You should be able to see your group full lock after today after we put people in a, you didn't sign up death. And then there is a function on canvas where you should just message my group that you're in, usually on campus. Oh, and then this is a last in a reminder next Tuesday, February sixth, your first assignment is huge. There's been some hypotheses in the literature around the role of sex halo, things like estrogen and androgens. So this question is in cancer epidemiology studies, which of the following have been used as proxies for greater exposure to androgens like testosterone in utero. Is it a exposure to DES during pregnancy. B, is it male pattern baldness? DES exposure has been linked to more rare cancers in the offspring, including vaginal cancers. There's also a suggestion of an increase in breast cancer, but it's actually attributed to higher exposure to estrogens rather than testosterone anderds. The majority of students thought that exposure to DES during pregnancy and this was given to present many decades ago to prevent complications during pregnancy. My birthday, surprisingly actually is associated with lower levels of testosterone that thought to be higher levels of estrogen during pregnancy. So it's an interesting ticket. So my ratio, I mean I don't know if this is HIPAA or not? You're second before, meaning I had much lower exposure to androgens and higher exposure to estrogen. So I covered the first 2, like, background, a wide diet, maybe important for cancer, and then we discussed a bit about observational randomized trials. So, I'm going to finish these last 2 topics and then get into, like body weight and physical activity. So I won't get into a lot of specifics, but be kind of broad. The best way to to measure diet in small studies is to have dietary records. If you eat lots of fruits and vegetables, your blood beta carotene levels will be highs. Now, bial markers are not you know, there are few biomarkers that tell you exactly what somebody is eating, but they're like indirect. There are things like iPhone apps, like, you know, you take a photo of your mail and then it somehow, it's measured. Those could be useful but they're not perfect like for example they won't distinguish between a diet coke and sugar sweetened beverage, which would be something very important. It's not like a simple exposure. There's no really good dietary assessment to that. I mean you would have to have like almost a perfect measure of caloric intake. And almost aperfect measure of energy expenditure. So the balance in minus out and neither one of those are really that feasible in epidemiologic studies. For micronutrients, you have biomarkers, like you can measure blood beta carotene, which again doesn't tell you exactly how much. And then things like carcinogens and contaminants. I think a good example, carcinogen is that there's something this is something Laura Live, studies called the chromeide. Food frequency questionnaire, I just show one here. There's an item like, I think the current one has about 140 items. And, you know, so for example, skim or low fat milk, 8 ounce glass and there's 9 categories. And your report over the past year, so this is your consumption. The longer-term memory is sometimes even better than short- term memory. Long-term memories, and actually that's what you really want for for cancer studies. Remember we want long-term dietary. And take. An important question is the accuracy of how accurate are these. Dr. Willett led some of the studies and, you know, he did a lot to show that nutrition can be assessed in epilogic studies. And one of the first studies, and now they've been multiple studies like this, is this is like in a nurse's health study and what they did is they sent the questionnaires. The 4 weeks is a pretty, you know, that gives you a pretty good long-term estimate. What a person would be consuming, like, over a year or so on average. And then like you average them. These are the correlations between some of the items. A perfect correlation would be 1.0. There's actually a lot of measurement error in the lab of getting like the exact energy of expenditure for example. Some of that could be error from your gold standard. But in any case, these are the kind of correlations to keep in mind that when you're looking at diet and cancer, like most of the studies have correlations. In a sense it's not so much that the absolute measure is worse than the others. It's actually that you have less variation. Population. I should know this answer, but depending on the time of the year, the season of theyear, was there any variability or these estimates kind of consistent? By season. There is no, I mean, like, point for me, like point 2 is definitely too low. Point 8 would be. You'll be very happy if you get that in theology for tradition. Personally, I'd say like below point 5 would be problematic. The other thing to keep in mind is one of the advantages of the nurses. A lot of studies have one questionnaire for somebody's lifetime so like age 50 they start to study they fill out their questionnaire and then they could be followed for 30 years. So some of reports have like 8 or 9 questionnaires over their life. So that kind of, you tend to get Probably better information like more people. Measurement error can be used to adjust findings in studies. People sometimes don't like that, but that's, you know, one way that it's dealt with. Another way, sorry, the slides a little, complicated, but, Yes, so let's see. You have like, what this show, let's just focus on foli here. An FFQ for food for can see questionnaire and then this one is average, so they're 2 for averages. And then a single and. 2 weeks of diet records. So full aid is measured in the blood. And again, as I mentioned, your dietary foliage should be correlated with your blood flow. This is the, food frequency process, 2 food flips. The higher the correlation, the better the measurement but it's not like a big increment. So this is like showing that at least for falling food fields, a food frequency questionnaire is really not much worse than a one day diet record, or one week directed. For sodium where the diet records are better. Than the food frequency question for Sodium. The reason for that is that, sodium varies a lot in foods like, you know, things like folate or protein, potassium. Those items should actually be pretty consistent. But sodium depends on processed foods and some add a lot of sodium. Some add much less. When the study started like in 1,980, one of the big, improvements was like optical scanners like you fill in the little bubbles. Food frequency questionnaire is, like, you know, It's almost like pennies. I mean, this is like, 1980. Wow, we can send this out to 100,000 people. Diet records have been matching like every meal you're bringing a little scale. That made the study very feasible to do in large numbers, even though it was all done by the mail. But like diet records, you need training from a dietician. So it would be like, mag, like even 170, women that studies. The FFQ is definitely, you know, not as good, but it's not much worse. With the diet records is a lot more variability in the foods that are accessible, which is an advantage in a way, but then you have to have a dietician look through all the items like somebody's eating. I just used the WCRF the ICR, that are, you know, they have a, their, their existence is, is to assess nutrition and the cancer. And so I was on like their panel for about 10 years. So the way they assess the data, so they look at all the like just about any question. There's also experts in the group that help and integrate epidemiologic findings with the like mechanistic data. And then like the, at the end of the days that these experts sit around and come up with convincing probable or limited data or evidence. I'm not sure if this will be keep going in the future, but they had like 3 big reports. In 1990, there was evidence from case control studies pretty consistently that saturated fat and tank is associated with a higher risk of dress cancer. And now that they're even like, I think this number is probably like 10 times larger. There's like, it's completely flat. The cohort study is pretty. Consistently show no association with the fat. And why do you think is the main reason for the difference? I mean, there are several differences between these 2 designs and I assisted later through each one of them. These studies, what was the main? Some people who were like pro stat hypothesis. They argue like, well, the cohort studies have more measurement error because because they have a lock follow, whereas the case control studies. Ask about recent diet. And maybe recent diet is more important. Now that would be a, you know, at least a plausible argument. But there's a, like you can look at the subset of cohort studies that have like 5 years of follow up. A healthy diet dramatically reduces your risk for, you know, most cancers except prostate. Not much there, a little bit for colon cancer, colorectal, that is a significant, but it's much weaker. And this is looking at like high versus low one tile like that for brass. In case control studies, like what people do like to get the cases are relatively easy to identify. And then you have to get controls. And controls like they were done by like random digit dialing because you want to get, so for example if you're doing a case control study in Boston. The selection bias is probably even more important than the recall bias. So, but it is quite amazing how many, it's actually a little hard for me to explain why case control studies like so often get a protective or if they're looking at something, bad, like, you know, perceived to be bad, they have a positive association. There's still some people who will argue the case control studies get the right answer. There are not many things that actually get strong convincing evidence, but there are some items that we'll see that get like probable evidence. And they would still be considered probable, still pretty strong evidence, which that they could actually make recommendations. For now, this is just a summary of. The findings and a lot of these. Will be talked about later in the course, but this is a list of what the WCR FX here came up with as related to cancer with strong evidence like probable or convincing. And I'm also excluding alcohol, which is part of diet in a way, but that's a different topic. If people did well in all of these, lower sugar sweetened barriages, lower red meat for example. They, you would prevent about 5% of the total cancer. Interestingly, this is dominated by colon cancer. So almost like for all at least. From what we know from what they list as probable or convincing evidence. Dietary patterns are a combination of foods and beverages that constitute an individual's complete dietary intake over time. There are some advantages, from looking at a dietary pattern than just the specific item like red meat. It's also, you know, in some ways it reduces like the confounding and just as an example. It's a more general statement. It's probably more conservative than trying to find a whole diet. You just say, okay, we see a vegan diet is beneficial. But it's not like you have to make a statement like, oh, like red meat is bad or cheese is bad. Most of them are based on scores on prior knowledge. There is something called alternative healthy eating index scoring. And it's potentially more conservative than trying to find a single factor. There are different ways, so what do you mean by dietary pattern? I'm gonna talk a little bit late, I'll mention. The frequency questionnaire does pretty good at. Picking up a dietary pattern, which to me intuitively kind of makes sense. So, so you're getting like good general information. Of course, you're losing some specificity over what I specific item might be. And so I think it makes sense that you are likely to pick up, you have good information, diet. There's like a lot of dietary patterns. But I'm almost thinking now it's becoming like there's too many. The interesting thing is like we're doing this summary for the world's cancer research fund. It's summarizing dietary patterns in colorectal cancer. Some of them you might be like, they're too many. So our randomized trials would be ideal, but. There is limited utility for most questions for nutrition and cancer. But I just want to spend, you know, make sure I have some time to get into obesity. So this is just a quick summary of what I've talked about so far. Red process needs fibre whole grains, dairy, calcium, fruits, vegetables. They contribute to about 5% of total cancer and about 40% of colon cancer. Is going to be obesity and fiscal activity, which we'll see is probably more important. Now, you know, how is adiposity measured? I think it's actually not as bad as people think, at least for some cases we'll see. And then there's, yeah, I have to have a list here. So most of if someone gained like, you know, 20 pounds like from age 30 to 50 I must they suddenly became like a body builder that's mostly fat. There are 13 cancers that have been established as causally related to a higher BMI. Early life BMI is actually associated to. Protective effectiveness cancer. In post metopausal women like weight gain, for example, it's definitely a risk factor. And then, I'm gonna talk a bit about visceral, and a little bit about her patic fat. Excess body weight might account for about 5, maybe 10% of where in Kansas. Smoking in lung cancer is a contributing factor. But when you look at like that it's dirty cancers, they do add up. And but for others it's, you know, a liver are pretty strong. Obesity is much higher in women than in men, almost like twofold. And that's predominantly because the end of mutual cancer and breast cancer. In Asian, this is using BMI as the standard BMI. And you can see from men the big ones are liver colorectal kidney. For women it's breast. There are some racial differences in obesity that probably contribute. It's not like maybe the big dominant factor, but it does contribute to some of the differences in cancer rates. The more adipose tissue have, the more likely it is to be breast cancer. So diet and physical activity impact on obesity and obesity affects all of these estrogen levels. obesity is very important. Body weight, BMI, and estrogen level. There's a linear association. So an estrogen which you'll hear about in future, like I guess there's electron breast cancer, a group that will be looking at at the mutual community. Now, and then I'm gonna talk, most of my talk will be about this middle part here, but just. The main risk factor for gallbladder cancer, which is rare in the US, is golf. If the stones are there asymptomatically for years, that could cause God blood cancer. And then, I don't know, carcinoma with the oesophagus, and that's, Jail can't just another one of your topics. No squams, which is in the upper part of the esophagus, is due almost entirely to smoking and alcohol. Poor diet quality, probably continues, but smoking alcohol, the lower part, adamo carcinoma is probably continues. So the chronic They're rotation due to the acid. Now, I'm going to talk a lot about insulin and inflammation. Insulin is a growth factor. Log insulin reduces soft full of fluorine. People that have genetic variant that makes their insulin levels a way higher than average. Those variants are consistently associated with what some of these cancers, particularly colorectal cancer. So that kind of gives pretty good causal evidence. Mendelian randomization studies suggest that it's actually the insulin level that's the causal risk factor, which kind of makes sense. Islam is going to be related to a lot of things. So it's hard to PIN it just to insulin, but I don't increase like 100 other things. insulin and IGF one receptors that are important for metabolic signaling. There there's lots of mechanistic data that supports the effect of insulin. In the previous life I used to. That was a pathology resident. I would do lots of autopsies. So. Yeah, so, anyway, just quickly go back here. It's hard to measure this real fat, like you can't do it like just like a questionnaire or something you need the more sophisticated measures. And it's amazing like when you look, you know, do autopsy and like some people have a lot of fat around it work. There's definitely a good correlation between waistcoat and visceral fat. You do guess a lot of people that actually have high missile fat. So if you had to guess like one. Is a marathon runner. One is a couch potato. Which one do you think this is? Yes, so people even like the same waste or comfort. A lack of exercise, sedentary lifestyle, probably diet, smoking actually. For the same BMI, the Asian population will tend to have higher higher visceral fat. This is why in some Asian countries like their high rates of diabetes, even though if you look at the overall BMI, they're not that. There's very little data that examine directly visceral fat and cancer risk. Some studies have examined visceral Positives just by CT scan. Most of these studies We're done in either Japan or South Korea. Most people had a DMI less than 25, so we considered that normal, right? Viceral fat is associated with cancer. Levels like very low. But even within the normal range. You can see like people have. levels around 30 to 160 or like 200. You have about like, What's the fivefold difference in this year of that? I'll just. discuss this. Body mass index and weight gain seem to be much stronger risk factors for cancer when you look at non smokers than in smokers. So smoking is often associated with lower BMI. But actually increases visceral fat. For subcutaneous fat, which is most of the fat in your body, it has, little effect, maybe even slightly inverse. BMI is a bad measure in smokers of visceral fat. Some people use smoking to keep their body weight low. When they stop smoking, they start gaining weight and you know smoking also reduce it. So, it's still probably better to stop. But yeah, so, it’s still likely better to not smoke. Most estimates, which includes the whole population, like typical estimates that people come up with is 5 to 7% of cancer. Are related to smoke out of excess body weight. If you look at non-smokers probably get it more realistic estimate which is almost 20%. That's pretty bad. Physical activity is more possibly associated with a lot of cancers. There's 2 cancers, cross state and melanoma, where physical activity has a positive association. Being more active, people reported being more active of a virus. Does anybody have a suggestion why there's an association with prostate cancer? The message is not to not be physically active because of melanoma, but to not being physically active due to melanoma. If you're physically active outdoors, it'd be interesting to studies separate by the whether they exercise in a chair or outdoors. Probably like resistance training, I think does increase testosterone. Physically active people are more likely to get PSA tests. If anything, they have a lower rate of prostate cancer mortality. Physically active. But you're more Likely to be diagnosed with these. I think like running, if anything, reduces. But it's probably to do with screening. Physical activity is related to obesity related cancers and tobacco related cancer. Some people think it's possible that physical activity is directly protected for lung cancer. There could also be a bias because like light cancer is strongly related to smoking smokers. Can't exercise that much to get one disease, which, you know, smokers who have lung disease like daphragm are actually higher risk for. The only group there wasn't, well, the occupational activity was not detected for lung cancer and I also endeavor smokers. So, so this kind of argues that smoking could be a founder. Even though you do measure smoking, it may not be measured that well or perfectly and you get lung disease anyway. Physical activity is very important for visceral fat. Associated with lower risk of almost every cancer in the digestive system. So why is physical activity related to cancer? At least I think this is likely to be the biggest reason. There could be other things, but. Just physical activity isvery important for abdominal fat. This is from a systematic review. What you can see is like that this is much sneaper than body percent body change. So the studies that caused the about a 5% weight draw had about a 20 to 25% drop in this real fat. You can find some studies like this one for example where maybe it had to do with the tendency of exercise. You can really reduce your visceral fat without having a big impact on your weight change. So that one, you don't have to worry about that, that's bonus. Once a very active, again, tend to have very low visceral fat. Once they are inactive, still have pretty highness of fat. Liver fats also probably important for liver cancer. They're actually a very small proportion of the fat. Subcontaneous fat is much harder to change. I just can't, you know, do subcutaneous fat that much by exercise. You probably have to have a big massive reduction in date. Mendelian randomization studies suggest visceral fat is not a associated with any material. It's the subcontaneous fat, which kind of makes this pretty nice model. This is very comprehensive. Like I think if you understand This slide you conceptually understand also. Physical activity and obesity epidemiology. If you look carefully at the epidemiology of physical activity. And cancer, I think you can explain a lot of it. And there could be other things going on. There's Maybe. At least by population, what people do is much more But resistance would have some of the effects too.