Morning Day 1
https://youtu.be/LRHw6gtwLL8

Dr. Eve Stoody: Okay, good morning. My name is Eve Stoody, and I'm the Lead Nutritionist for Nutrition Guidance at USDA Center for Nutrition Policy and Promotion, and I'm also the designated federal officer for this 2020 Dietary Guidelines Advisory Committee. It is really my pleasure to welcome you to meeting 4 of the 2020 and also to welcome you to Texas. We are holding this meeting at the USDA Agricultural Research Service Children's Nutrition Center in Houston, Texas, and thanks to Dr. Danny Beer and their team for really welcoming us and being fantastic hosts for this event.

This is the second—we also want to welcome all of us who are joining us on YouTube. This meeting will be, like our previous meetings, will be live. So, this meeting will be live-streamed. There will be—and just a note that there will be different links for the morning and afternoon, just the nature of YouTube.

[0:01:00] So, for those of you who are joining us online, when you registered, in your registration email, you should have received four links, two for today and two for tomorrow. We'll try to remind you to change links after lunch.

So, we are very happy to have 19 of our 20 members here with us today. Unfortunately, Dr. Linda Van Horn was not able to join us here in person, but she is going to join us remotely as much as she is able.

We have about 1,000 people who have registered for this meeting with about 150 who will join us at some point in person here in Houston. And as always, just thank you for your interest and in your support of the Dietary Guidelines.

So, just a little bit of background and a reminder. The 2020 committee was established to conduct an independent review of current research on nutrition and health to be considered by the Departments of Agriculture and Health and Human Services in the development of the *2020-2025 Dietary Guidelines for Americans*.

[0:02:03] This committee was selected by Secretaries Purdue and Azar from USDA and HHS from nominations received from the public, and they were selected based on their education, experience, and expertise, and they were balanced on a number of factors, including things like geographic location.

The committee was announced in February of 2019, and just as a reminder, this is not a committee that was convened to provide expert opinion or to represent a specific viewpoint, but rather, they were selected as independent scientists who will work together to review current evidence on diet and health.

Since this is a federal advisory committee, the federal government is required to outline the duties, the missions and specific duties of the committee, and we have done this through our charge to the Dietary Guidelines Advisory Committee. You can see this charge on our slide. We presented it at every meeting, and it's also on our website.

[0:03:00] And their charge is to examine the evidence on specific topics and scientific questions identified by the Departments, and I'll talk about those here in—more on the next few slides, to develop a report that outlines their science-based review and recommendations to the Departments with rationale, and then to submit the report to the Secretaries of USDA and HHS for consideration as the Departments develop the next edition of the *Dietary Guidelines*.

So, as we've talked about previously, USDA and HHS added a new step to this process, to identify the specific topics—the specific questions that the Advisory Committee were asked to address. In the past, we did outline some topic areas, but in general, the committee identified the specific questions that they would consider.

For this committee, we added the step for the committee where the Departments identified those topics and questions and asked the committee to address those. We did this for a number of reasons.

[0:03:58] One, it was in part due to recommendations from the National Academies on our process to kind of have the question development occur in a separate step, and we also really felt like it promoted a more transparent, inclusive, and deliberate process.

And I do want to note that the topics and questions were not developed in isolation. The process was led by the Center for Nutrition Policy and Promotion at USDA and the Office of Disease Prevention and Health Promotion, our partners at HHS, but it did include input from a number of federal agencies, as well as consideration of thousands of public comments.

And so, in that process, specifically CNPP and ODPHP developed an initial list with input from some of our federal partners. We posted a list of topics and questions for public comment for 30 days.

We received about 6,000 public comments on those topics and questions and refined the list based on that input.

[0:04:55] We did prioritize the crit—prioritize the topics and questions using four criteria: relevance to the *Dietary Guidelines*, and I'll talk more about that in just a second, importance to public health, potential impact on the federal programs and policies that we inform and avoiding duplication of other federal efforts.

Now, as I think everyone in this room knows, in the field of nutrition, there are many possible questions of scientific and public interest that are—have the potential to be explored. So, this includes things on food groups, on very specific foods, questions on nutrients, food safety, food labeling, menu labeling, food settings, food policies, food behaviors, medical nutrition therapy, and more, and we really feel like the *Dietary Guidelines* have an important slice of that nutrition conversation.

So, the *Dietary Guidelines* have a specific goal and a specific timeline, and that is to provide food-based dietary guidance to the general public at least every five years.

[0:05:57] Now, we do have a number of partners who work with kind of in this larger nutrition conversation, so for example, the National Academies developed the nutrient recommendations known as the Dietary Reference Intakes, and there are a number of federal agencies and others involved in this space, including the Department of Health and Human Services Food and Drug Administration, who work on food safety and labeling issues, but the point being here that there's a lot of pieces, and the hope is that we all work together to kind of speak to this larger—the bigger nutrition picture.

Now, the topics and scientific questions we've asked the committee to address focus on diet and health across the life span. And so, kind of a main emphasis for this round I would say is about that emphasis on the life span.

The topics and questions we asked the committee to address build on topics and questions examined by previous *Dietary Guidelines*. So, Dietary Guidelines Advisory Committees, I should say. So, we didn't start from scratch. We had a lot to work with from our previous committees.

[0:06:59] So, for example, the 2015 committee did a number of questions on dietary patterns and added sugars. The 2010 committee had a number of specific questions on seafood and alcohol.

A number of committees have addressed kind of elements of dietary fats, beverages, and frequency of eating, perhaps not as—in kind of a broader scope, but pieces of it.

Previous committees have also described current intakes of Americans as well as status of health across the American population, which will be talked about today, and since 2005, Advisory Committees have conducted food pattern modeling analysis.

So, that's kind of the exposure element.

In terms of the outcome, the committee was asked to consider a range of outcomes.

So, many previous Advisory Committees have looked at the outcomes of body weight, or obesity, cardiovascular disease, type 2 diabetes, and cancer, and we asked the committee to examine those in kind of that health discussion, but also, some additional outcomes.

[0:07:58] So, for example, neurocognitive health has become really a more recent interest in nutrition science, so we did include brain health as part of many of the questions that the committee were asked to consider, sarcopenia, in particular, trying to think about the older adult population and having more targeted outcomes for that population, bone health, which is of course important for older adults, but also children and adolescents, as well as the outcome of all-cause mortality.

We actually haven't had many committees that have kind of considered that broader all-cause mortality outcome.

Now, each committee that we've had also looks at some unique topic areas, and for 2020 process, these are the Birth to 24 Months population. There had been a growing interest in us including this population. Traditional dietary guidance has focused on 2 years and older. And then, the 2014 Farm Bill really solidified that inclusion in this edition.

And an expanded focus on pregnancy and lactation. Previous Advisory Committees hadn't necessarily excluded pregnancy and lactation, but they hadn't had as focused questions on pregnancy and lactation, and perhaps, more specific, they hadn't really considered outcomes related to pregnancy and lactation.

[0:09:07] And so, that's an addition here as well. And both of those are no small additions, as you'll hear today shortly.

So, in summary, I'd say that there are many similarities between the work of this committee and previous Advisory Committees, but there are some new topics. I think a lot of what we've been seeing is that a lot of the questions are more expanded. So, they're kind of the similar concept areas, but kind of broader exposures and more outcomes, and there also are, of course, some new populations.

Now, as we've talked about previously, and as with all of our Dietary Guidelines Advisory Committees, the committee's task is time-limited.

As we've discussed, USDA and HHS request the committee's report by May of 2020, and that is so that the Departments can meet our mandate to release the next edition of the *Dietary Guidelines* within five years, which is by December of this year, December of 2020.

[0:10:01] So, as we move into the last phase of the committee's work, which is pretty crazy to think, and similar to previous committees, the 2020 committee and federal staff have been working to refine, streamline, and prioritize the remaining work within the remaining time, and you'll hear more about that over the course of the next two days.

So, all meetings of the full committee are open to the public. As I noted, this is the 4th meeting. If you were not able to join us for meetings 1, 2, and 3, that information is archived on our website, including recordings of the meetings, as well as presentations, transcripts, and minutes.

Similar to the 2nd meeting, this meeting will include an opportunity for individuals who have registered to provide oral comments to the committee.

However if you did not—did not have the opportunity to travel here to provide public comments in person, the written public comment period is always open.

[0:10:58] We opened it in March of 2019, and it will stay open into May of 2020.

So, this meeting will be held today and tomorrow from 9:00 am until 4:30 pm Central, and I just note that because we usually function on Eastern time, and some of us arrived early today thinking we were still there. So, but we'll be on—the meeting will be on Central time.

The agenda is available at DietaryGuidelines.gov, and Dr. Schneeman will give an overview of the agenda in her remarks.

We do want to announce today that there were—we will host, the committee will host a meeting on its report on May 11th, which is a Monday. This will be a meeting, as we just talked about that we've asked for the committee's report in May.

Their last meeting was scheduled for March and we wanted to provide the committee an opportunity to come together to discuss its final recommendations and refine its report, but also, for the public to be able to hear some of the discussion around the committee's final recommendations before they submit their report to the Departments.

[0:12:05] I will say that this is the first time that we've had hosted a meeting specifically focused on the committee's report and we hope that it kind of is helpful in hearing first-hand about their recommendations before they submit the report.

So, we'll provide more information about this, we will publish this in the Federal Register, we'll include information on our website, we'll send out Listserv messages for those of you who signed up as we have more information, but for now, please save the date for Monday, May 11th. This meeting will be held by webinar only. We will not have—there won't be travel for that meeting.

So, we encourage you to follow along at DietaryGuidelines.gov in between the meetings as well as here today.

The committee will talk about a number of different questions that they are reviewing. If you want more information about the questions that they are talking about, you can go to DietaryGuidelines.gov.

[0:12:59] There's a rotating banner at the—in the middle of that page, the orange banner there, and if you click on "View Protocols," it'll take you to a list—a website with a list of questions, and if you click on your—you can click on your question of interest and it will take you to a web page devoted to the committee's review on that question.

So, if you have something of interest that you really want to learn more about, we encourage you to go to the website.

So, with that, I turn it over to the chair of the committee, Dr. Barbara Schneeman.

Dr. Barbara Schneeman: Thank you, Eve. And let me add my welcome certainly to the committee members. It's great to see you all and have a full, a fairly full representation from the committee, and also, to the attendees here in the room, but also to all of those who are listening on the webinar.

[0:14:00] We do appreciate the interest in the *Dietary Guideline* process and the work of this Advisory Committee.

And I want to extend a special thank you to the CNRC for hosting the meeting here. I see Dr. Veer sitting over here on the side. Thank you very much for the invitation to be here, and the staff has been fantastic in terms of helping us and making sure that things move smoothly, so thank you.

So, I will move into the slides.

So, let me start, first of all, by just giving you an overview sort of following on from what Dr. Stoody presented.

I'm going to talk more specifically about our subcommittee structure, our approaches to examine the evidence, and the information to be discussed at this meeting.

[0:14:59] In a sense, I'm now going to talk more about how this committee has moved forward with the charge that we received from USDA and HHS.

So, we'll look at the subcommittee status in the agenda for this meeting.

So, just to remind you, these are the subcommittee structures set up so that between—in the time between the public meetings, work can proceed. And we have six subcommittees and one cross-cutting. I know the font is small there. Dietary Patterns, Pregnancy and Lactation, Birth to 24 Months, Beverages and Added Sugars, Dietary Fats and Seafood, and Frequency of Eating, and the cross-cutting group is the Data Analysis and Food Pattern Modeling subcommittee, so, aligning with those topics that you heard.

And I'm not going to read out the names, because as we go through the subcommittee reports, you will be getting that information.

[0:16:03] Just to remind you that the subcommittees review the evidence and provide advice to the parent committee, so the final decisions are being made by the full committee and they're done in this public meeting format, which we'll be having today and tomorrow.

So, just, again, we've talked about that—this each meeting, how the committee approaches the review of the evidence, the examination of the evidence, and we use three approaches to examine the evidence: data analysis, food pattern modeling, and the NESR systematic reviews, and each of these scientific approaches has a protocol, and the protocol is a plan for how one of the scientific approaches will be used to examine the evidence related to one of the questions that the committee has been asked to address.

[0:17:01] As they've been developed, each of the protocols are available, and Dr. Stoody gave you the web link for that, and we, in posting the protocols, we have invited feedback from the public, and we found that feedback to be very helpful.

People have provided additional references or additional considerations.

So, information on the approaches and the protocols have been presented at previous meetings and additional information then is available at the DIetaryGuidelines.gov.

So, in the next few slides, I'm just going to go through a brief overview of the information to be presented by the subcommittees, so you see the general format of how each of the subcommittee reports is structured.

So, throughout the presentations, you will see an analytic framework which defines the core elements of the diet and health relationship to be examined.

[0:18:02] So, you can see that analytic framework includes the intervention, exposure, and the comparators that will be used.

In some cases, we have intermediate outcomes. Obviously, we're very interested in the health outcomes when available for our review. Then, key factors that could impact the relationship, confounders, covariants, moderators are specified in the analytical framework, and also, key definitions are given.

So, each of the protocols also look at inclusion and exclusion criteria.

And so, you will hear discussion of those criteria in each of the systematic reviews. And these criteria are developed up front and are used to screen the articles that will be included or excluded from a review.

[0:18:59] So, there are a number of standard criteria that apply across the different reviews that the subcommittees have used consistently across the reviews.

And so, these include areas such as the study design, and I'm not going to read all of the inclusion/exclusion, because we have talked about these at each of the public meetings, and it's also available, completely available to you on the DietaryGuidelines.gov.

So, standard inclusion criteria include that study design, what kinds of studies are included, what are excluded, the publication status: peer-reviewed articles, the language of publication: English is what we've included, the country of origin of the country that's studied: very high or high human development so it's comparable to the US population and can be generalized to the US population, and then the study participants: we're primarily interested in studies in humans, males and females, and so, exclude animal or in vitro studies.

[0:20:10] In addition, the health status of study participants in included in our inclusion and exclusion criteria, and generally, you'll see that while we're obviously interested in participants who are healthy, we do also include participants who may be at risk for chronic disease, including those with obesity. And so, that concept applies.

What we're excluding are studies in which the participants had been diagnosed with a disease or hospitalized and that who are participants with the outcome of interest that we're looking at, and so, they're in a treatment study, or infants who were born preterm or low birth weight.

[0:21:01] So, that sets up what we include versus exclude in terms of health status.

Now, some of the criteria need to be tailored to the specific review, and those kind of tailored criteria might include diet-related interventions or an exposure of interest, health outcomes, the endpoint and/or an intermediate, whether or not that data are available, the date of publication, depending on what we already have from previous versions of the *Dietary Guidelines*, the work of other Advisory Committees, the size of the study groups, study duration, and the age of the study participants.

And so, those will be clearly specified in the protocols that are published.

So, in the NESR systematic reviews, what you will—because we're now moving into that phase where the subcommittees have been doing their work and they are presenting more than the protocols, they're moving into presenting their draft conclusions, you'll see a flowchart of the literature search and screening results, a description of the evidence that is being examined in depth by the subcommittee, the summary of the evidence synthesis, and some draft conclusion statements and grades for those particular questions.

[0:22:27] And I do want to highlight that what we're going to be presenting, just in the interest of time, are in fact summary statements. The committee's review includes a much more detailed discussion of the included articles, which will be provided in the committee's final report and supporting online materials.

The intent is to summarize the information today and tomorrow for discussion across the full committee.

[0:22:59] And again, a lot of what we're doing now, because it does involve a committee discussion, we're presenting things that are in their draft format so that it will only be finalized once we submit our report.

So, there will be data analysis questions that are presented today, and they include—they also follow a protocol and they include some similar elements, including the analytical framework, the analytical plan, the results, and then draft conclusion statements that the committee will be discussing today.

So, for both the NESR systematic reviews and the data analysis questions discussed today and tomorrow, conclusion statements, draft conclusion statements will be presented.

And so, that draft conclusion statement is an answer to the question of the evidence that is being reviewed.

[0:24:00] They have been drafted by the subcommittees and they're being brought to the full committee for discussion at these public meetings.

And again, these are considered draft until the committee submits its report to the Secretaries. So, they shouldn't be interpreted as the committee's final view or recommendations. It's—the committee is working toward its final decision.

So, I do want to note that after the conclusion statements are discussed by the committee at the public meetings, the systematic reviews will go through a peer review process, and that is being coordinated by USDA's Agricultural Research Service so that these reviews will be peer-review before the committee finalizes.

And we have, in fact, invited Dr. David Klurfield from ARS to provide remarks at the next meeting, the March meeting, on the process that is being used for the peer-review process.

[0:25:10] And we will then post the draft conclusion statements online after that peer review is completed. So, you'll be learning more about that as we move forward. And that is a new part of the DGAC process, so we're learning about it as we go.

So, subcommittee status. I just want to summarize so that you understand the full scope of the work. I can assure you that the subcommittees have been very busy and there's a lot of demand on in terms of time.

I also would note that I know everyone on this committee is fully appreciative of the excellent staff that has been working with us, keeping us on schedule, keeping us on track, and doing the tremendous amount of work that it takes to pull the evidence together so that the committee can do its evaluation.

[0:26:13] So, if we could go back to that slide please?

So, just the draft conclusions for approximately 30 questions will be presented at this meeting, including both NESR systematic reviews and data analysis evaluation. And so, across the subcommittees, NESR has screened over 265,000 articles and extracted data and assessed risk of bias for over 500 articles, and I can assure you, those numbers will only still grow as we keep moving forward.

We've been utilizing nearly 50 different types of data analysis from the NHANES What We Eat in America, we've begun to work on the food pattern modeling, and we've refined the report outline and are beginning to prepare some of the report content.

[0:27:08] So, the task at hand is large. There's a huge amount of work that has been done. We know that there's still a huge amount of work to be done. So, members and staff, members of the committee and the staff have been working to refine, streamline, and prioritize the remaining work so that we can meet the timeline.

So, in our meeting number four, the meeting that we're at, we'll describe the status and provide updates on the work of the committee.

As Dr. Stoody noted, there's an agenda available at DietaryGuidelines.gov.

So, just to make sure we—sort of make sure we connect with our YouTube participants, we'll be sure that the meeting begins at 9:00 am Central time and the afternoon session will begin at 1:00 pm Central time.

[0:28:04] Breaks, however, can't really be set at a specific time because of the nature of the reporting that we're doing, but we'll take breaks as they fit within the discussion framework.

So, for today's agenda, following the opening remarks, we'll start with the subcommittee updates, and the subcommittees we expect to hear from today are Birth to 24, Pregnancy and Lactation, Dietary Fats and Seafood, Beverages and Added Sugar, and the Data Analysis and Food Pattern Modeling, the cross-cutting working group.

And obviously, with each of those subcommittees, we anticipate there will be committee discussion.

So, for tomorrow's agenda, again, we'll start at 9:00 am, and the subcommittee updates that will be held tomorrow are the Dietary Patterns subcommittee, the Frequency of Eating, some committee discussion, and then, we've also scheduled public comments, which will take place in the afternoon, and we are looking forward to those public comments.

[0:29:12] So, and just to note that, yes, there's been a lot of interest in the DGAC work, the committee has received approximately 17,775 written public comments since the work began. If there's interest in commenting on the new protocols that are presented in today and tomorrow's public meetings, it's most useful to the committee if those comments on the protocols are received by Friday, February 7th.

And again, we've found the comments on protocols to be helpful, but for the committee to keep progressing with its work, we need them by February 7th.

[0:29:59] But as noted by Dr. Stoody, the written public comment period for more general comments is open until we complete our work in May of 2020.

So, with that, that concludes my comments, and I'll just turn to the committee members just to see if there's anything, a question or comment that any committee members want to make?

So, with that, I'm going to—Dr. Kleinman, you may have some comments as well, but I'll turn it over to you for the first subcommittee report.

Dr. Ronald Kleinman: Thanks, Barbara. I think that was very complete and I have very little to add. This is our 4th meeting together, so it's an opportunity for us all to hear what each of the subcommittees has been working on, and a great deal of work has taken place since the last meeting. So, the remainder of the day today and tomorrow will be these report-outs from each of the subcommittees.

[0:31:03] I think we'll go right into the first one now, and in terms of breaks, we recognize that there are some biological imperatives here. And so, we will try to take a brief break perhaps between the first and the second presentation.

So, with that, I'm going to turn this over to Kay Dewey and she—sorry, to—yeah, to Kay Dewey, to talk about the subcommittee that looked at Birth to 24 Months.

Dr. Kathryn Dewey: Thank you very much, Ron and Barbara. I am very pleased to be able to report to you today on behalf of this subcommittee, and the members of this subcommittee have been working very hard, many hours every week to get to this point.

We have a number of questions that have been addressed, and the NESR staff have been extremely busy screening the literature, preparing the results, extracting the data, and preparing evidence portfolios for us to review.

[0:32:08] And so, today, we will be presenting draft conclusions for the eight topics shown here. Although it's 8 topics, there are 66 conclusion statements for me to go through, and if I did read every single one of them in full, it would take more than an hour, so I'm going to try to go through them as quickly as I can while not skipping anything important.

Those include three question—topics on the relationship between human milk and infant formula, and three outcome areas: micronutrient status, atopic disease, and long-term health outcomes.

Then, there are five questions on complementary feeding and five outcome areas: atopic disease, developmental milestones, growth, size, and body composition, micronutrient status, and bone health.

[0:33:00] We still have work to do for five other topics that are listed here: two additional questions related to human milk and infant formula, and those relate to growth, size, and body composition and developmental milestones.

And then, the three new questions that we have on nutrients from supplements or fortified foods and three outcome domains: growth, size, and body composition, bone health, and micronutrient status.

These are some of the key definitions for our reviews, which we have presented previously, but to remind you of those, and the scope of the questions we're investigation, I wanted to go through them.

Human milk refers to mother's own milk. So, our reviews do not include examinations of donor milk.

And we've used the term human milk feeding instead of breast feeding to be clear that we have examined human milk fed at the breast as well as human milk that has been expressed and fed fresh or after refrigeration or freezing.

[0:34:07] Infant formula refers to commercially-prepared infant formulas that meet FDA or Codex Alimentarius standards. In practice, this has been a tricky definition to apply because there are a lot of studies that examine experimental infant formulas with ingredients such as dietary nucleotides or DHA prior to putting them on the market.

So, we have included this evidence if the formula has met the FDA or Codex standards. We did this because we thought it was important to examine infant formulas with ingredients that are commercially available.

And lastly, complementary foods and beverages refers to foods and beverages other than human milk or infant formula that includes liquids, semisolids, and solids, that are provided to an infant or young child to provide nutrients and energy.

[0:34:57] We want to thank the public for submitting comments on the work that was presented during meeting 3. We carefully reviewed and discussed all of those comments, and we would very much welcome public comments on what we present today, as Dr. Schneeman mentioned, by February 7th.

So, to begin, I will review some draft conclusions for the relationship between duration, frequency, and volume of exclusive human milk and/or infant formula consumption and micronutrient status.

This is the analytical framework that we developed, which shows the scope of this question, and we divided the duration, frequency, and volume of exclusive milk—human milk or infant formula into a series of four comparisons that align with the first feeding decisions that caregivers make.

And those include whether or not to feed human milk, and then for caregivers who do decide to do so, how long to feed human milk, so the duration of human milk consumption, and then how long to feed human milk exclusively.

[0:36:12] So, you'll note that we examined exclusive human milk consumption prior to the introduction of infant formula only, and that's to avoid overlap with another review, which we will also present today, that examines the timing of introduction of complementary foods and beverages.

And then, if caregivers have decided to supplement human milk with infant formula, our final comparison examines the intensity of proportion or amount of human milk that is fed to mixed-fed infants.

And then on the right, you can see that we examined iron, zinc, iodine, vitamins D and B12, and fatty acid status from birth to 24 months.

[0:36:57] This flowchart shows the literature review and screening results. We used two different literature searches, which are noted with the letters A and B in the flowchart.

Literature search A was from the Pregnancy and Birth to 24 Months Project, which used a search date range of January 1980 to March 2016. And this literature search was very large because it was intended to find studies for several questions related to human milk and infant formula.

Literature search B was smaller because it was intended to capture just the literature published in the last three years.

And you can see that, ultimately, 23 articles were identified that met the inclusion criteria for the question about feeding human milk and infant formula and micronutrient status outcomes.

On this slide, we want to give you a snapshot of the evidence by showing how many of those 23 studies provided evidence for each component of our analytical framework, and you can see that where there was evidence to address a topic, the number of studies was small.

[0:38:11] Now, a small number of studies may provide sufficient evidence to determine associations, for example, if the evidence is consistent has a low risk of bias. However, that was generally not the case in this body of evidence. You can also see that the majority of evidence addressed ever compared with never consuming human milk.

So, we'll go one by one through those comparisons.

This is the evidence related to ever versus never consuming human milk, and these were generally studies that compared infants who were fed human milk with infants who were fed an infant formula that had a novel composition at the time of the study, such as added DHA or different levels of iron, and infants who were fed a conventional infant formula.

[0:39:01] Now, as you can imagine, the evidence would show that the formula's composition can impact nutrient status outcomes, for example, formula with DHA can impact DHA status.

And this complicates our synthesis of the evidence because infants in these studies were fed a wide variety of infant formulas.

The 23 studies in this body of evidence generally studied healthy, full-term infants who were recruited at or close to birth and who were from the US and several other countries.

As I've already mentioned, the majority of evidence examines ever compared with never consuming human milk, and the duration of human milk consumption.

It's important to note that other components of the infants' diets varied between studies, and also, didn't tend to be well-reported.

[0:39:57] For example, the exclusivity of human milk, the types and amounts of formula fed in addition to human milk, the types and amounts of complementary foods and beverages in addition to human milk or infant formula, and any intake of supplements.

At the bottom of this slide, you can see the outcomes that were reported by the studies for each of these nutrients.

Now, there was evidence available from a small number of studies, and generally, they did not show consistent associations between the comparisons that are shown in this slide.

So, for ever compared with never consuming human milk, there were not consistent associations with anemia, hemoglobin, hematocrit, and the other indicators of iron status shown here, or with zinc status.

Also, that was true for the duration of any human milk consumption among infants fed human milk and anemia and markers of iron status, zinc status, vitamin D status, and fatty acid status.

[0:41:04] And lastly, the same was true for the duration of exclusive human milk consumption before the introduction of infant formula and fatty acid status.

The most substantial evidence that we reviewed was from 7 studies that examined the relationship between ever compared with never consuming human milk and fatty acid status, and these studies indicated that there may be an association between feeding human milk compared with infant formula and fatty acid status, and this body of evidence had an adequate number of sufficiently-powered studies with some inconsistencies that can likely be explained by methodological differences, for example, the use of formulas with different fatty acid composition.

There were several limitations that included the risk of bias, especially confounding the study directness, because these studies were mostly designed to examine the effects of infant formula composition rather than to directly compare infants fed human milk with those fed infant formula.

[0:42:12] And also, generalizability. For example, in two studies, there were no non-white participants, and other studies did not report race or ethnicity. Also, it's unclear whether the experimental formulas are similar to current formulas on the market in the US.

So, we did draft a conclusion statement regarding ever versus never consuming human milk, and this states that moderate evidence indicates that ever compared with never consuming human milk may be associated with fatty acid status.

The difference in fatty acid status between infants who are fed human milk and infant formula likely depends on the fatty acid composition of the human milk and the infant formula being compared.

[0:43:00] We found insufficient evidence available to determine the relationship between ever compared with never consuming human milk and iron and zinc status from birth to 24 months, and no evidence for the relationship between ever versus never consuming human milk and the other micronutrient status outcomes: iodine, vitamin B12, and vitamin D status.

Continuing on, with regard to duration of human milk feeding, insufficient evidence was available to examine this relationship for iron, zinc, vitamin D, and fatty acid status, and there was no evidence to determine that relationship for iodine and vitamin B12 status.

In addition, regarding duration of exclusive breast—human milk consumption, there was insufficient evidence for the relationship to fatty acid status and no evidence for the relationship to iron, zinc, iodine, vitamin B12, and vitamin D status.

[0:44:11] And finally, with regard to intensity, proportion, or amount of human milk in mixed-fed infants, there was no evidence to examine the relationship to iron, zinc, iodine, B12, vitamin D, or fatty acid status.

So next, we will review the draft conclusions for the relationship between duration of exclusive human milk or infant formula consumption and food allergies and atopic allergic diseases and long-term health outcomes.

Now, these questions have been answered with existing NESR systematic reviews, and our updated protocols, which are available at DietaryGuidelines.gov, describe that we will use these reviews as is because they were completed recently and capture over 35 years of evidence.

[0:45:06] The papers from those reviews were published in the American Journal of Clinical Nutrition in 2019.

However, we would like to ask the public to please submit public comments if you know of any articles published since 2016 that meet the inclusion criteria and would also significantly affect these conclusions.

The committee did carefully review the conclusion statements in the existing NESR systematic reviews, and we flagged those that we thought warranted an informal search to identify new evidence that has emerged since 2016, focusing on other published systematic reviews.

We did not locate any studies that would have modified the conclusions, but again, we do appreciate any comment that the public would like to provide.

[0:45:56] So, as I mentioned the committee will be answering these questions using the 9 existing NESR systematic reviews completed as part of the Pregnancy and Birth to 24 Months Project by the Infant Milk Feeding Practices Technical Expert Collaborative, and the link for the documentation is provided here.

We would like to sincerely acknowledge the work of this group of scientists who comprised this Technical Expert Collaborative and conducted these reviews with NESR.

For this set of reviews, the literature search was conducted between January 1980 and March 2016.

For never versus ever feeding human milk and atopic disease, 44 articles met the inclusion criteria, and you can see the distribution of the outcome that was examined. Almost all of this evidence was from observational studies.

[0:47:00] For duration of any human milk feeding and atopic disease, 35 articles met the criteria and almost all, again, of the evidence was from observational studies.

For duration of exclusive human milk feeding prior to the introduction of infant formula, only 1 article met the inclusion criteria.

This summarizes what was concluded regarding the relationship between never versus ever feeding human milk and these outcomes.

Firstly, moderate evidence suggests that never in comparison to ever being fed human milk is associated with a higher risk of childhood asthma.

Again, just to emphasize, these statements are worded so that the risk is related to never feeding human milk. And in this case, there were 17 independent studies contributing to that conclusion statement.

[0:48:00] For the second one, limited evidence does not suggest a relationship between never versus ever being fed human milk and atopic dermatitis in childhood.

For the other relationships, evidence about never versus ever being fed human milk and atopic dermatitis was inconclusive and there was insufficient evidence to examine how it related to the other outcomes that are listed here. Again, I'm not going to read every word. All of these statements are available in the published articles.

This shows the conclusion statements for the relationship between shorter versus longer duration of any human milk feeding and these outcomes.

Moderate evidence, mostly from observational studies, suggests that among infants fed human milk, a shorter versus a longer duration of any human milk feeding is associated with a higher risk of asthma in childhood and adolescence.

[0:49:04] This included 20 independent studies.

Limited evidence does not suggest a relationship between duration of any human milk feeding and allergic rhinitis or atopic dermatitis in childhood.

Evidence about the relationship between shorter or longer duration of human milk feeding and atopic dermatitis from birth to 24 months is inconclusive and there is insufficient evidence to determine the relationship with the other outcomes in this set, as shown here.

In terms of the shorter or longer duration of exclusive human milk feeding before introduction of infant formula, there is insufficient evidence to examine this relationship to all of the outcomes that were examined.

[0:49:57] Moving on then to the long-term outcomes, this shows the evidence that was available to examine those.

First, with regard to never versus ever feeding human milk and cardiovascular disease outcomes, there were 13 articles that met the inclusion criteria and you can see the types of outcomes that these studies examined.

For duration of any human milk feeding, there were 24 articles.

And for duration of exclusive human milk feeding and cardiovascular disease outcomes, there were 6 articles included.

So, I'll go through those conclusion statements as well.

For never versus ever feeding human milk, limited evidence suggests that never versus ever being fed human milk is associated with higher blood pressure within a normal range at 6-7 years of age.

[0:51:04] The evidence about the relationship of never versus ever being fed human milk with blood lipids in childhood was inconclusive, and there was insufficient evidence for the relationship to the other CVD outcomes examined.

In terms of shorter versus longer duration of any human milk feeding, moderate evidence suggests that there is no association between the duration of any human milk feeding and blood pressure in childhood.

And I wanted to call out one study here that was quite important. There was compelling evidence from the Promotion of Breastfeeding intervention trial.

That is the only randomized trial in this body of evidence, and it showed no significant relationship between duration of any human milk feeding and blood pressure at 6 ½ or 11 ½ years of age.

[0:52:02] There was also inconsistent evidence across 6 independent prospective cohort studies.

For the second bullet here, the evidence about the relationship of shorter versus longer duration of human milk with blood lipids in childhood and adulthood and with

metabolic syndrome was inconclusive and there was insufficient evidence to determine the relationship to the other CBD outcomes.

Continuing on with shorter versus longer duration, limited evidence suggests that there is no association between the duration of exclusive human milk feeding and blood pressure in childhood or metabolic syndrome at 11.5 years of age, and most of this evidence comes from this one non-US sample that was assessed using a very strong study design.

[0:52:58] And there was insufficient evidence to determine the relationship of the duration of exclusive human milk feeding with the other endpoint CVD outcomes.

The other long-term outcome examined was diabetes, and in this case, there were 21 articles that met the inclusion criteria for the comparison of never versus ever feeding human milk, and you can see that most of those were with regard to type 1 diabetes.

For duration of any human milk feeding and diabetes, 37 articles met the criteria, and 30 were focused on type 1 diabetes.

For duration of exclusive human milk feeding, there were 18 articles that met the criteria, again, 17 about type 1 diabetes.

So, this summarizes what was concluded about never versus ever feeding human milk.

[0:54:02] Limited evidence from observational studies suggests that never versus ever being fed human milk is associated with a higher risk of type 1 diabetes.

There's insufficient evidence to determine whether or not there is a relationship between never versus ever feeding human milk and type 2 diabetes, pre-diabetes, and the other outcomes shown here.

In terms of the duration of human milk feeding, moderate evidence from observational studies suggests that among infants fed some amount of human milk, a shorter versus a longer duration of human milk feeding is associated with a higher risk of type 1 diabetes.

Limited but consistent evidence suggests that the duration of any human milk feeding is not associated with fasting glucose or insulin resistance in childhood or during the transition from childhood into adolescence.

[0:55:01] And there's insufficient evidence for the relationship to type 2 diabetes, pre-diabetes, or the other outcomes shown here.

And then, in terms of shorter versus longer duration of exclusive human milk feeding, limited evidence from observational studies suggests that a shorter duration is associated with a higher risk of type 1 diabetes.

Limited evidence from a single study that used a strong design also suggests that the duration of exclusive human milk feeding is not associated with fasting glucose or insulin resistance at 11.5 years of age.

And there is insufficient evidence to determine the relationship with type 2 diabetes, pre-diabetes, and the other outcomes shown here.

[0:55:58] Moving on, next we'll review the draft conclusions for the relationship between complementary feeding and the five outcome domains that are listed here: micronutrient status, growth, size, and body composition, developmental milestones, including neurocognitive development, food allergies and atopic allergic diseases, and bone health.

These have also been answered with existing NESR systematic reviews and the protocols, again, are at DIetaryGuidelines.gov.

And we will be using these reviews as is, again, because they were completed recently and capture over 35 years of evidence.

These papers were also published in the American Journal of Clinical Nutrition in 2019.

However, as mentioned previously, we would like to ask the public to please submit public comments if you know of any articles published since 2016 that meet the inclusion criteria and would significantly affect the conclusions that I will be presenting.

[0:57:01] So, the committee will be answering these questions using 10 existing NESR systematic reviews completed as part of the Pregnancy and Birth to 24 Months Project by the Complementary Feeding Technical Expert Collaborative, and this gives the link for the complete documentation of that work.

Again, we would like to acknowledge the work of this group of scientists who comprised the Complementary Feeding Tech, who conducted these reviews with NESR.

This literature search spanned from January 1980 to July 2016.

For complementary foods and beverages, they were divided into two overarching types of questions: the timing of introduction to complementary foods and beverages and the types and amounts.

[0:57:59] So, for this first set of outcomes, which are micronutrient status, there were 9 studies that met the criteria for the timing of introduction.

Most of these examined iron status. A few examined zinc, vitamin D, vitamin B12, folate, and/or fatty acid status.

For the types and amounts of complementary foods and beverages, 31 articles met the criteria. Most examined iron-fortified cereals and meats, with respect to iron status, several

examined zinc and fatty acid status, and very few studies examined vitamin D, vitamin B12, and folate status.

So, I'll begin with the relationship between the timing of introduction of complementary foods and beverages and micronutrient status.

Moderate evidence suggests that introducing complementary foods and beverages at 4 months of age compared to 6 months of age offers no long-term advantages or disadvantages in terms of iron status among healthy full-term infants who are breast-fed, fed iron-fortified formula, or both.

[0:59:10] And there were 9 studies that met the criteria for this question.

There is not enough evidence to determine the relationship between timing of introduction and zinc, vitamin D, vitamin B12, folate, or fatty acid status.

Additional factors that need to be considered in examining the relationship between the age at which complementary foods and beverages are introduced and micronutrient status include birth weight and timing of umbilical cord clamping, both of which affect iron stores of the newborn, post-natal growth, type of feeding, at the breast or formula or mixed feeding, and intake and absorption of iron from sources other than human milk, including the types and amounts of complementary foods and beverages being consumed.

[1:00:01] This summarizes the conclusions for the types and amounts of complementary foods and micronutrient status. 31 studies met the inclusion criteria for this review.

And strong evidence suggests that consuming complementary foods and beverages that contain substantial amounts of iron, such as meats or iron-fortified cereal, helps maintain adequate iron status or prevent iron deficiency during the first year of life among infants with insufficient iron stores or breast-fed infants who are not receiving adequate iron from another source.

However, the benefit of these types of complementary foods and beverages for infants with sufficient iron stores, such as those consuming iron-fortified infant formula, is less evident.

There's not enough evidence to determine the relationship between other types and amounts of complementary foods and beverages containing lesser amounts of iron, such as fruits and vegetables, and iron status.

[1:01:05] Then, in terms of the other nutrients of interest, limited evidence suggests that consuming complementary foods and beverages that contain substantial amounts of zinc, such as meats or cereals fortified with zinc, support zinc status during the first year of life, particularly among breast-fed infants who are not receiving adequate zinc from another source.

However, the benefit of these types of complementary foods for infants consuming fortified infant formula is less evident.

Moderate evidence suggests that consuming complementary foods and beverages with differing fatty acid profiles, particularly long-chain polyunsaturated fatty acids, can influence fatty acid status.

Continuing on this theme, during the second year of life, good sources of micronutrients are still needed, but there is limited evidence to indicate which types and amounts of complementary foods and beverages are associated with adequate micronutrient status.

[1:02:10] And there's not enough evidence to determine the relationship between the types and amounts of complementary foods and beverages and vitamin B12, vitamin D, or folate status.

Now, I'm going to move on to the next outcome domain, and that is food allergies and atopic allergic diseases.

For the timing of introduction of complementary foods and beverages, 31 studies met the inclusion criteria, and most of them examined food allergies.

For types and amounts of complementary foods and beverages, 39 met the criteria, and most examined the most common allergenic foods.

This has to do with the timing of introduction of complementary foods and beverages.

[1:03:01] Moderate evidence suggests that there is no relationship between the age at which complementary feeding first begins and the risk of developing food allergy, atopic dermatitis, or eczema, or asthma during childhood.

There's insufficient evidence to determine the relationship between age at which complementary foods or beverages are first introduced and risk of developing allergic rhinitis during childhood.

Now, the rest of this series of slides focuses on the specific types of complementary foods being introduced. And so, these are divided into several different slides.

I wanted to mention that the studies are mostly focused on food allergy to that particular food component, and in this case, we will be talking about peanut, tree nuts, and sesame seeds.

[1:04:09] There is strong evidence to suggest that introducing peanut in the first year of life, after 4 months of age, may reduce the risk of food allergy to peanuts, and this evidence is strongest for introducing peanut in infants at the highest risk, with severe atopic dermatitis and/or egg allergy, to prevent peanut allergy, but is also applicable to infants at lower risk.

However, the evidence for tree nuts and sesame seeds is limited.

Limited evidence also suggests that there is no relationship between consumption of peanut, tree nuts, or sesame seeds during the complementary feeding period and risk of atopic dermatitis or eczema and asthma.

And there's not enough evidence to determine if there is relationship between consuming peanut, tree nuts, or seeds and allergic rhinitis.

[1:05:03] What I want to also mention is that many of the studies included in this review exclusively enrolled or primarily enrolled subjects who were at a greater risk of allergies and/or atopic disease than the general population on the basis of family history. However, despite this, the reviewers concluded that the results are probably generalizable to infants and toddlers who are at lower risk for atopic disease, although the magnitude of the associations may be smaller.

There were 28 studies that examined the consumption of eggs as a complementary food in relationship to the risk of developing any atopic disease, including 6 randomized controlled trials.

From that body of evidence, it was concluded that moderate evidence suggests that introducing egg in the first year of life, after 4 months of age, may reduce the risk of food allergy to egg.

[1:06:06] Limited evidence suggests that there is no relationship between the age of introduction to egg and the risk of atopic dermatitis or eczema and asthma.

And there's not enough evidence to determine the relationship between egg and allergic rhinitis.

For fish, 24 studies examined fish as a complementary food, including 1 randomized controlled trial.

From this body of evidence, there is limited evidence that suggests that introducing fish in the first year of life, after 4 months of age, may reduce the risk of atopic dermatitis and eczema.

And there is not enough evidence to determine this relationship to the risk of allergy to fish or other foods, asthma, or allergic rhinitis, and also, not enough evidence for the relationship to the risk of food allergy, atopic dermatitis, eczema, asthma, or allergic rhinitis.

[1:07:05] There were 17 studies that examined the consumption of wheat or cereals and these outcomes, and all of these were observational studies.

So, limited evidence suggests that there is no relationship between the age of introduction of cow's milk products, such as cheese and yogurt, and the risk of food allergy and atopic dermatitis and eczema.

There is not enough evidence to determine if there's a relationship between consuming milk products during the complementary feeding period and the risk of asthma or allergic rhinitis.

Did I skip something?

[inaudible sidebar conversation 1:07:51-1:08:18]

There are a lot of outcomes here. So, sorry, I'm going to go back to wheat and soy, and I did mention there were 17 studies that examined the consumption of wheat or cereals, and these were all observational.

And there's not enough evidence for those related to wheat to determine the relationship to risk of food allergy, atopic dermatitis and eczema, asthma, or allergic rhinitis.

For soy, there were 4 prospective studies that examined this relationship, and that indicated that there was not enough evidence to determine if there is a relationship between soybean consumption and the risk of any of these outcomes.

[1:09:03] Okay, I think I will move on. Okay.

There were several observational studies that also examined the relationship between other types of complementary foods and beverages that are generally not considered to be major allergens, for example, fruit, vegetables, and meats, and this conclusion was that there was limited evidence from observational studies that suggests that introducing foods not commonly considered to be allergens in the first year of life, after 4 months of age, is not associated with risk of food allergy, atopic dermatitis, or eczema, asthma, or allergic rhinitis.

There were also several observational studies that examined dietary diversity or dietary patterns, and these were 11 prospective cohort studies, and 3 case-controlled studies.

[1:10:06] But there was not enough evidence to determine a relationship between these aspects of the diet and any of these outcomes.

Okay, moving on to the next set of outcomes, which is growth, size, and body composition, there were 81 studies that met the inclusion criteria for the timing of introduction of complementary foods and beverages, and 49 that met the criteria for types and amounts.

So, in terms of timing of introduction, moderate evidence suggests that the first introduction of any complementary food or beverage between 4-5 months compared to approximately 6 months of age is not associated with weight status, body composition, body circumferences, weight, or length among generally healthy full-term infants.

[1:11:03] Limited evidence suggests that introducing complementary foods and beverages before 4 months of age may be associated with higher odds of overweight and obesity.

And there's not enough evidence to determine the relationship between introduction of complementary foods and beverages at 7 months or later on growth, size, or body composition.

In terms of types and amounts of complementary foods, moderate evidence indicates that a higher versus lower meat intake, or meat versus iron-fortified cereal intake over a shorter duration during the complementary feeding period does not favorably or unfavorably influence growth, size, and/or body composition.

And there's insufficient evidence to determine a relationship between meat intake and prevalence or incidence of overweight or obesity.

[1:11:59] Limited evidence suggests that the type or amount of cereal given does not favorably or unfavorably affect these outcomes.

In terms of fatty acids, moderate evidence suggests that consumption of complementary foods with different fats and/or fatty acid composition does not favorably or unfavorably influence growth, size, or body composition.

And there's not enough evidence to determine the relationship to the prevalence or incidence of overweight or obesity.

Limited evidence suggests that sugar-sweetened beverage consumption during the complementary feeding period is associated with increased risk of obesity in childhood, but is not associated with other measures of growth, size, and body composition.

There is limited evidence that showed a positive association between juice intake and infant weight for length and child BMI z-scores.

[1:12:59] No conclusion could be made about the relationship between other complementary foods as listed here, and growth, size, body composition, or overweight or obesity, and also, no conclusion could be made about the relationship between distinct dietary patterns during the complementary feeding period and growth, size, body composition, or these other outcomes.

There is a much smaller body of evidence regarding developmental outcomes, so for the timing of introduction of complementary foods and beverages, only 3 studies met the criteria, and for types and amounts, only 8 studies met those criteria.

So, not surprisingly, given that small evidence base, there was insufficient evidence to draw conclusions about the relationship between the timing of introduction of complementary foods and beverages and developmental milestones.

[1:13:57] One of the issues with this body of evidence is that there is the potential for reverse causation. In other words, the child might be more developed, and therefore, be more demanding of introduction of other foods and beverages.

And so, with observational studies, it's very difficult to study this relationship.

There was also insufficient evidence to draw a conclusion about the relationships between the types and amounts of complementary foods and beverages consumed and developmental milestones.

There was also a very small evidence base in terms of bone health. 3 studies met the criteria for timing of introduction of complementary foods and beverages, and 8 met the criteria for types and amounts.

So again, not surprisingly, the conclusion was that there was insufficient evidence to draw conclusions about the relationship of timing of introduction of complementary foods and beverages and bone health.

[1:15:02] And similarly, insufficient evidence was available between the types and amounts of complementary foods and beverages and bone health.

Okay, so those are the 66 conclusion statements that we had to get through today, and now, I'm going to present some of the discussions that we've had related to refining and prioritizing the remaining work in front of us.

So, as I mentioned, we have two questions regarding human milk and infant formula and outcome domains including growth, size, and body composition.

So, for this one, it's a very, very large literature, and for this purpose, we decided to examine outcomes related to body composition only, which includes obesity and overweight.

[1:15:57] Our rationale for this is that we already know that growth curves differ between infants fed human milk and those fed infant formula.

In fact, the US government convened an expert panel several years ago to review such evidence, and as a result, the CDC adopted the World Health Organization Growth Curves from birth to age 2 years, which reflect the growth of breast-fed children.

On the other hand, the relationship between human milk or infant formula consumption and body composition outcomes including obesity warrants further examination, and for that reason, we have altered the protocol for this, which is going to be available on DietaryGuidelines.gov.

We also discussed the remaining questions that examine intake of nutrients from supplements and fortified foods, and for this, we decided to prioritize, for the first question related to growth, size, and body composition, to focus only on iron, and iron from supplements.

[1:17:07] For the second one, related to bone health, we decided to focus only on vitamin D, and again, only from supplements.

And for the third question, related to nutrient status, we decided to focus on iron and vitamin D from supplements only.

Our rationale for limiting these reviews to the nutrients from supplements is that the existing reviews from the previous project, which I just reviewed with you today, examine complementary foods and beverages and included fortified foods. So, we feel that the real need for new work here is on these nutrients from supplements.

Our rationale for examining iron and vitamin D only is that we would like to review evidence about nutrient supplements that are currently recommended for this age group.

So, that is where we will be moving forward as we continue the work.

[1:18:02] So, our next steps are summarized here.

There will be a literature search on iron and vitamin D from supplements and nutrient status.

There will be screening of the literature also for iron and vitamin D from supplements. Oh, that will include the screening of the literature as well as vitamin D from supplements and bone health.

We will them have to extract the data, assess risk of bias, and develop conclusions and grades for the five questions that are listed here. And again, those relate to human milk and infant formula consumption, growth, size, and body composition, and developmental outcomes, and then the specific nutrients from supplements, and the three outcome areas that I mentioned.

And then lastly, we will be drafting—going through the peer-review process and drafting the report.

[1:18:59] And with that, I would like to, again, thank the members of the subcommittee and very much thank and acknowledge the very hard and extensive work by our support staff, who are listed on this slide.

Thank you very much.

Dr. Ronald Kleinman: Thank you, Kay.

[Applause]

Dr. Ronald Kleinman: For an incredibly complete summary of the work of the subcommittee.

So, we've already had some cross-cutting conversations between a few of the subcommittees, but this is our opportunity now, as a full committee, to ask any further questions or to comment on what Kay has presented. So, I'll open it up to the committee now for questions.

Rick?

Dr. Richard Mattes: Thank you very much.

Dr. Ronald Kleinman: And, don't forget to say your name when you—

Dr. Richard Mattes: Oh, Rick Mattes. So, I have five questions, but a lot of them will be really short, I think, responses.

[1:19:59] The first is you used the term intensity of feeding, and I'm just not clear on what intensity means. So, clarification, that would be helpful.

Your recommendation regarding fat intake and fatty acid status just referred to association, whereas all the other recommendations, that directionality to them, if it's possible to tweak that, I think it would be more useful. If it's not, it's not.

In the report on never versus ever and risk of type 1 diabetes, you found an association there. This is my lack of knowledge, is there plausibility of that? Is there a mechanism that would make that make sense?

With the peanut recommendation, again, I'm old-school.

[1:20:58] Is there some subset of people that may actually be at risk, so a general recommendation saying early introduction is okay holds risk for some subgroup of the population, or it really is a clear bill of health for such a recommendation?

Dr. Kathryn Dewey: Can you repeat that again?

Dr. Richard Mattes: So, the recommendation for early exposure to peanut seemed to be just generally positive, and I'm just wondering if there is a subgroup of individuals that might be at risk. Because if people just look at that recommendation, they think it's good to go, but maybe, there are some that would be at risk. I don't know.

Dr. Kathryn Dewey: Okay.

Dr. Richard Mattes: And lastly, for the sugar recommendation, it says that sugar-sweetened beverage consumption during complementary feeding is associated with increased obesity, but not associated with body composition. I'm just not clear how to juxtapose those.

[1:22:03] ***Dr. Kathryn Dewey:*** So, those are very good questions, and I'm going to rely on others in the room to help with some of the answers.

For the intensity of breastfeeding, this is part of three different aspects of when children are fed both infant formula and human milk. It relates to how many of the feeds are human milk versus formula, or the amounts, or in some other way judging the proportion. So, the intensity refers to how much of that is human milk. It's a guestimate in most cases because they're not measuring human milk intake. So, that's why different words are used by different researchers.

Is there any—if anybody wants to add anything from the staff, who knows these definitions by heart?

Yes, please, Darcy.

Darcy: [indiscernible 1:33:08] Just one clarification, which is that intensity to composure and amount, we included any evidence that was examined either at a single point in time or over a duration of time, and that might have included another variable in the definitions, such as months or years, that sort of thing.

[1:23:16] Dr. Richard Mattes: So, in any writeup, that will be defined somewhere?

Dr. Kathryn Dewey: In the paper that was published, that is given, yes.

And then, in terms of fat composition of complementary foods, and that we said there is an association without the direction, and that was on purpose because it really depends on what fatty acids are in those foods.

So, if there is an increased amount of polyunsaturated fatty acids, for example, that will generally show up in the fatty acid status as a positive relationship in the child. But it's not simple to summarize that in the conclusion statement.

[1:24:00] So, in the paper that was published, it goes through exactly what all those relationships were.

We can talk further about whether there's some way to modify that, but for that question, we're relying on the existing review that's been published already, and that's their exact wording.

Dr. Richard Mattes: So, it is possible for it to be inverse in some instances? Or could it just be stated as a direct relationship?

Dr. Kathryn Dewey: Well, I would have to read again exactly which studies that—there's always theoretically the possibility that if you increase intake of omega-6, you might reduce omega-3 status, or vice—I mean so that's why I don't want to get too specific about it right now.

Dr. Sharon Donovan: Yeah, and I think in some of the ever versus never types of questions, because the composition of breast milk fatty acids differ from formula, because

the breastfeeding mom's maternal diet and the formulas are added oils. So, I think in some cases, they're higher, and some cases, they're lower.

[1:25:02] So, rather than a conclusion statement that was three paragraphs long to go through each of them, it was basically a general statement of there's associations between dietary intake and the outcome.

Dr. Kathryn Dewey: So, I thought you were referring to fatty acids from complementary foods and beverages, but were you also referring to the never versus ever human milk and those questions?

Dr. Richard Mattes: I'm not sure where it—where my brain ticked off as you were going through, but for either of them, I'm—

Dr. Kathryn Dewey: Okay, yeah. So, there were two different questions where fatty acid status was an outcome. One was from complementary foods and beverages. That's what I was answering.

For human milk ever versus never, duration, etcetera, we also shied away, as Sharon explained, from stating a direction because it's, as we were talking yesterday in our subcommittee meeting, it's complicated because of the composition of human milk, and the possibility that the mammary gland has endogenous synthesis of many of these fatty acids.

[1:26:05] And so, it's something that we will describe in more detail in the writeup.

And then, you asked about never versus ever breastfeeding and type 1 diabetes and the plausibility of that argument.

Yes, there is a biological rationale for that. I'm not sure I'm ready to explain it thoroughly here, but it relates to the components that are in human milk and their relationship to development of physiological function, immune status, and reaction to antigens.

If anyone else wants to go further than that, be my guest.

Dr. Ronald Kleinman: I think that's absolutely fair summary.

But one of the things that I think is a little bit confusing is the absence of any relationship to pre-diabetes.

[1:27:03] ***Dr. Kathryn Dewey:*** Type 2.

Dr. Ronald Kleinman: Yeah. But you'd expect that those same markers would be present in type 1 in advance of that disease expressing itself.

So, we might want to pay a little bit more attention to that as we put this together. Because you'd expect insulin resistance, glucose intolerance, A1Cs. They don't—they rise

gradually both in type 1 and in type 2. So, just the point of for further discussion in the statement.

Dr. Kathryn Dewey: That's a great idea. I think we will take that up.

And then, your fourth question was regarding peanut exposure in the first year of life, and I think the question was are there infants who are at risk from that exposure because they are at high risk to begin with?

[1:28:01] Now, I am, again, going to defer, I think, to the clinicians, but my understanding is that those with a family history are usually advised to be under the sort of supervision of a healthcare provider when they first introduce that allergen, to be careful about that.

So, do you want to go further than that?

Dr. Ronald Kleinman: No, I think that's absolutely right. And the studies use test—use individuals, infants, who have strong family history. So, these are the highest-risk infants. So, presumably, if they pass this test, everyone else who's at lesser risk isn't going to be put at greater risk as a result of the introduction. So, that—is that your question?

Dr. Richard Mattes: Yeah, that's exactly my question. So, the follow-up is does the recommendation need to have that caveat in it, or does that group of high-risk people sort of fall out of the definition of the healthy population that we're making recommendations for, and so it's not necessary?

[1:29:05] ***Dr. Kathryn Dewey:*** Well, I'd like to say we're not yet at the point of making dietary recommendations. Right now, we're only drafting conclusion statements from the evidence. How to put all of those together into a recommendation is the next challenge.

Yeah, there was one more question from Rick, and that had to do with sugar-sweetened beverages and why were those related to overweight or obesity and not to the continuous markers of body size or composition.

I think that the strongest evidence we have is from one very large study where the outcomes were dichotomous only.

And so, that's why we felt comfortable saying that. We didn't have the same amount or strength of evidence for the direct continuous measures of weight for height, or BMI, or anything like that.

[1:30:03] That's my recollection. I'd have to go back to that paper and look at it again, but that was what I remember.

Additions to that?

Dr. Elizabeth Meyer-Davis: So, is this on? Don't pick it up? Okay. Just start talking? Alright, I can start talking. Okay.

So, back to the—so, this is Beth Meyer-Davis. So, Kay, I have a question, a follow-up really to Rick's about type 1 diabetes. It's not specified in the question itself. But I wonder if, in your look at infant feeding with regard to type 1 diabetes, you were looking also at occurrence or appearance of diabetes autoimmunity?

Dr. Kathryn Dewey: What was that?

Dr. Elizabeth Meyer-Davis: The appearance of diabetes autoimmunity, markers of diabetes autoantibodies as a prelude to development of type 1 diabetes.

Because that's where some of the mechanism comes in, in answer to your question, Rick, and there is some literature on that.

[1:30:03] Dr. Kathryn Dewey: So, Darcy—oh, Darcy's quicker than me. I'm looking here. You're shaking your head, so those markers were not—

Darcy: [indiscernible 1:41:30]

Dr. Kathryn Dewey: Okay, so it was only the other ones that we defined, yeah. And again, that—this was done by the previous Birth to 24 tech, and all of those definitions of outcomes are in those published papers.

Dr. Ronald Kleinman: Joan?

Dr. Joan Sabate: Yes, Joan Sabate. Regarding the timing, regarding the types of foods and the outcomes that you have examined, basically anthropometrics, biology code, measures of fatty acids and minerals, so on and so forth.

And also allergy, what was the outcome measured on these studies, I mean within the period of 24 months?

[1:32:03] During childhood? In adolescence? Or in adulthood? Or all of this above?

Dr. Kathryn Dewey: The age of outcome assessment, if I'm correct, varied depending on the outcome domain. So, if I remember correctly, micronutrient status was generally the more short-term, within the first 2 years of life. I'm looking at Julie. She remembers. Growth, size, and body composition went up to—was it 18 or adulthood? Development went I think as far as was available. Atopic and allergic disease went all the way to adulthood? Is that right? Went to 18. And bone health? 18.

So, most of them went pretty long-term. But the evidence base may or may not have been very strong out of those longer-term time points.

[1:33:00] Dr. Ronald Kleinman: Are there other questions?

Dr. Barbara Schneeman: So, given the number of conclusion statements where you've had to say insufficient evidence or no evidence, I'm interested to know, is the subcommittee working on a research agenda, and particularly prioritizing some of the most critical needs as far as research?

Dr. Kathryn Dewey: Yeah, we are trying to keep track of research recommendations as we go. From the previous reviews that have been published, they also did a good job of summarizing the research needs. So, that's kind of already there.

It's going to be a huge list, as you can imagine. So, prioritizing them is something that I feel we need to discuss.

In the context of dietary guidelines, it might revolve around not necessarily what are the most interesting questions, but which ones might have the biggest influence on what we advise people to do?

[1:34:03] So, if there's already compelling evidence from outcomes x, y, and z for, let's say breastfeeding, well, do we need to go further then and find outcomes, other outcomes to add to that or not?

Whereas, for some of the other dietary recommendations for this age group, there's almost nothing, and in those cases, we don't—we may not know what to say at all. And so, in that case, it might be a higher priority.

So, I'm just thinking out loud, actually, about how would you prioritize in this particular situation?

Dr. Ronald Kleinman: Alright. So, I think adults need to have a little break, and we've been going for over an hour and a half.

So, we're going to take exactly 10 minutes to stand up and stretch or do whatever else you need to do, and then we'll return and hear from Sharon Donovan and the Pregnancy and Lactation subcommittee report. Thank you.

[1:35:05] So, 10:48.

[Break 1:35:08-1:47:44]

Dr. Barbara Schneeman: So, I think we'd like to get started again, so Eve has an announcement to start. Great. So, Dr. Stoody has an announcement before we start.

[1:48:01] ***Dr. Eve Stoody:*** Great, thank you. If you'll go ahead and take your seats.

We will start in a minute.

Alright, so thank you. Thanks for joining us again after the break.

I do want to just make a quick announcement. We are in a multi-story building, and sometimes, fire alarms do happen. So, if you hear one, please hold tight. We are told, if we are asked to evacuate, we'll hear an announcement.

[1:49:00] Sometimes, they just evacuate the floor that's involved and the floor above and below. So, if that is to happen, we'll hear an announcement, and the exit is just right there at the top of the stairs.

And thank y'all. I know several have—that is the preferred kind of in and out for the meeting, if you can make that happen, just to kind of help minimize some of the distraction here at the front of the room.

So, just a quick announcement, and I'll turn it back over to the committee.

Dr. Ronald Kleinman: Thank you very much, Eve. So, I'm going to turn it over now to Sharon Donovan, and she's going to summarize the work of the Pregnancy and Lactation subcommittee.

Dr. Sharon Donovan: Okay, the microphone's on.

So, my name is Sharon Donovan, and it's my pleasure to present on behalf of the Pregnancy and Lactation subcommittee.

So, if I can have slides, please?

Dr. Ronald Kleinman: No, all from memory.

[1:49:58] We need to have the slides brought up, please.

Dr. Sharon Donovan: So, I'll go ahead and start talking while that's coming up.

Dr. Ronald Kleinman: There you go.

Dr. Sharon Donovan: So, this shows the subcommittee members, and I'd like to thank them all for all of their hard work on our weekly calls, and the work between the calls.

So, my goal today will be discuss the evidence synthesis, grading, and conclusion for eight reviews, but before we get started, I wanted to just provide just an overview to remind people of the questions that were assigned to our subcommittee.

So, there were three major categories.

One—the first was nutrients from supplements and fortified foods, and this could be consumed before and during pregnancy and lactation.

[1:51:00] So, we looked at up to six months prior to conception, during pregnancy, and/or lactation.

We are examining six nutrients, so B12, folate, iron, iodine, vitamin D, and omega-3s. They should sound fairly familiar from Kay's presentation.

And five outcomes, so human milk composition, gestational diabetes, hypertensive disorders of pregnancy, neurocognitive development of the infant, and micronutrient status of the mother.

So, that was our first set of questions.

The second relate to dietary patterns during pregnancy, and with five outcomes. I'm not going to read all of those, but you can see these are related to the maternal dietary pattern during pregnancy, and three outcomes during lactation, so milk composition, infant neurocognitive development, and postpartum weight loss.

We also had a third area, which was maternal diet and food allergies and atopic diseases in the infant.

[1:52:03] So, as noted, the NESR staff has been working very diligently, and thus far, has screened 21,500 articles and extracted data and assessed risk of bias from 42, and obviously, additional searches and extraction are underway.

So again, just within each of these three areas, just to briefly remind you of where we are in the process.

So, for folate, we have addressed all five questions. And so, the effect of maternal folate from supplements or fortified foods on human milk composition and gestational diabetes was presented in meeting 3, and that information's available on the DietaryGuidelines.gov.

Today, I will be presenting on maternal folate from supplements and fortified foods on hypertensive disorders of pregnancy, neurocognitive development of the infant, and micronutrient status of the mother.

[1:53:05] As noted, the—our committee is currently in the process of refining and prioritizing the additional searches for these rest of the nutrients and these outcomes. So, you can just do the math to see this would have been quite a number of systematic reviews to address all of these.

So, in terms of dietary patterns, today I'll be presenting a new systematic review on the impact of dietary patterns on human milk composition, and as with the B-24 Project, there were four previous NESR systematic reviews that were developed as part of the Pregnancy and Birth to 24 Project.

So, we examined those, as Kay described. We looked—we went through each of the statements.

[1:53:57] *We* also looked at any papers that had been published since January of 2017, which was the end of these reviews to see whether any primary research, and we also looked at existing systematic reviews published since that time to see whether they caught any papers, mainly with an eye to "Has there anything really been published in the last two years that would impact the conclusions made in those systematic reviews?"

And as with B-24, we've decided to accept those existing reviews, NESR reviews, and so, we view those outcomes.

Currently, we're looking at the dietary patterns on gestational weight gain, postpartum weight loss, micronutrient status and infant neurocognitive development, and the plan is to present those at meeting five.

Also underway is the question on maternal diet and food allergies and atopic diseases, which will also be presented in March.

[1:55:00] So, jumping in to our first—our folic acid questions. So, "What is the relationship between folic acid supplements and/or fortified foods consumed before and during pregnancy on the risk of hypertensive disorders?"

So, just as a reminder, the definitions that we've used for dietary supplements, basically from the Dietary Supplement and Health Education Act. So, products other than tobacco that is intended to supplement the diet.

And fortification, again, the FDA definition of deliberate addition of one or more essential nutrients.

So, briefly, you've seen the layout for the analytical framework.

So, in terms of folic acid, our interventions and exposures were exposure to including intake of folic acid from supplements, fortified foods, or the combination, and the comparators were a different level of exposure, including no exposure from supplements, fortified foods, or the combination.

[1:56:15] In this case, the population was the women before and during pregnancy, either healthy or at risk for chronic diseases, and in this case, hypertensive disorders of pregnancy.

We had intermediate outcomes that we examined, including blood pressure and proteinuria. And then, we had the longer-term outcomes of eclampsia, preeclampsia, and gestational hypertension.

Summarized at the bottom are the key confounders, and most of those are ones that we're including in all of our systematic reviews.

We also have other factors to continue—consider for the hypertension—hypertensive disorders, which include physical activity and substance abuse and gestational age.

[1:57:03] So, this search was done in combination—I'm sorry, not this one. This search was—actually it was. I'm sorry. So, this was done in combination with the search for folic acid and hypertension and gestational diabetes, and as I mentioned, gestational diabetes was presented at the last meeting.

So, we screened 622 articles and we included 8 related to hypertension, and you can see up on the right that the included articles were 3 RCTs, 2 non-randomized control trials, and 3 prospective cohorts, and all of them directly asked the question of the relationship between folic acid supplements consumed during—before and during pregnancy.

[1:57:58] And we basically will present later, but we did not find the evidence on fortified foods, in folate and fortified foods.

So, describing first the 3 RCTs.

The sample characteristics, between 123 and 450. All of these RCTs were conducted in Iran, and 2 were from the same study. The interventions—so again, they were 25 and a normal pre-pregnancy BMI. The race and ethnicity and SES were not reported, but again, they were all conducted in the same country.

The interventions varied by dose. So, 0.5, 1, or 5 milligrams of folic acid.

And they were all initiated in the first trimester and continued through delivery.

All reported preeclampsia and blood pressure and some reported other outcomes: proteinuria, eclampsia, gestational hypertension.

[1:59:03] So, the two non-randomized control trials, one was conducted in Italy and one in China.

Range from 146 to nearly 5,000 subjects. Again, Caucasian, and race and ethnicity in China was not directly reported, nor was SES. The group in Italy had pre—this was in a higher-risk group, so these were women who had preeclampsia in a previous pregnancy, and so, this will factor into some of our conclusions.

So, this was the one thing that you can imagine, with these different studies, they had different levels of exposure, and also in this study, they had 5-methytetrylhydrofolate as a supplement, and they ranged in initiation, but they all went through delivery.

[2:00:04] And then, the three prospective cohort studies, you can see the end, these were in Australia, Canada, and Denmark.

The women were between 20 and 30 years of age, and you can see the race and ethnicity. They range from low to high SES within these countries.

So, in these, they actually compared no supplement with a folate or folic acid alone, and they had initiation and duration of various times. So, by trying to look at the evidence, we're taking into account when the timing of the initiation and the duration was.

And the primary outcome was preeclampsia.

So, the summary of the evidence, so none of the RCTs found an association between folic acid supplementation and the incidence of hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, or eclampsia, and none of the studies compared folic acid supplementation to a control group that had no supplementation.

[2:01:13] So, in these studies, the control did have a lower level of exposure.

In contrast, when we looked at the non-randomized control trials, both found a significant association between folic acid supplementation from early pregnancy through delivery and reduced risk of preeclampsia and gestational hypertension compared to controls with no folic acid supplementation, and you can see, for preeclampsia, significant reduction, both—in this case, both for high-risk and low-risk, and for gestational hypertension, again, a significant reduction.

And one non-controlled RCT was among high-risk population of women who had previously been diagnosed with preeclampsia.

[2:02:04] So, when we looked at the three prospective cohort studies, the results were mixed. One found an association with folic acid in the first trimester and lower incidence of preeclampsia, but specifically for women with a higher BMI. Another found an association, a significant association between folic acid use between 12 and 20 weeks of gestation and preeclampsia, again, in women at high risk. And a third found no association.

So, our draft conclusion statement is that limited evidence suggests that folic acid supplementation during early pregnancy may have a beneficial effect on reducing the risk of hypertensive disorders pregnancy among women at high risk, either having a history of preeclampsia or a higher pre-pregnancy BMI compared to no folic acid supplementation.

[2:03:00] This conclusion was supported by three—two non-randomized controlled and the three prospective cohorts. The studies were all direct in terms of the question, and they were consistent for the higher-risk women, and as with all the studies, there was some concerns about risk of bias, precision, and generalizability, particularly for some of the studies that were not done in the US.

So, there was moderate evidence suggesting that higher levels of folic acid supplementation during pregnancy compared to lower levels, including no folic acid, does not affect the risk of hypertensive disorders during pregnancy among women at low risk.

So, we have a separate conclusion for women at high risk and low risk.

And there's no evidence available to draw a conclusion about the relationship between folic acid from fortified foods before and during pregnancy and risk of hypertensive disorders during pregnancy.

[2:04:05] So, turning now to the relationship between folic acid supplements or fortified foods consumed by the mother before and during pregnancy and developmental milestones, including neurocognitive development of the infant. This is another new systematic review.

So, the analytical framework intervention and exposure were the same.

In terms of the outcomes, in this case, the population for the outcome is the infant. So, we had infants and toddlers, birth to 24 months, but we also incorporated children and adolescents from 2 to 18 for some of the developmental outcomes, and you can see these are listed, because not all of the evidence is available in early childhood.

[2:05:00] So, for example, we were looking at academic performance, also attention deficit disorder, ADHD, anxiety, depression, and autism. So, in addition to some of the developmental milestones, we needed to extend the search criteria.

So, with key confounders, some of the aspects that we added to this one were child's sex, breastfeeding practices, intensity and duration, and you can see, in other factors to be considered, we also looked at—took into account the family history of a diagnosis of a neurocognitive disorder.

So, we had a total of 1,831 articles that were screened, and 6 were included. There were actually 4 studies that produced the 6 articles, 2 RCTs that have 3 articles, 1 prospective cohort published in 2 articles, and 1 nested case control, and they all addressed the question of, again, folic acid supplements consumed during pregnancy on the neurocognitive outcomes.

[2:06:16] So, the sample characteristics are shown: range of 39 to 130, 17-37 children. They were conducted in the UK, Germany, and then a study that incorporated participants from three countries in Europe. You can see the mothers are 20 to 31, mostly white and higher SES. And the outcomes, the children were older, so the children in these studies were between 6 ½ and 8 ½.

The interventions, again, varied by dose. They also had an intervention with or without fish oil.

[2:07:01] The initiation was at 14 or 20 weeks gestation and through delivery.

And again, the outcomes are shown below, but we'll go through those.

So, the one prospective cohort was done in Norway. This was a very large study. Again, the maternal age and high SES, and in this case, the children were assessed at 3 years of age.

The dose basically was determined from a questionnaire of folic acid supplementation, and they looked at kind of two different phases. So, they looked at early, which could be 4 weeks before conception, through 8 weeks of gestation, and then those mothers who were supplemented who reported the folate between 9 and 29 weeks of gestation, so kind of looking at the two different, early and late.

[2:08:02] So, the outcomes were language competence and then language delay.

The nested case control was a study from Israel, which in this case, 60 percent were low SES. They assessed the children between 6 and 12.

The major outcome was ASD, autism spectrum disorder diagnosis.

And in this case, the folic acid exposure was assessed by pharmaceutical prescriptions. So, they basically were able to look at the women who were prescribed folic acid or not. And they looked before and during pregnancy, and the duration assessed before and during pregnancy or both.

So, the summary of the evidence, that generally, folic acid supplementation before or during pregnancy was either not associated with or had a beneficial association with the following outcomes.

[2:09:04] So, language development, 2 articles from the prospective cohort studies showed a lower risk of severe language delay in 3-year-olds whose mothers consumed folic acid supplements during early pregnancy.

For ASD, the one nested case control found a significant association between folic acid supplementation before and during pregnancy and lower ASD risk in 8 to 12-year-old children.

So, for cognitive development, the findings were inconsistent, and no conclusion could be drawn.

For social-emotional development, included 1 study with concerns and no conclusion could be drawn.

When we looked at movement or physical development, academic performance, ADD or ADHD, anxiety, and depression, there was no evidence on supplementation before or during pregnancy.

[2:09:57] And developmental milestones or neurocognitive development, there was no evidence on supplementation during lactation and/or intake of folic acid from fortified foods consumed before or during pregnancy and lactation.

So, the draft conclusion statement: limited evidence suggests folic acid supplementation during early pregnancy may be associated with lower risk of delayed language development in the child.

So again, the conclusions were based on 2 studies from one prospective cohort study. The studies, they were direct in terms of the question. We had some issues with consistency and there was some concerns, again, regarding risk of bias, precision, and generalizability because it was one study, one prospective cohort study.

[2:10:59] There was limited evidence to suggest that folic acid supplementation before and during pregnancy may be associated with lower risk of autism spectrum disorder in the child.

So again, this was based on the one nested case control study from Israel. Consistency could not be assigned, and there was some concerns regarding risk of bias, precision, and generalizability.

Insufficient evidence is available to determine the relationship between folic acid from supplements and fortified foods consumed before and during pregnancy on cognitive development or socio-emotional development.

And there is no evidence on supplements or fortified foods, folate, on movement or physical development of the child, academic performance of the child, and also, the ADD or ADHD.

[2:12:00] So, these are supplements and/or fortified foods. And so, for these, these are grades not assignable.

There was also no evidence for the relationship between folate supplements and fortified foods before and during lactation, pregnancy and lactation on anxiety or depression, so grades not assignable.

So, basically, this is looking at lactation. So, there was no evidence available to look at supplements consumed during lactation on developmental milestones, including neuro-behavioral development, and no evidence on fortified foods consumed either during pregnancy or lactation, so all the conclusions were based on folate from supplements before or during pregnancy.

So, the final folate question from a new systematic review is looking at the relationship between folic acid consumption and maternal micronutrient status.

[2:13:09] Again, similar framework. Basically, if you look at the health outcomes, when we looked at the folate status, we looked at plasma blood folate, B12, hemoglobin, mean corpuscular volume, and red cell—red blood cell distribution with—were the outcomes.

4,512 articles were screened, of which there were 4—I'm sorry.

I'm sorry 14 for micronutrient status, and of those 14, there were 9 RCTs, 3 prospective cohorts, 1 randomized cohort, and 1 uncontrolled before and after study.

[2:14:01] All of the studies addressed directly the question of supplements consumed before or during pregnancy and lactation and micronutrient status.

So, to go through the 9 RCTs, they range from a very small study to a study of 189. 3 were conducted in Canada, 2 in the US, and 1 each in Iran, the UK, Mexico, and France. The women in most studies were between the ages of 26 and 34, mostly Caucasian and high SES, but one study was in lower—teenage mothers with lower SES, and in one study, it was conducted in 100 percent iron-deficient anemic women.

So, the interventions varied across the 9 RCTs, ranging from 300 micrograms to 5 milligrams of folic acid, and also, one study looked at the methyltetrahydrofolate, and one study looked at folenic acid.

[2:15:07] The initiation varied from preconception during pregnancy as well as postpartum, and the duration was between 1 and 12 months.

And most included serum plasma or red blood cell folate. And other outcomes, common outcomes were B12, hemoglobin, and mean corpuscular volume.

So, the 3 prospective cohorts, again, were—you can see the end, conducted in Ireland, Germany, and Canada. Again, 29 to 30-year-old women, and within these countries, race, ethnicity, and SES were not reported.

They looked at folic acid supplementation via a questionnaire versus none, and there was various times of initiation of and duration of the studies. So again, when we're looking at the literature, we're trying to take into account dose as well as the timing of exposure.

[2:16:06] All of these reported plasma folate, and two reported red blood cell folate, and one incidence of folate deficiency.

The retrospective cohort—sorry, I think I said it wrong before. The retrospective cohort was conducted in Turkey.

They compared zero versus 400 micrograms per day of folic acid. They initiated preconception, but the timing of assessment varied by the participant. So, they all—they didn't have a specific time point.

The outcomes, again, folate, hemoglobin, and incidence of folate deficiency.

And there was one uncontrolled before and after study conducted—small study conducted in Japan, and there was a limitation of—was—there was not a lot in terms of the participant characteristics other than all from the same SES.

[2:17:12] So, these were women that they gave a supplement of 1 milligram per day of folic acid, and then they were each sort of their own control. They initiated this anywhere between 3 and 25 weeks postpartum, and the duration was 4 weeks.

So, all but one study found a significant association between folic acid supplementation and at least one outcome measure.

So, 9 of 13 found positive association between folic acid supplementation and plasma or serum folate.

9 of the 10 found a positive association between supplementation and red blood cell folate.

[2:17:56] And 2 of 5 reported a positive association between folic acid supplementation and hemoglobin.

And there was no association found between folic acid supplementation and these other measures that we had included.

So, based on that, we have drafted a conclusion that strong evidence suggests that folic acid supplementation before and during pregnancy is positively associated with folic acid status, using the outcomes of serum and plasma and/or red blood cell folate.

The studies, again, were direct and precise and consistent, some concerns regarding generalizability, but we felt that the evidence was strong.

There was moderate evidence suggesting that folic acid supplementation during lactation is positively associated with red blood cell folate and may be positively associated with serum and plasma folate.

There was insufficient evidence available to determine the relationship between folic acid supplements before and during pregnancy or during lactation on hemoglobin, MCV, or B12, so grade not assignable.

[2:19:09] And no evidence to determine relationship of folic acid supplemented during these times on red blood cell distribution width.

And again, there was data, no evidence on folic acid from fortified foods before and during pregnancy and folate status.

So, that's the summary of the three, and our final three searches on folic acid, and so, now I'm going to turn to the questions related to dietary patterns.

So, the first is a new NESR systematic review on dietary patterns consumed during lactation and human milk composition and quantity.

[2:20:00] So again, a dietary pattern, as is being defined and used by all of the subcommittees. So, we're looking at quantities, proportions, varieties, combinations of the different foods.

So, to set up the analytical framework for dietary patterns, the intervention and exposure is consumption of and/or adherence to a dietary pattern versus consumption or adherence to a different dietary pattern or a different level of consumption. For example, we'll discuss studies that had different fatty acids.

So, the population for milk composition, again, women during lactation, healthy or at risk of chronic disease.

Human milk quantity, these are exclusively or predominantly breastfeeding women who are healthy or at risk of chronic disease.

[2:20:55] So, we had a number of outcomes for human milk composition, and these, the milk samples were all collected—needed to be collected after 14 days postpartum so we were looking at more mature human milk, not colostrum.

So, we had macronutrients, we have water-soluble vitamins, including choline, fat-soluble vitamins, iodine and selenium for the minerals, human milk oligosaccharides, and any bioactive—of these bioactive proteins.

And for human milk quantity, was assessed in milk collected after 14 days.

So, the search, over 3,000 articles were screened, of which 7 were included in the final summary.

So, these were three RCTs that produced 4 articles, and 2 cross-sectional studies.

[2:21:56] And I just wanted to mention that, in general, cross-sectional studies are not included, are excluded, but because oftentimes, for human milk composition, that's the only type of data that's available, there's not a lot of RCTs or prospective cohorts, so we made a decision, and this had been previously published and was open for public comments. So, that is just one difference when we're looking at human milk.

So, all of them addressed the relationship between maternal dietary pattern during lactation and either human milk composition or quantity.

So, the 3 RCTs, again, relatively small studies, 7-15 mothers, conducted in the US and Canada. 29 years of age, and SES was—and race and ethnicity not reported.

[2:22:56] So, the initiation's between 6 and 6 months postpartum. The durations were 4-14 days. And they were reporting different varied patterns, so carbohydrate, either lower carbohydrate or higher fat versus within the acceptable macronutrient distribution range, or the AMDR. Another looked at higher fat or higher carbohydrate and lower fat. And another higher fat versus consumption within the AMDR.

So, you can see the various outcomes. Most of the studies reported outcomes on fatty acids, and one for B12.

So, for the cross-sectional studies, these were conducted in the US and Canada. They were, on average, 30—nearly 30—I'm sorry, US and China.

[2:23:59] The moms in the US were highly educated, and in China, high-middle income. And within the US, race/ethnicity reported mostly white.

So, initiation, between 21 days postpartum and 6 months, and 9 ½ months postpartum. So, these were ones that looked more at the overall dietary patterns. So, the study in the US compared milk composition with vegan, vegetarian, and non-vegetarian mothers, and the study from China basically divided the mothers into four different dietary patterns. So, you can see mushrooms/meat/seafood, soy/nuts/dairy, fruits/vegetables, and then grains/potato/beans/eggs.

So, summary of the evidence, so one cross-sectional study assessed the relationship between maternal dietary patterns and total fat levels in human milk and found no association.

[2:25:05] Three RCTs assessed the relationship between maternal diet based on macronutrient proportions and total fat level in milk. Two found a positive association, or positive relationship between greater than 35 percent of energy from fat and total fat in human milk. And one study found no association between macronutrient proportions and maternal diet and total fat.

So, there—the draft conclusion statements for total fats is that insufficient evidence is available to determine the relationship between dietary patterns consumed during lactation and total fat in milk.

And there's limited evidence to suggest that maternal consumptions of diets higher in fat during lactation is related to higher total fat.

And a grade of limited.

[2:25:59] The studies were consistent, but there were concerns about precision, generalizability, and consistency, and we had a long conversation yesterday, because these are also being used for other outcomes that—probably measuring fat in human milk is one of the most difficult components, because some studies were measuring during the fed state versus the fasted state, and because the content of milk differs from foremilk to hindmilk, so within a single feeding, if they're just taking a single sample or not a full breast expression, or sampling over 24-hour periods, all of these things can really affect the composition. So, that was some of the concerns that we have about the precision.

So, 2 cross-sectional studies and 3 RCTs assessed the relationship between maternal dietary patterns, including based on macronutrients and proportions and levels of saturated fatty acids, MUFAs and PUFAs, and there were mixed results.

[2:27:04] So, in terms of saturated fats, MUFAs, and PUFAs, there's limited evidence to suggest that maternal dietary patterns during lactation, including diets based on

macronutrient distributions, are related to the relative proportions of saturated fat, MUFAs, and PUFAs.

And we meant to very specifically say relative proportions, because studies also presented concentrations, and there were not affects on concentrations, they were primarily with the proportions of these fatty acids.

So again, some concerns about risk of bias and limited precision and generalizability were some of the concerns the committee had.

So, 1 RCT assessed the relationship between maternal diet based on macronutrient proportions and milk quantity, and there was no association.

[2:28:01] We also, there was 1 that looked at—1 RCT on the relationship with total protein levels in milk, and there was no association.

And the last, 1 cross-sectional study assessed the relationship between maternal dietary patterns and B12, and this was the study that compared the vegan, vegetarian, and non-vegetarian, and while there was no association with dietary patterns, we found that 56 percent of the vegan women were taking a B12 supplement. And so, we felt that there—we were really kind of unable to determine the impact of dietary patterns on B12.

So, in terms of the draft conclusion statements on quantity, there is no evidence available to determine relationship between dietary patterns and milk quantity.

And insufficient evidence to determine relationship on maternal diets differing in macronutrient distribution during lactation and milk quantity.

[2:29:05] Again, similar. So, for total protein, no evidence for dietary patterns.

And no evidence for dietary patterns differing in macronutrient composition.

And for B12, again, insufficient evidence is available to determine the relationship between maternal dietary patterns during lactation and vitamin B12 concentrations in human milk.

So, there were no studies found that assessed the relationship between maternal dietary patterns and human milk levels of these other nutrients that were part of our framework, so our water-soluble vitamins, fat-soluble vitamins, iodine, selenium, human milk oligosaccharides, or bioactive proteins.

So, I'm not going to read all these, but basically, these are the draft conclusion statements that there was no evidence, and so, all are grades not assignable.

[2:30:04] So, now I just will go through summarizing the results from the existing NESR reviews. So, as was mentioned, as part of the Pregnancy B-24 Project, there were four

systematic reviews that were conducted that are pertinent to the Pregnancy and Lactation subcommittee.

So, the first was the relationship between dietary patterns during pregnancy and the risk of hypertensive disorders during pregnancy, and the second was the risk of gestational diabetes.

And there were two systematic reviews looking at dietary patterns during pregnancy on infant outcomes, so gestational age at birth and birth weight standardized by gestational age and sex.

So, we are, as I mentioned, adopting the existing reviews, but new protocols are posted on DietaryGuidelines.gov.

[2:31:02] So, again, if you're interested in the complete documentation, they're available at DietaryGuidelines.gov. In addition, also just to acknowledge, this was the member of the Pregnancy Technical Expert Collaborative, or tech, who worked on this and drafted the conclusions.

And these four systematic reviews, as with the ones that Kay mentioned, were published in the American Journal of Clinical Nutrition in 2019. So, the two maternal outcome systematic reviews were combined in one paper and the two infant systematic—pregnancy outcomes, birth outcomes were in another.

So, you can not only review the actual results of the systematic reviews on DietaryGuidelines.gov, but you can also refer to these manuscripts.

[2:32:01] So, just to briefly review the evidence, so for the first, "What is the relationship between dietary patterns during pregnancy and the risk of hypertensive disorders?"

So, this systematic review included 8 studies from 4 cohorts and 1 RCT, and this was over a 37-year range of evidence.

So, I'll just reiterate, and I mentioned before, but Kay mentioned, but we also did then look to see what was published after January 2017 in order to make our final decision on whether we would go ahead and accept the existing reviews.

So, for these questions related to dietary patterns and risk of hypertensive disorders, they're limited evidence in healthy Caucasian women with access to healthcare suggests that dietary patterns before and during pregnancy higher in vegetables, fruits, whole grains, nuts, legumes, fish, and vegetable oils, and lower in meats and refined grains are associated with reduced risk of hypertensive disorders during pregnancy, including preeclampsia, gestational hypertension.

[2:33:11] Not all components of the assessed dietary patterns were associated with all hypertensive disorders. So, limited—the grade was limited.

Evidence is insufficient to estimate the association between dietary patterns before and during pregnancy and the risk of hypertensive disorders in minority women and those of lower socioeconomic status, so grade not assignable.

So, the relationship between dietary patterns during pregnancy and gestational diabetes, this was included 10 prospective cohorts and 1 pilot RCT. Again, collected between publications January 1980 and January 2017.

[2:33:56] So, this systematic review concluded there was limited but consistent evidence suggesting certain dietary patterns before pregnancy are associated with a reduced risk of gestational diabetes. These protective dietary patterns are higher in fruits, vegetables, whole grains, nuts, legumes, and fish, and lower in red and processed meats. Most of the research was conducted in healthy Caucasian women with access to healthcare.

Evidence is insufficient to estimate the association between dietary patterns during pregnancy and the risk of gestational diabetes. So again, a conclusion on diet before pregnancy but not actually during pregnancy, so grade not assignable.

So, in turning now to the infant outcomes, the relationship between dietary patterns during pregnancy and gestational age at birth, there were 10 prospective cohorts and 1 RCT, again, over the same time range.

[2:35:00] So, limited but consistent evidence suggests that certain dietary patterns during pregnancy are associated with lower risk of preterm birth and spontaneous preterm birth. Protective dietary patterns are higher in vegetables, fruits, whole grains, nuts, legumes, and seeds, and seafood for preterm birth only, and lower in red meat, processed meats, and fried foods.

Again, noting limitation, most of the research was conducted in healthy Caucasian women with access to healthcare.

And this is kind of the opposite, that there's—evidence was insufficient to estimate the association on dietary patterns before pregnancy and gestational age at birth, as well as preterm birth.

So, the last, the relationship between dietary patterns during pregnancy and birth weight standardized by gestational age and sex, there were 18 prospective cohorts, 1 retrospective cohort, and 2 randomized control trials.

[2:36:03] So, the conclusion's that no conclusion can be drawn on the association between dietary patterns during pregnancy and birth weight outcomes. Although research is available, the ability to draw conclusions was restricted by inconsistency of study findings, inadequate adjustment of birth weight for gestational age and sex, and variation in study design, dietary assessment methodology, and adjustment for key confounding factors.

And insufficient evidence exists to estimate the association between dietary patterns before pregnancy and birth weight outcomes, and in this case, there were not enough studies available to answer the question.

So, our ongoing work is mentioned that we are refining and prioritizing work on dietary patterns during pregnancy and micronutrient status, dietary patterns during lactation and developmental milestones of the child, including neurocognitive development, and dietary supplements and fortified foods for all the other nutrients besides folate.

[2:37:15] So, as noted, we'll review the evidence, grade, and draft conclusion statements for these following questions.

Dietary patterns and pregnancy and gestational weight gain.

Patterns during lactation and postpartum weight loss.

And maternal diet during pregnancy and lactation on the risk of child food allergies and atopic diseases.

And the plan is then to present these at the meeting in March.

So again, thanking the subcommittee members, as well as our support staff, which we would not be able to get through all of this work without all of their hard, behind-the-work scenes.

So, I'll be happy to take questions.

[2:37:58] [Applause]

Dr. Ronald Kleinman: That was a great summary. So, any questions from the committee?

Rick?

Dr. Richard Mattes: Only one this time. Rick Mattes. So, what's known about the validity of self-reported supplement use during pregnancy and lactation? Is it different from the general population? Can we believe this data more or less than general studies about diet and outcomes? And in any of these trials, was there objective verification of compliance with a prescribed dose?

Dr. Regan Bailey: So, you can get at compliance sometimes in a clinical—

Dr. Sharon Donovan: Do you want to—

And say your name.

Dr. Regan Bailey: This is Regan, answering with Sharon, not for Sharon. So, there are ways to look at compliance with supplements by putting POWA in and getting recovery from urine.

[2:39:04] So, that's one way to test it. I can't speak to whether or not that was done in your studies, but I just wanted to make that comment.

Dr. Sharon Donovan: I think it's a great question, and I don't know if anyone else is aware of studies where they've looked at self-reported compliance of pregnant versus non-pregnant women. Obviously, women during pregnancy may be taking supplements more often, and may be more motivated, but I don't think there's the evidence.

And just thinking offhand, and if anyone can speak to that in terms of the studies that we reported, I'm not sure that anyone actually confirmed intake of the folate supplements.

Jamie?

Dr. Jamie Stang: Yeah, Jamie Stang. Yeah, I was on the Pregnancy tech, and studies, for the most part, did not report compliance.

[2:39:58] I know from unpublished work that the compliance rates start out high, and as you go through pregnancy, they drop off. But in terms of actual published documentation of what that compliance would be, I'm not aware of any.

Dr. Richard Mattes: So, just this is a comment. That may be a good point to add into the discussion of this section.

Dr. Sharon Donovan: That's a great point. And also, research needs, to have better collection of that type of data.

Female: Good grant idea.

Dr. Sharon Donovan: Perfect.

Dr. Carol Boushey: I have one, too.

Dr. Barbara Schneeman: No, go ahead.

Dr. Carol Boushey: Okay. So, this is Carol Boushey. And I'm looking at the analytical framework for the folic acid with supplements, and you don't have to look at it, you have it memorized, so but folic acid in supplements and/or fortified foods consumed before and during pregnancy and lactation.

And one of the studies, I think had 11 people, or 15, or something like that, and you had said it was a small sample size.

[2:41:03] And in the Frequency of Eating group, we actually did—went through the process of figuring out sample size so that we could screen out some of the smaller studies. And I wonder if you might consider doing that for some of your studies so that you can determine if those studies actually didn't meet sample size.

So, it wasn't that you went crazy over it anyway, but still, it might be nice to have that documentation.

Dr. Sharon Donovan: Yeah. No, that's a great point. I remember we had this conversation at the last meeting. And I think we also talked about, for the RCTs, that because they're more controlled, the end was not as necessarily as much of a consideration.

But I think—I don't remember if the study with 11 was an RCT or—so I can't speak to that directly. But I think it's an excellent point. And as you can see, the studies varied from 11 to 45,000. So, it's quite a mixed literature that we're trying to assess and draw conclusions from.

[2:42:05] ***Dr. Barbara Schneeman:*** So, I had a ques—this is Barbara Schneeman. I had a question, again, going back to the supplementation. I know that in your protocol, you allowed for multivitamin supplements, and I'm just wondering then, as you went through the data and the evidence, where you're trying to then look at the impact of one nutrient, folic acid, how did you deal with the multivitamin side of it?

Dr. Sharon Donovan: So, I think when we looked at that, then the control group would have had that exposure without the folic acid.

So, we didn't just look at folic, folate within a multivitamin supplement alone. So, it needed—they could have other vitamins without folic acid or those vitamins with the folic acid.

[2:42:58] ***Dr. Ronald Kleinman:*** Any other comments or questions? Everybody must be very hungry.

Alright then. Any concluding remarks?

Dr. Barbara Schneeman: My only concluding remarks would be to thank the subcommittees. You've covered a lot of information in actually a relatively short period of time. And also, thank you to the staff for the work that's done to help pull this together.

So, I think our next subcommittee is going to be Dietary Fats and Seafood subcommittee, but I think we're best to start that after the lunch break, because I know they have a lot to report back on as well, correct?

[2:43:56] So, I'll just open it up to the committee. Do you have any general comments at this point before we break? Particularly, if you start to see things where you're seeing threads across the different subcommittee work, or things that sort of tie these areas together?

Everyone's anxious for lunch.

Dr. Ronald Kleinman: Hunger wins.

Dr. Barbara Schneeman: Okay, so we'll adjourn for now, and then reconvene at 1:00. And it is important that we start at 1:00, because that's for the webinar folks, that's when we'll start the YouTube again. So, have a good lunch.