Resit Research Exam Semester 3 – 2020-2021 -

Resit May 6, 2021, 13.00-15.30 hr

NOTE ON SCIENTIFIC INTEGRITY:

- By taking the exam, the student declares that no plagiarism is or will be committed. If the lecturer has the suspicion that fraud has been commit-ted, the student will be contacted. If needed, the case will be redirected to the Examination Board.'
- We expect you to take this exam individually, without consulting fellow students or others

INSTRUCTIONS

- **Hand in your answers before 15.30 hr. Students with special facilities can submit until 16.00 hr.**
- **Write your name and student number on the first page of each question!**
- The questions must be answered in English. If you cannot remember a specific English term, you may use the Dutch term.
- Be precise in your answers. Adding correct but irrelevant information will not increase your score. Adding incorrect information, even if it is irrelevant, will lower your score.
- You are allowed to use a calculator of the type Casio FX-82MS.

- During the exam, you may want to consult these books
  - Baynes & Dominiczak: Medical Biochemistry
  - Campbell: Statistics at square one
  - Donders: Literature Measurement errors
  - Fletcher: Clinical Epidemiology
  - van Oosterom en Oostendorp: Medische Fysica
  - Petrie and Sabin: Medical Statistics at a Glance
  - Turnpenny: Emery's Elements of Medical Genetics

  https://libguides.ru.nl/friendly.php?s=ebooks:

- The form with statistical formula's is available at Brightspace.

Name:

Student Number:

Question 1 – Cancer etiology and prognosis – Prof. Dr. B. Kiemeney (20 points)

Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort.

Abstract, British Medical Journal (BMJ)

Introduction: To assess the associations between the consumption of sugary drinks (such as sugar sweetened beverages and 100% fruit juices), artificially sweetened beverages, and the risk of cancer.

Design: Population based prospective cohort study.

Setting and participants: Overall, 101 257 participants aged 18 and over (mean age 42.2, SD 14.4; median follow-up time 5.1 years) from the French NutriNet- Santé cohort (2009-2017) were included. Consumptions of sugary drinks and artificially sweetened beverages were assessed by using repeated 24-hour dietary records, which were designed to register participants' usual consumption for 3300 different food and beverage items.

Main outcome: Prospective associations between beverage consumption and the risk of overall, breast, prostate, and colorectal cancer were assessed by Cox proportional hazard models, accounting for competing risks. Hazard ratios were computed.

Results: The consumption of sugary drinks was significantly associated with the risk of overall cancer (n=2193 cases, hazard ratio for a 100mL/day increase 1.18, 95% confidence interval 1.10 to 1.27, P<0.0001) and breast cancer (N=693, HR=1.22, 95%CI 1.07 to 1.39, P=0.004). The consumption of artificially sweetened beverages was not associated with the risk of cancer. In specific subanalyses, the consumption of 100% fruit juice was significantly associated with the risk of overall cancer (N=2193, HR=1.12, 95%CI 1.03 to 1.23, P=0.007).

Conclusion: In this large prospective study, the consumption of sugary drinks was positively associated with the risk of overall cancer and breast cancer. 100% fruit juices were also positively associated with the risk of overall cancer. These results need replication in other large-scale prospective studies. They suggest that sugary drinks, which are widely consumed in Western countries, might represent a modifiable risk factor for cancer prevention.

Table 1.1: Hazard ratio's for different types of cancers

	All cancers Hazard ratio (95% CI)	Breast Cancer Hazard ratio (95% CI)	Colorectal Cancer Hazard ratio (95% CI)
Sugary drinks except 100% fruit juices, per 100 mL/day:	1.19 (1.08 to 1.32)	1.23 (1.03 to 1.48)	1.11 (0.72 to 1.71)
100% fruit juices, per 100 mL/day:	1.12 (1.03 to 1.23)	1.15 (0.97 to 1.35)	1.05 (0.75 to 1.46)

A. Please take a look at Table 1.1 and explain in words the association given by the Hazard Ratio for "Sugary drinks except 100% fruit juices" and "Breast cancer". (3 points)

B. What is the risk of cancer of someone who drinks half a liter per day (=500 mL/day) of "sugary drinks except 100% fruit juices" compared to someone who doesn't consume such drinks at all? Please make use of Table 1.1. (3 points)

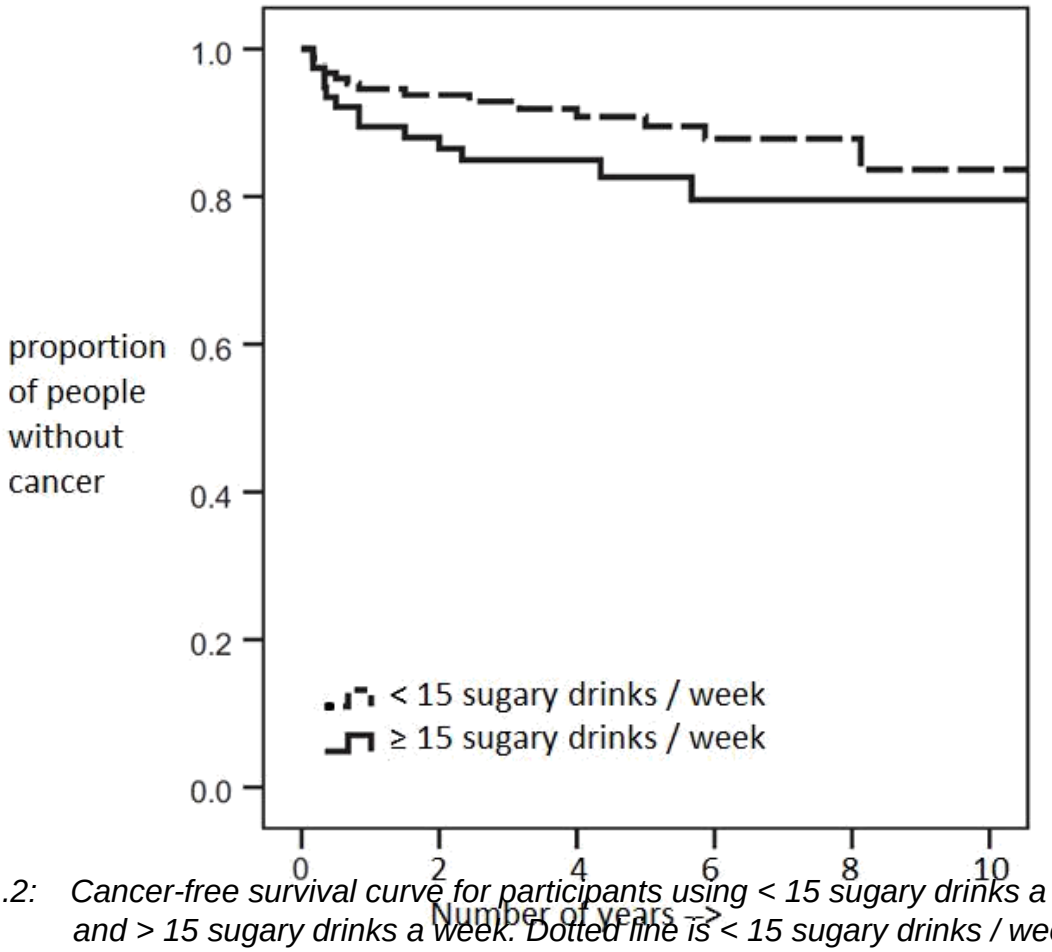

Figure 1.2: Cancer-free survival curve for participants using < 15 sugary drinks a week and > 15 sugary drinks a week. Dotted line is < 15 sugary drinks / week, solid line is ≥ 15 sugary drinks a week.

C. Please take a look at Figure 1.2. Is it possible to determine the median cancer-free survival time for the group of people that drink ≥ 15 sugary drinks / week? Please motivate your answer (you may draw inside the figure). (2 points)

D. A newspaper picked up this study and printed a new headline "Sugary drinks cause cancer!". Provide 2 reasons why this conclusion is overstated. (4 points)

E. Suppose that 60% of the population drinks 100 mL of "sugary drinks except 100% fruit juices" per day and no-one drinks more than that. In that case, what is the population attributable risk for all cancers of 100 mL of "sugary drinks except 100% fruit juices" per day? Please explain your answer. (3 points)

F. In this study, daily intake of sugar from sugary drinks was positively associated with overall cancer and breast cancer. What would happen to the Hazard Ratio's (HR) for sugary drinks if the authors decided to correct in their analysis for sugar from sugary drinks? (3 points) And what would that imply? (2 points) (in total 5 points)

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Question 2 – Modelling physiological systems – Dr. T. Oostendorp (15 points)

Angle meters

In movement sciences, angle meters are used to record the orientation of limbs (the same principle is used in smart phones). Figure 2.1 and 2.2 show an example.

Figure 2.1. Angle meter attached to the upper leg.

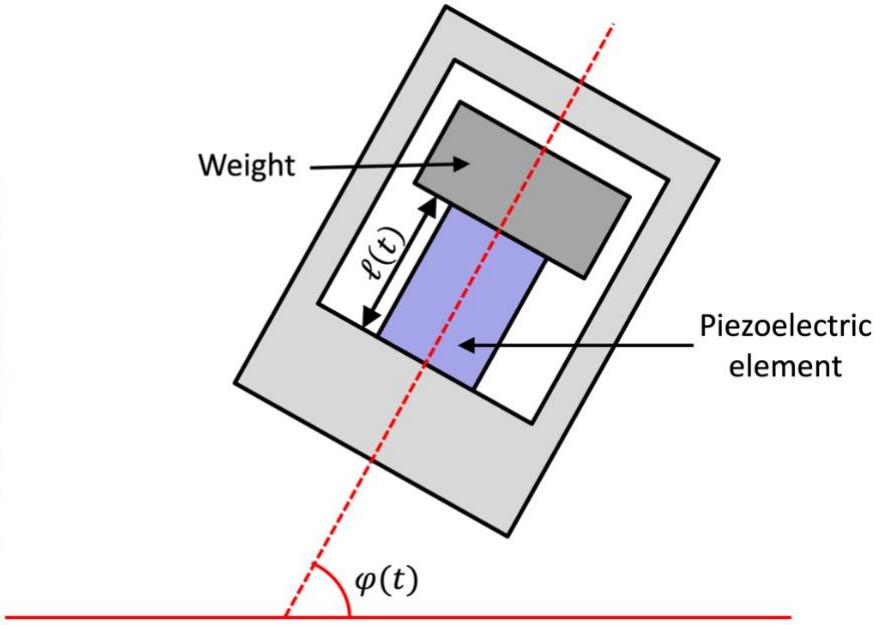

Figure 2.2 Inside of the angle meter

The piezoelectric element is compressible, and acts as a spring with spring constant .. The equilibrium length of the element is $\ell_!$. The element cannot bend sideways.
When being compressed, the piezoelectric element exerts a frictional force on the weight that is proportional to the velocity by which the element is being compressed: $0_{\text{friction}} = -2\ {}_{34}{}^{3}\ \ell(5)$, with $\ell(5)$ the length of the element. The mass of the weight is 6, the mass of the piezoelectric element can be ignored. $7(5)$ is the angle between the axis of the angle meter and the horizontal plane (see figure 2.2), and 8 is the gravitation constant.

The angle meter is attached in such a way that displacement can be ignored; the only relevant motion is rotation.

A. Show that the differential equation for $\ell(5)$ is

$$m\frac{d^2}{dt^2}\ell(t) = -b\frac{d}{dt}\ell(t) - k(\ell(t) - \ell_0) - mg\sin(\varphi(t))$$

(4 points)

The electric signal $s(t)$ produced by the angle meter is proportional to the deformation of the piezoelectric element: $s(t) = c(\ell(t) - \ell_0)$.

B. What is $s(t)$ when the angle meter is maintained at vertical orientation ($\varphi(t) = 90°$) for a long time? (3 points)

The step response of an angle meter can be obtained by instantaneously changing the ori-entation from $0°$ to $90°$. Figure 2.3 shows the step responses of two different angle meters, A and B. Both angle meters are the same in every aspect, except that for one angle meter, the value of the friction parameter 2 is larger than for the other one.

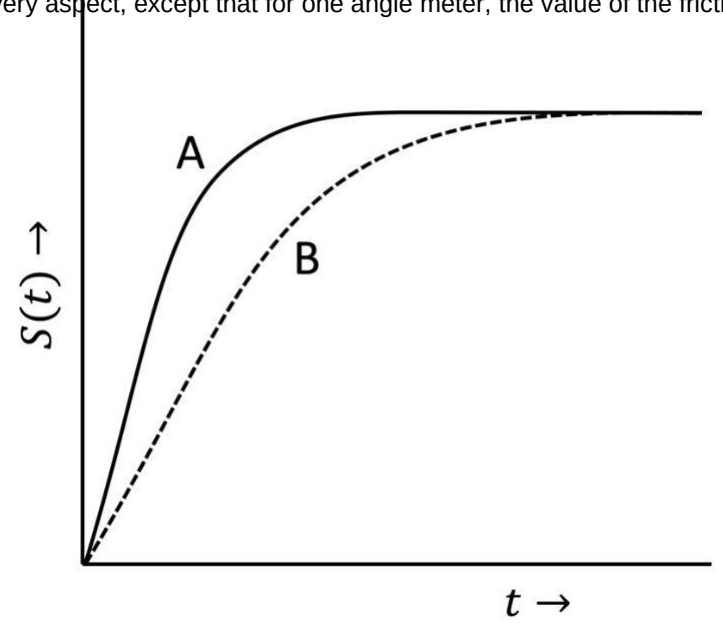

Figure 2.3 Step responses of two different angle meters, A and B.

C. Which of the angle meters, A or B, is the one with the larger value for 2? Explain your answer. (3 points)

D. Fill in the missing parts, indicated by highlighted dots, of the script below. (5 points)

```
duration <- 10
deltaT <- 0.01
nSteps <- ……
m <- 1
k <- 1000
b <- 50
L0<-5
g <- 9.81
c <- 100
t <- numeric(nSteps)
v <- numeric(nSteps)
L <- numeric(nSteps)
S <- numeric(nSteps)
v[1] <- 0
L[1] <- 5
S[1] <- 0
for (i in 1:nSteps)
{
  t[i+1] <- t[i]+deltaT
  if (t[i+1]<5)
    phi=0
  else
    phi=pi/2
  Ftot = ……
  a=Ftot/m
  ……
  L[i+1]=L[i]+deltaT*v[i+1]
  S[i+1]=c*(L[i+1]-L0)
}
plot(t, S, type='l', xlab='Time (s)', ylab='S
     (V)', main='Angle meter output')
```

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Question 3 – Molecular Cancer Research – Dr. F. Doubrava-Simmer & Dr. E. Ooster-wijk (15 points)

Part I. Evaluation of Western Blot setup

For visualization of the proteins ERK, AKT and GAPDH in a Western blot experiment, a researcher had the following antibodies at his disposal:

- Mouse-anti-human GAPDH antibody
- Rabbit-anti-human ERK antibody
- Goat-anti-human AKT antibody
- Goat-anti-rabbit antibody with green fluorescent label
- Goat-anti-mouse antibody with green fluorescent label
- Rabbit-anti-goat antibody with green fluorescent label

A. Which antibody combinations should the researcher use? In addition, explain the rationale for the use of each selected antibody. (3 points)

Part II. Evaluation of Western Blot analysis

To investigate the effect of the MCT1 specific inhibitor AZD3965 in combination with hypoxia, a Western blot was performed using antibodies for MCT1, MCT4 and Tubulin and protein extracts from two cell lines derived from small cell lung cancer tissue DMS114 and DMS79. The result is shown in Figure 3.1.

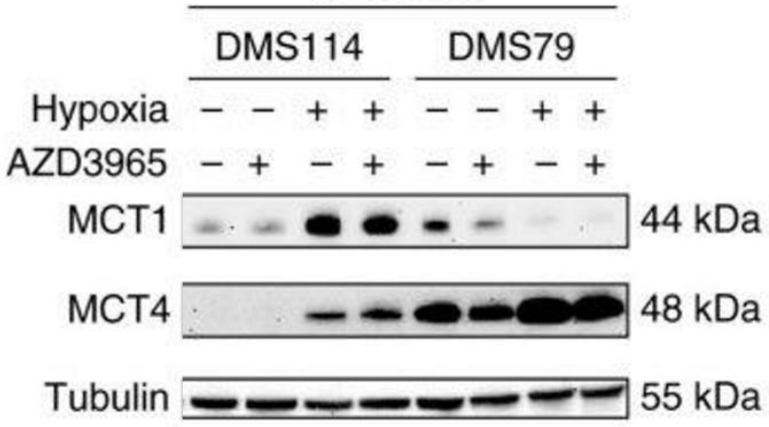

Figure 3.1 Western blot analysis of MCT1, MCT4 and tubulin.

B. What is your interpretation of the result for tubulin in Figure 3.1? And, what does this mean for the interpretation of the MCT1 and MCT4 protein differences observed in the cell lines DMS114 and DMS79? (2 points)

C. What is the effect of hypoxia on MCT1 expression? And, what is the effect of hypoxia on MCT4 expression? (2 points)

D. What is the effect of the inhibitor on MCT1 expression under hypoxic conditions? Explain the effect for both cell lines. (2 points)

Part III. Evaluation of Western Blot analysis & Signal Transduction

The BRAF V600E mutation occurs in approximately 8% of the colorectal cancers. To inves-tigate the effect of the BRAF inhibitor Dabrafinib, a Western blot was performed using nine different antibodies, and protein extracts from the colon cancer cell line HT29. The result is shown in Figure 3.2.

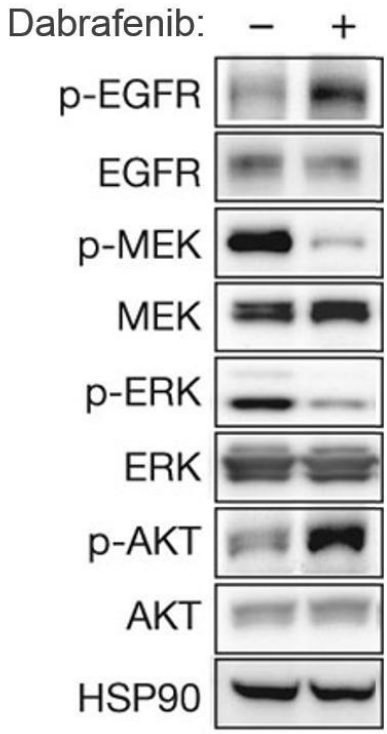

Figure 3.2 Western blot analysis of HT29 cells after drug treatment.

E. What does the “p” signify in p-EGFR? And explain the difference between p-EGFR and EGFR. (1 point)

F. Explain the effect of the BRAF-inhibitor Dabrafenib on the colon cancer cell line. (2 points)

G. Cetuximab is another targeted inhibitor with a different mode of action. This drug is a monoclonal antibody that binds to EGFR. The binding is with a higher affinity than that of the endogenous ligands, and in this way the drug inhibits EGFR activity.

What would be the effect on the HT29 cells of treatment with Cetuximab instead of Dabrafenib? Describe the expected image for the nine antibodies compared to the un-treated result from Figure 3.2. Also, include an explanation in your answer. (3 points)

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Question 4 – Statistics: Meta-analysis and more – Dr. J. in ‘t Hout (15 points)

Based on the following article:

Henssler, J., Müller, M., Carreira, H., Bschor, T., Heinz, A., & Baethge, C. (2020). Con-trolled drinking—non-abstinent versus abstinent treatment goals in alcohol use disorder: a systematic review, meta-analysis and meta-regression. *Addiction*.

The proportion of untreated patients with alcohol use disorder exceeds that of any other mental health disorder, and treatment alternatives are needed. A widely discussed strategy is whether controlled drinking up to a certain amount versus total abstinence is preferred.

A literature search was conducted until February 2019 aiming at controlled (randomized and non-randomized) clinical trials (RCTs and non-RCTs) among adult populations with alcohol use disorder, with an intervention group aiming at Controlled Drinking (CD) and a control group aiming for alcohol abstinence (AA). This resulted in two RCTs and 12 non-RCTs (where participants could choose their preferred approach).

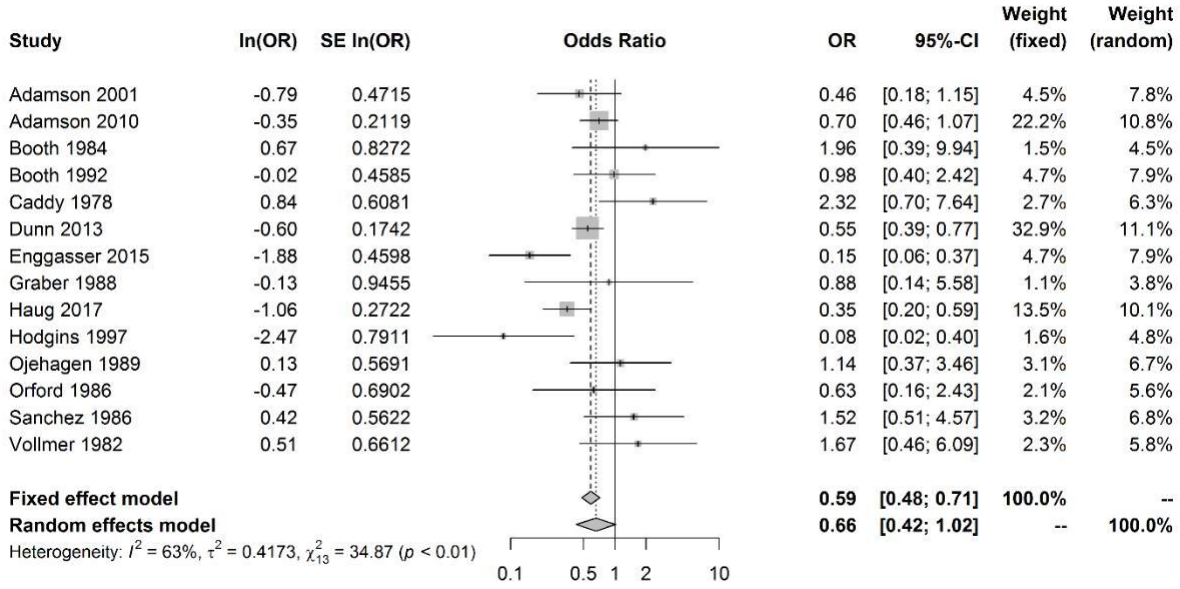

Figure 4.1 Forest plot of odds ratios of number of responders in the Controlled Drinking group versus the Alcohol Abstinence group (response: abstinence or controlled/low risk drinking; OR: Odds Ratio, SE: standard error, ln: natural logarithm, CI: confidence interval).

A. Figure 4.1 shows the overall results of the meta-analysis. Explain the “diamond” of the random effects model at the bottom of the forest plot in Figure 4.1. (1 point)

B. Interpret in words the pooled result for the CD versus AA regimen (which regimen seems most beneficial, and its statistical significance) for the fixed effect model. Explain your answer. (2 points)

C. Explain why the weight of the study of Adamson 2010 is relatively larger in the fixed ef-fect analysis than in the random effects analysis. Use the formulas for the weights in both settings. (2 points)

D. The number of months of follow-up of the participants in the studies may also play a role in the results. Below you can find the results of a meta-regression for follow-up duration. Explain how a meta-regression is conducted in this situation (dependent variable, independent variable, statistical model, experimental unit). (2 points)

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-1.0035	0.3030	-3.3118	0.0009	-1.5974	-0.4096	***
Follow_up	0.0427	0.0187	2.2907	0.0220	0.0062	0.0793	*

E. Explain whether the results of the CD or the AA regimen improve after longer follow-up. (2 points)

F. Give two valid reasons for the observed heterogeneity of 63% (apart from duration of follow-up). (2 points)

G. The authors also conducted meta-regression for the relation with calendar year. The results are presented in figure 4.2. What is the name of this plot? (1 point)

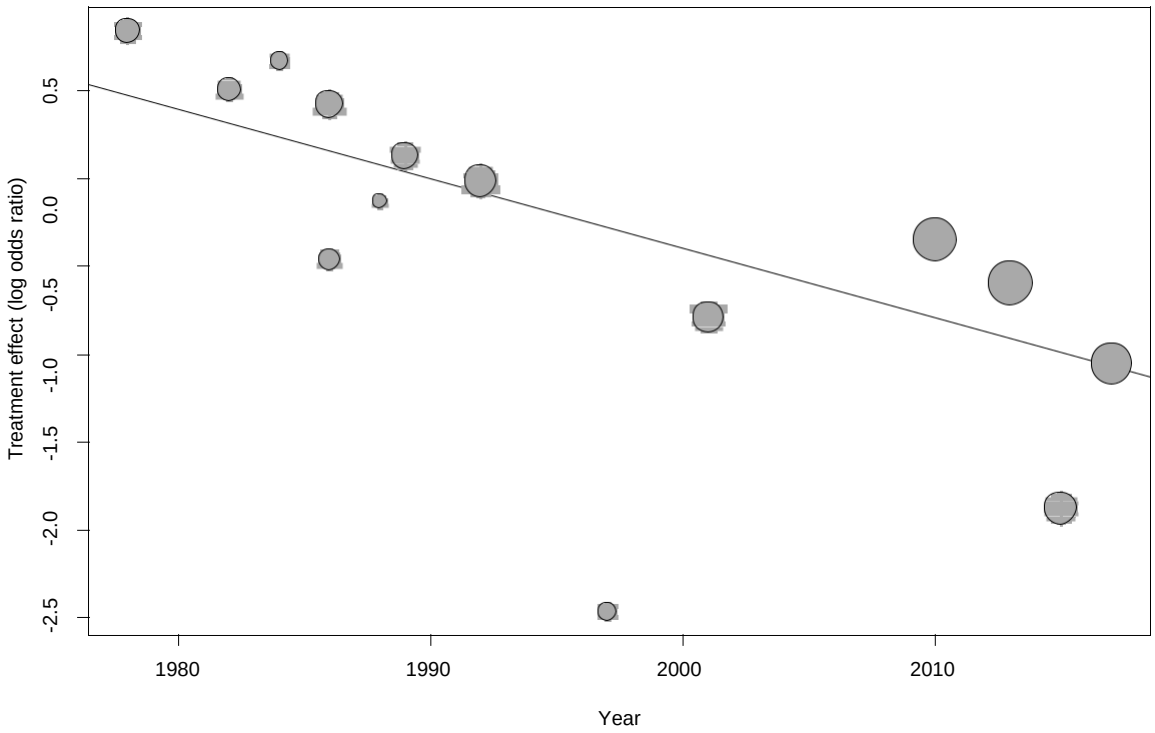

Fig. 4.2 Plot of meta-regression results.

H. How is the size of the circles related to the imprecision of the study estimates? (1 point)

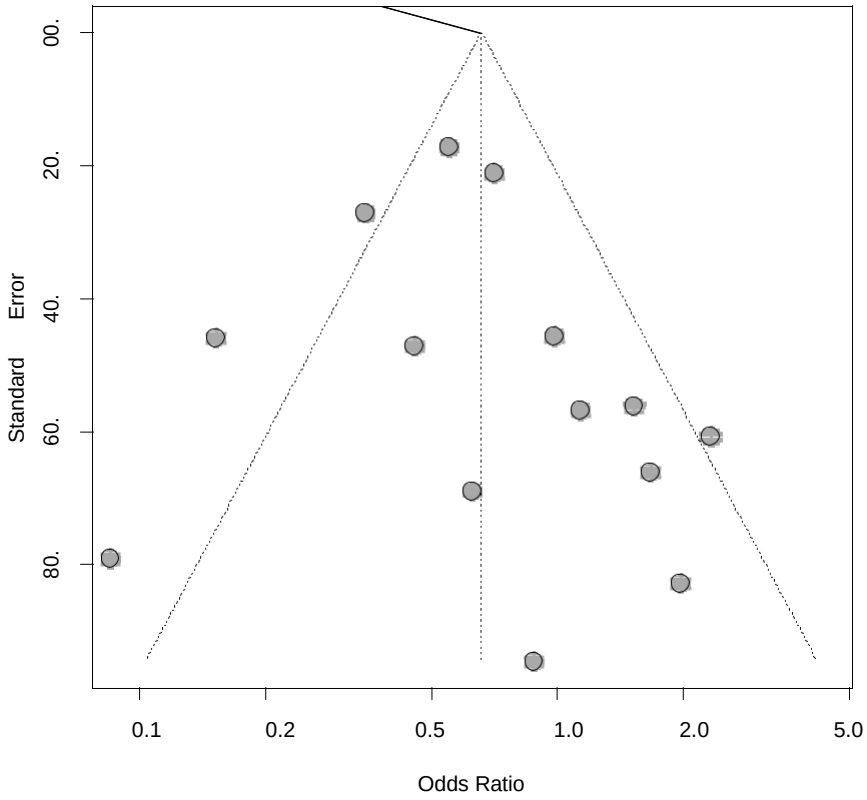

Fig. 4.3 Funnel plot.

I. Figure 4.3 shows a funnel plot. What is the aim of a funnel plot, and related to that: why is the x-axis on logarithmic scale? (2 points)

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Question 5 – Measuring and modelling reflexes – Dr. E. Tanck & Dr. T. Oostendorp (20 points)

Statics

A young woman (60 kg) is doing static exercises to strengthen the m. triceps (see figure 5.1 in which two positions of the static exercise are visible). A physical therapist is interested to know how high the ground reaction force is when the arm of the woman is (about) straight and the rope is at (about) 60 degrees from the horizontal plane (figure on the right).

Known data: The weight of the woman is 60kg. The force that the woman is applying to the rope is 100N. Use g = 10 m/s^2 for the gravitational acceleration.

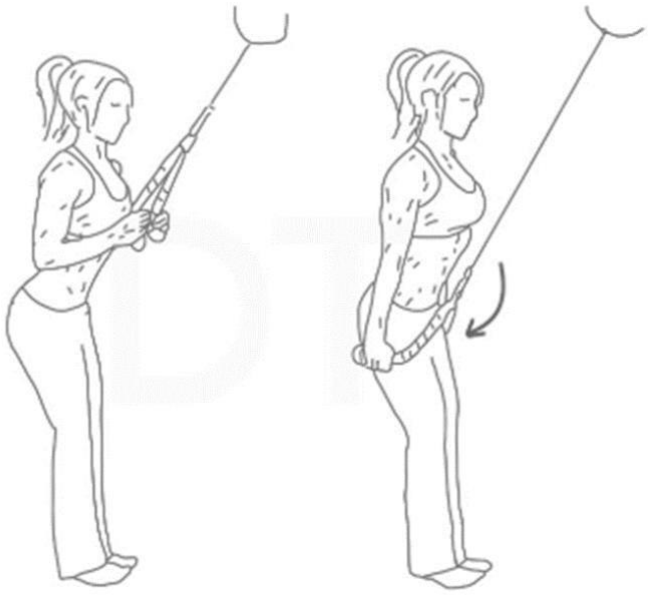

Figure 5.1 Exercises to strengthen the m. triceps.

A. Describe precisely what free body diagram (FBD) you would draw to calculate the ground reaction force. Describe all components of the FBD including the direction and location of these components. (5 points)

A. The woman is doing another exercise and is standing on her toes (see FBD of her foot in figure 5.2, NB: figure is not on scale). You see a FBD with resultant ankle forces (F_{RX} and F_{RY}) in the joint center, and a resultant ankle moment (M_R).

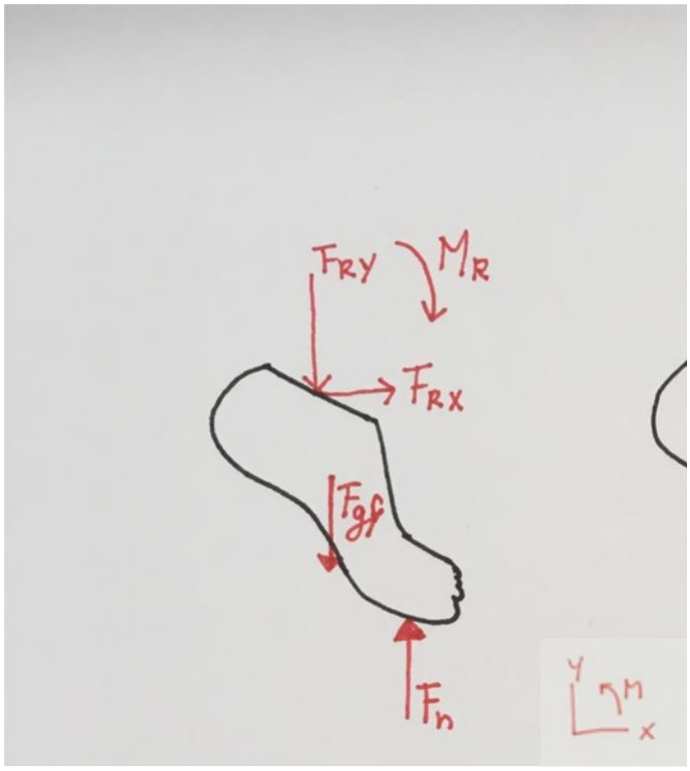

Figure 5.2 Free Body Diagram of the foot of the woman.

Write down the equilibrium equations and draw the moment arms in figure 5.2
(4 points)

∑

∑

∑

C. At the right of figure 5.3 you see also a FBD with joint contact forces (Fcx and Fcy) and the force in the achilles tendon (Fa). The biomechanical situation of the left and right FBD is similar. Known data: Fn=300N; Fgf= 20N; F_{RX}=0N; F_{RY}=280N; M_R= 15Nm; Fa=750N (direction at 80 degrees from horizontal plane).

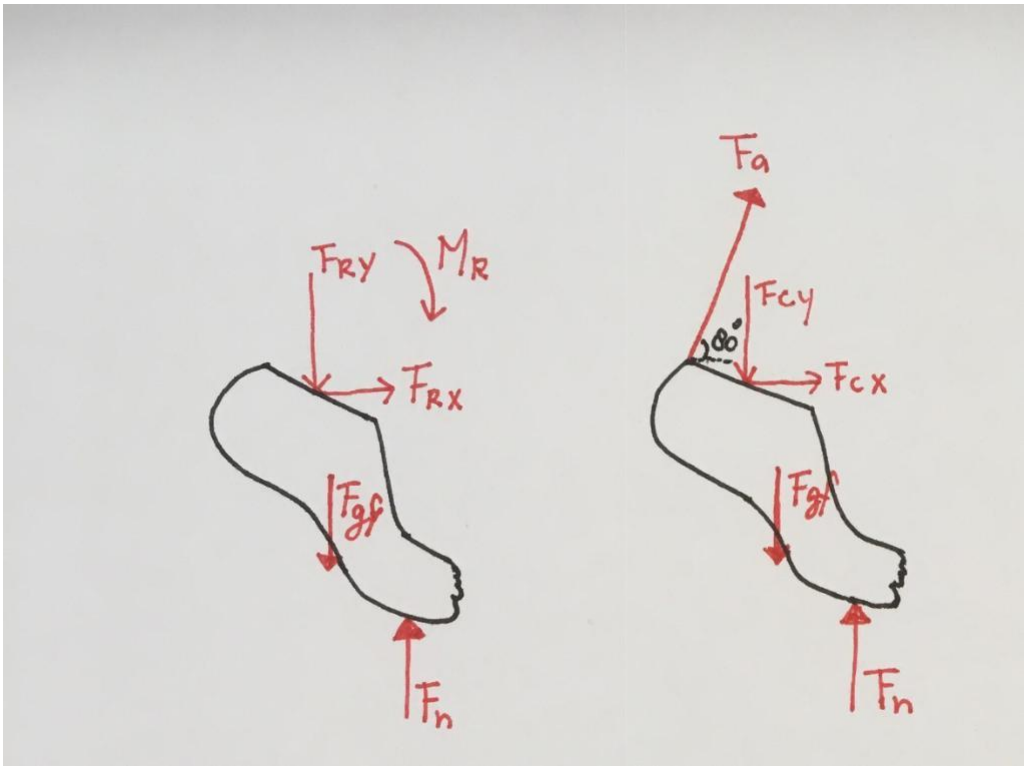

Figure 5.3 Free Body Diagrams of the foot of the woman.

Calculate Fcx, Fcy and the moment arm of Fa to the joint center. Motivate your answers. (6 points)

The ground reaction force is recorded using a force plate. Figure 5.4 shows the signal of the force plate as the woman is changing her posture.

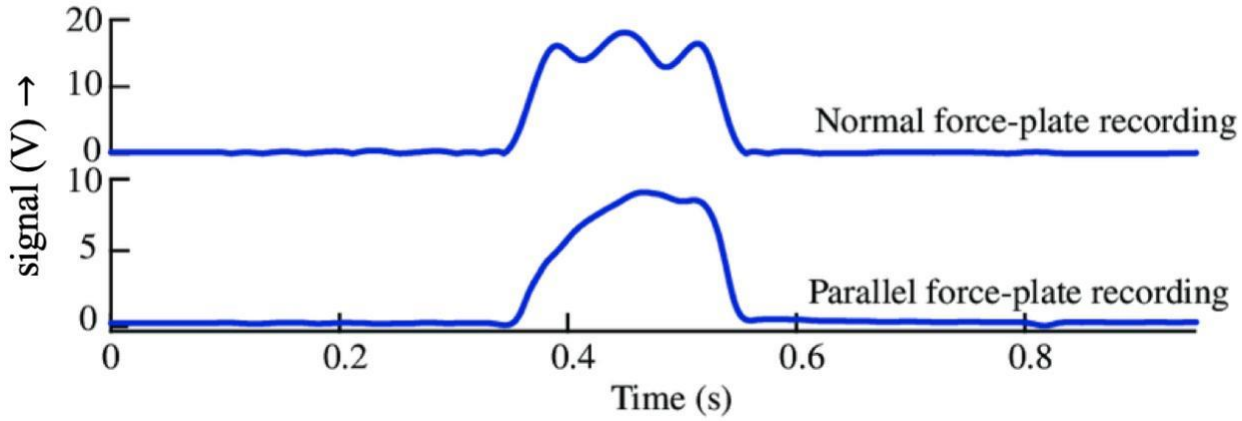

Figure 5.4

D. What sample rate should be used in order to obtain a clear rendering of the signal? Explain your answer. (2 points)

In order to avoid aliasing, the signal must be filtered prior to sampling.

E. What kind of filter should be used, and what should be its cut-off frequency? Explain your answer. (3 points)

End of the exam. Did you write your name and student number on the first page of each question?