. But it's been using that same cross-sectional metric of asking people, "Do you take a supplement now?" and kind of getting those snapshots over time. *(K. Dodd)*

Are there any special considerations for iron in women of reproductive age in this aspect of analysis?

Well, iron is sort of a special-case nutrient in that there is nothing you can do to the nutrient distribution from foods to smooth it or make it like a normal distribution. So we don't typically use the EAR method when we're using iron intake. We use the full probability method, and that's outlined in the dietary reference intake books, the applications for dietary assessment, because iron is a special-case nutrient. *(R. Bailey)*

The requirement distribution for iron isn't nice and normal, and that's the problem. That's one of the—and that's also explained in—the statistical rationale behind those cutpoint methods is explained in that. *(K. Dodd)*

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Thank you Regan and thank you to our audience for joining today's webinar. Please join us next week for webinar 6, the first session in the section on assessing diet-health relationships.