# Comparing the consenting and non-consenting populations in BIOMAK

- A side project in the BIOMAK study by the dept. of Medical Biochemistry at St Olavs hospital


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# Abstract

The BIOMAK project is a prospective study of the diagnostic accuracy for cardiac troponin I analyzed by different methods and compared to diagnostics based on troponin T. Non-responders are a common issue in large studies and can be source of so-called nonresponse bias, where the respondents and non-respondents differ so much that the interpretation of the results of the research are affected, in that the external validity of the findings are weakened. To prevent this from happening, it is necessary to compare the responding and non-responding populations.
In the BIOMAK project, patients were included by responding to a letter sent by post, but data about the patients were also registered in the hospital's systems. We have extracted data about the patients age, gender, and discharge diagnoses, and compared the responding and non-responding population on this.
The results show that the respondents had more chronic cardiac diagnoses, such as arrythmias and ischemic diseases, than non-respondents. The young and the old responded less frequently, and more men than women responded. There were small differences between non-respondents and respondents, and there is therefore a strong possibility that the findings in BIOMAK are representative for the general population of patients admitted to hospital with suspected ischemic heart disease.



# Sammendrag

BIOMAK-studien er en prospektiv studie av diagnostisk nøyaktighet av hjertespesifikk troponin I, målt med forskjellige metoder og sammenlignet med diagnostikk basert på troponin T. Ikke-respondenter er et kjent problem i store studier, og kan være kilde til skjevhet i resultatene (på engelsk kalt nonresponse bias), hvor ulikhetene mellom respondentene og ikke-respondentene er så store at gyldigheten av resultatene i forskningen påvirkes, i det at den eksterne validiteten svekkes. For å unngå at dette skjer, er det nødvendig å sammenligne det responderende utvalget med det ikke-responderende utvalget, i denne studien den samtykkende og den ikke-samtykkende populasjonen.

I BIOMAK-prosjektet ble pasienter blant annet inkludert ved å svare på et brev de ble tilsendt per post, men data om pasientene er også registrert i sykehusets datasystemer. Vi har ekstrahert data om pasientenes alder, kjønn og diagnoser og sammenlignet ikke-respondentene og respondentene basert på dette..

Resultatene viser at den samtykkende befolkningen har mer kroniske kardiologiske sykdommer, slik som arytmier og iskemisk sykdom. Den yngre og den eldre befolkningen svarte mindre, og større andel av menn enn kvinner samtykket. Forskjellene mellom ikke-respondenter og respondenter var små, og det er derfor en høy sannsynlighet for at funnene i BIOMAK er representative for den generelle befolkningen av pasienter innlagt på sykehus med mistenkt iskemisk hjertesykdom.


# Introduction

Troponin is a protein complex involved in muscle contraction in skeletal and heart muscle cells. There are several types of troponins; troponin T, I and C, and all have different subgroups. Troponin I and T exist in heart specific types, cardiac types. When damaged, heart muscle cells (cardiomyocytes) release – amongst others – troponins into the bloodstream, and the concentration of cardiac troponin in blood is one of the diagnostic criteria for acute myocardial infarction (AMI) [(1)]. Per today, St Olavs Hospital in Trondheim uses cardiac troponin T (cTnT) on suspicion of acute coronary syndrome.

Biomarkers have an important role in medical diagnostics, and troponin has a decisive role in cases with suspicion of acute coronary disease. An AMI with ST elevation on ECG (STEMI) will in most cases be detected and treated because of said changes on ECG. For an AMI without ST elevations (NSTEMI), chest pain and a typical dynamic of TnT are diagnostic criteria [(1)]. The dynamic of TnT in an AMI is a typical "rise-and-fall" pattern; TnT elevates the first 2-3 hours after the cardiomyocytes are damaged, stabilizes on a plateau of maximal concentration in around 24 hours, for then to fall. To detect this pattern, TnT is analyzed in multiple blood samples with set time intervals when acute coronary disease is suspected.

BIOMAK [2] is a study on the diagnostic accuracy for NSTEMI for cardiac troponin analyzed by different laboratory methods. The study population is patients admitted to St Olavs Hospital with suspected acute coronary syndrome. To include patients in the BIOMAK study, patients were asked to consent by post. As in numerous other studies, BIOMAK experienced a proportion of non-respondents. Information about the non-respondents is often not available but using the hospital's registers of admittance (PAS), we were able to extract anonymous data about the patients' age, gender, and discharge diagnoses.

In this demographic, epidemiological study, the goal was to decide whether the responding population for the BIOMAK study was different than the non-responding one. Comparing the two populations is valuable to conclude on BIOMAK's external validity. If there is no significant difference between the two populations, the results from the BIOMAK study should likely be more directly applicable to the general population of patients admitted to hospital with suspicion of ischemic heart disease.

# Materials and methods

## Main population

Inclusion criteria for the BIOMAK study were that the patient was over 18 years old, did not have a ST-elevation myocardial infarction when admitted (STEMI), understood Norwegian and that the "myocardial infarction laboratory panel" was ordered during the patient's hospital stay. The "infarction panel" included – amongst others – cardiac troponin I (two types) and cardiac troponin T.

Patients being admitted and meeting the inclusion criteria, were asked for consent. Some patients were asked for written consent during their hospital stay. For those who did not consent during their hospital stay, letters were sent within 8 weeks after discharge. All patients were given the same information and asked the same questions. They were asked to consent by signing the paper and returning it to a nurse or in the pre-paid envelope by post. All consents were collected by the BIOMAK project administration. By signing the paper, the patients consented for the use of their blood samples and the gain of access to their medical records to use information about their health. The letter is attached in *appendix 1.* About 4-5 weeks after the first letter was sent, the patients who had still not responded were sent a reminder with the same information.

## Inclusion and data collection

The inclusion of patients in BIOMAK took place from 15th of January 2020, until GoLive for Helseplattformen on the 12th of November 2022. All patients who were asked for consent by letter are included in this sub-project in BIOMAK. The date of postage is used when calculating the patients' age. Only patients over the age of 18 were included. Birth years are categorized into 5-year intervals. This is done to maintain anonymity for the non-responding participants.

Information about hospital encounters - both out-patient contacts and hospital stays -, gender, birth year, diagnoses and eventual death are extracted from PAS, death being updated for the last time on the 31st of August 2023. A list of diagnoses relevant to the study was made before the project, without any knowledge of prevalence in the study population. It is based on the ICD-10 diagnostic system. This list is included below. All the diagnoses and diagnostic groups are thought to be relevant for the study and are categorized into heart relevant diagnoses, relevant differential diagnoses and relevant comorbidity. Some diagnoses are simplified into diagnostic groups and ICD-10 chapters as further detail level is not needed and to maintain anonymity. Regional Etisk Komité (REK) approved the list of diagnoses and its degree of detail, and the extraction of patient information. REK did not approve extraction of which department the patients were admitted to.

Extraction of patient data was done digitally, by going through a list of recently admitted patients and including those given one or more diagnoses from the list. Only diagnoses given in contacts during the last 8 weeks (about 2 months) before the letter was sent are used. Patients with no relevant diagnoses are included in the extraction of data and are listed as "No diagnosis / Ingen diagnose".

# LIST OF ICD-10 DIAGNOSTIC GROUPS:

## Heart relevant diagnostic groups:

I20: Angina pectoris

I21: Acute myocardial infarction

I21.0: Acute transmural myocardial infarction of anterior wall

I21.1: Acute transmural myocardial infarction of inferior wall

I21.2: Acute transmural myocardial infarction of other sites

I21.3: Acute transmural myocardial infarction of unspecified site

I21.4: Acute subendocardial myocardial infarction

I21.9 Acute myocardial infarction, unspecified

I22: Subsequent myocardial infarction

I25: Chronic ischemic heart disease

## Differential diagnoses of interest:

G45.9: Transient cerebral ischemic attack, unspecified

I26: Pulmonary embolism

I30: Acute pericarditis (pericarditis acuta)

I38: Endocarditis, valve unspecified

I40: Acute myocarditis (myocarditis acuta)

I41: Myocarditis in diseases classified elsewhere

I44: Atrioventricular and left bundle-branch block

I45: Other conduction disorders

I47: Paroxysmal tachycardia

I48: Atrial fibrillation and flutter

I49: Other cardiac arrhythmias (arrythmia cordis)

I50: Heart failure

I10: Essential (primary) hypertension

I61: Intracerebral hemorrhage (haemorrhagia cerebri)

I62: Other nontraumatic intracranial hemorrhage

I63: Cerebral infarction

I64: Stroke, not specified as hemorrhage or infarction

J40-J47: Chronic lower respiratory diseases

K: Chapter XI (K00-K93) Diseases of the digestive system

M80-M85: Disorders of bone density and structure

R00: Abnormalities of heartbeat

R07.4: Chest pain, unspecified

R10.4: Other and unspecified abdominal pain

R42: Dizziness and giddiness

R45.8: Other symptoms and signs involving emotional state

R55: Syncope and collapse

### Relevant comorbidity:

E10-14: Diabetes Mellitus

N18: Chronic kidney disease

No diagnosis

## Anonymity

The study is approved by Regional Etisk Komité (REK). REK gave strict limitations on how to obtain and handle data from patients who did not consent. All data about these patients were handled anonymously. Other data and combinations of data than what was used in this study were not available for this study.

## Study populations

The study population can be divided into two subpopulations: the consenting population and the non-consenting population. The two populations were compared on age, gender, and diagnoses.

## Statistical analyses

All mathematical calculations were conducted in Microsoft Excel. Prevalence of diagnoses was calculated as a proportion of patients who had at least one instance of the diagnosis as discharge diagnosis within 8 weeks before they were contacted by mail. This was done for each diagnose in both the consenting and non-consenting population. Furthermore, the difference between proportions in the consenting and non-consenting populations was calculated with a 95% confidence interval (CI). Calculations to compare rate of response in the male and female populations and based on age, were also done. The calculations of differences between gender and age groups were also done with a 95% CI.
The calculations of CI were done as suggested as the recommended methods in chapter 6 “Proportions and their differences” of the book *Statistics with confidence, 2nd edition* [3]. The formulas are shown in *appendix 2.*
The results were then colour coded to look for patterns, and then extracted into figures to summarize and give a visual representation of the most important findings. The figures were made in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) in close cooperation with the main supervisor.

## Confidence intervals

When doing many statistical comparisons (in this study more than 100) it is difficult to use regular statistical tests and p-values, because the probability for $p<0,05$ due to chance is high. It is the size of the difference in prevalence between the two compared groups that is of interest. In this study the results are presented with 95% CI to evaluate the differences and the uncertainty in these differences.

# Results

## The study population

The total number of patients asked for consent was 7497. 20 patients were under the age of 18 and not included; this gives a total of n=7477. 3557 patients responded and 3920 did not respond. The response rate was 47,6%. 37

patients were not given any relevant diagnosis and are listed as “no diagnosis/ingen diagnose” in the data, 14 of them responded.

| Gender | Responder | Non-responder |
|---|---|---|
| Male | 1928 (25,8%) | 2005 (26,8%) |
| Female | 1629 (21,8%) | 1915 (25,6%) |
| Both | 3557 (47,6%) | 3920 (52,4%) |

*Table 1: number of patients in the responding and non-responding populations divided into gender.*

## Gender and age differences

The male population responded significantly more than the female population. The difference in response rate between men and women was 3,1% (95% CI=0,8-5,3). Still, most of both genders did not respond.

The number of patients increased with age until 80 for both men and women and the age group with most patients is 75-79 years old for both genders, as shown in *figure 1*. The response rate also increases with age and was highest for the age groups with most patients; for the ages 55 to 79 there were more respondents than non-respondents. For the younger (20-49) and the older age groups (85-94) there was a lower response rate, and thus more non-respondents. These groups were also the ones with lower number of patients.

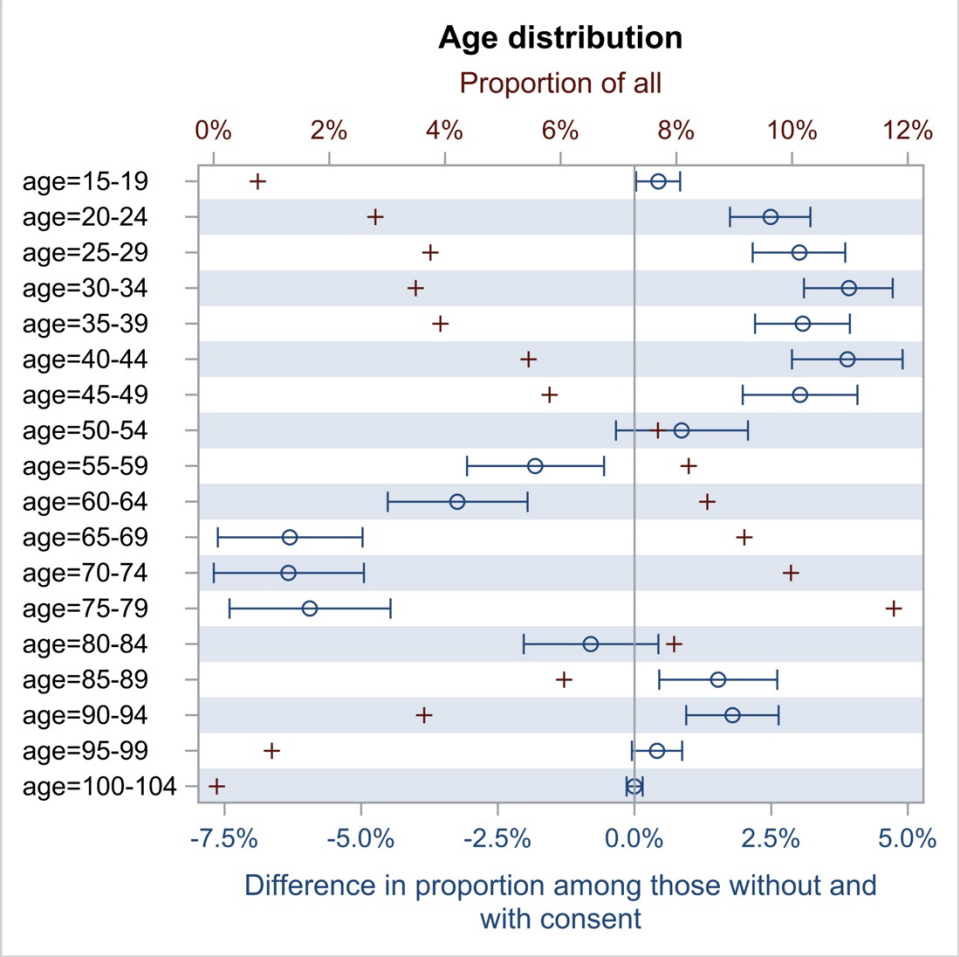


*Figure 1: Gender independent age groups*
*In red: percentage of BIOMAK’s total number of patients per age group*
*In blue: difference between non-respondents and respondents in percentage with 95% CI. Positive differences mean more non-responders, negative differences mean more respondents.*

## Differences in prevalence of disease

Most of the heart relevant diagnostic groups (*Table* 2) had more responders than non-responders, in other words a negative difference between non-responders and responders. The four largest groups in number of patients had differences in response rates over 2% (I20, I21, I21.4, I25).

| Diagnostic group | Non-response | Response | Total | Difference | CI lower limit | CI upper limit |
|---|---|---|---|---|---|---|
| I20: Angina pectoris | 239 | 343 | 582 | -3.5 | -4.8 | -2.3 |
| I21: Acute myocardial infarction | 210 | 313 | 523 | -3.4 | -4.6 | -2.3 |
| I21.0: Acute transmural myocardial infarction of anterior wa | 23 | 37 | 60 | -0.5 | -0.9 | 0.0 |
| I21.1: Acute transmural myocardial infarction of inferior wall | 20 | 40 | 60 | -0.6 | -1.1 | -0.2 |
| I21.2: Acute transmural myocardial infarction of other site | 12 | 14 | 26 | -0.1 | -0.4 | 0.2 |
| I21.3: Acute transmural myocardial infarction of unspecified | 2 | 1 | 3 | 0.0 | -0.1 | 0.2 |
| I21.4: Acute subendocardial myocardial infarction | 133 | 217 | 350 | -2.7 | -3.7 | -1.7 |
| I21.9: Acute myocardial infarction, unspecified | 55 | 91 | 146 | -1.2 | -1.8 | -0.5 |
| I22: Subsequent myocardial infarction | 3 | 2 | 5 | 0.0 | -0.1 | 0.2 |
| I25: Chronic ischemic heart disease | 548 | 741 | 1289 | -6.9 | -8.6 | -5.1 |

*Table 2: Heart relevant diagnostic groups. The differences between non-respondents and respondents are given in percentages with a 95% CI.*

Some of the differential diagnoses of interest also had a negative difference between non-respondents and respondents; I10: *Essential hypertension* and the arrythmia diagnoses (I44, I45, I47, I48, I49 and R00) all had high response rates. I48: Atrial fibrillation and flutter was the largest group in number of patients (n=1488) and had the highest response rate (7,0% difference between non-respondents and respondents), see *Table 3*.

Other diagnostic groups had a low response rate. J40-J47: *Chronic lower respiratory diseases* and R10.4: *Other and unspecified abdominal pain* had differences of respectively 1,8% and 1,6% between non-respondents and respondents. R45.8: *Other symptoms and signs involving emotional state* had a difference of 3,0%. The largest patient group is R07.4: *Chest pain, unspecified*. This diagnosis was given to 3229 patients, and the difference between non-respondents and respondents was 3,8%.

15 of the 26 relevant differential diagnoses showed no significant difference between non-respondents and respondents. This list includes a variety of diagnostic groups, both cardiovascular, structural, neurological, pulmonary and digestive (G45.9, I26, I30, I38, I40, I41, I44, I50, I61-I64, K00-K93, M80-M85, R42, R55).

| Diagnostic group | Non-response | Response | Total | Difference | CI lower limit | CI upper limit |
|---|---|---|---|---|---|---|
| I10: Essential (primary) hypertension | 621 | 711 | 1332 | -4.1 | -5.9 | -2.4 |
| G45.9: Transient cerebral ishcemic attack, unspecified | 17 | 14 | 31 | 0.0 | -0.3 | 0.3 |
| I26: Pulmonary embolism | 84 | 68 | 152 | 0.2 | -0.4 | 0.9 |
| I30: Acute pericarditis (pericarditis acuta) | 48 | 50 | 98 | -0.2 | -0.7 | 0.3 |
| I38: Endocarditis, valve unspecified | 0 | 2 | 2 | -0.1 | -0.2 | 0.0 |
| I40: Acute myocarditis (myocarditis acuta) | 2 | 2 | 4 | 0.0 | -0.2 | 0.1 |
| I41: Myocarditis in diseases classified elsewhere | 2 | 2 | 4 | 0.0 | -0.2 | 0.1 |
| I44: Atrioventricular and left bundle-branch block | 101 | 125 | 226 | -0.9 | -1.7 | -0.2 |
| I45: Other conduction disorders | 40 | 58 | 98 | -0.6 | -1.2 | -0.1 |
| I47: Paroxysmal tachycardia | 144 | 197 | 341 | -1.9 | -2.8 | -0.9 |
| I48: Atrial fibrillation and flutter | 649 | 839 | 1488 | -7.0 | -8.8 | -5.2 |
| I49: Other cardiac arrhythmias (arythmia cordis) | 300 | 385 | 685 | -3.2 | -4.5 | -1.9 |
| I50: Heart failure | 455 | 396 | 851 | 0.5 | -1.0 | 1.9 |
| I61: Intracerebral hemorrhage (haemorrhagia cerebri) | 6 | 5 | 11 | 0.0 | -0.2 | 0.2 |
| I62: Other nontraumatic intracranial hemorrhage | 1 | 3 | 4 | -0.1 | -0.2 | 0.1 |
| I63: Cerebral infarction | 61 | 49 | 110 | 0.2 | -0.4 | 0.7 |
| I64: Stroke, not specified as hemorrhage or infarction | 2 | 1 | 3 | 0.0 | -0.1 | 0.2 |
| J40-J47: Chronic lower respiratory diseases | 306 | 212 | 518 | 1.8 | 0.7 | 3.0 |
| K: Chapter XI (K00-K93) Diseases of the digestive system | 762 | 675 | 1437 | 0.5 | -1.3 | 2.2 |
| M80-M85: Disorders of bone denisty and structure | 186 | 162 | 348 | 0.2 | -0.8 | 1.1 |
| R00: Abnormalities of heartbeat | 145 | 170 | 315 | -1.1 | -2.0 | -0.2 |
| R07.4: Chest pain, unspecified | 1764 | 1465 | 3229 | 3.8 | 1.6 | 6.1 |
| R10.4: Other and unspecified abdominal pain | 276 | 195 | 471 | 1.6 | 0.5 | 2.7 |
| R42: Dizziness and giddiness | 191 | 177 | 368 | -0.1 | -1.1 | 0.9 |
| R45.8: Other symptoms and signs involving emotional state | 221 | 93 | 314 | 3.0 | 2.1 | 3.9 |
| R55: Syncope and collapse | 289 | 260 | 549 | 0.1 | -1.1 | 1.2 |

*Table 3: Differential diagnoses of interest. The differences between non-respondents and respondents are given in percentages with a 95% CI.*

In the diagnostic group I10-I14: *Diabetes mellitus* there were more non-respondents than respondents. The groups N18: *Chronic kidney disease* and *No diagnosis* showed no significant difference between non-respondents and respondents.

| Diagnostic group | Non-response | Response | Total | Difference | CI lower limit | CI upper limit |
|---|---|---|---|---|---|---|
| E10-E14: Diabetes mellitus | 370 | 280 | 650 | 1.6 | 0.3 | 2.8 |
| N18: Chronic kidney disease | 203 | 150 | 353 | 1.0 | 0.0 | 1.9 |
| No diagnosis | 23 | 14 | 37 | 0.2 | -0.1 | 0.5 |

*Table 4: Relevant comorbidity. The differences between non-respondents and respondents are given in percentages with a 95% CI.*

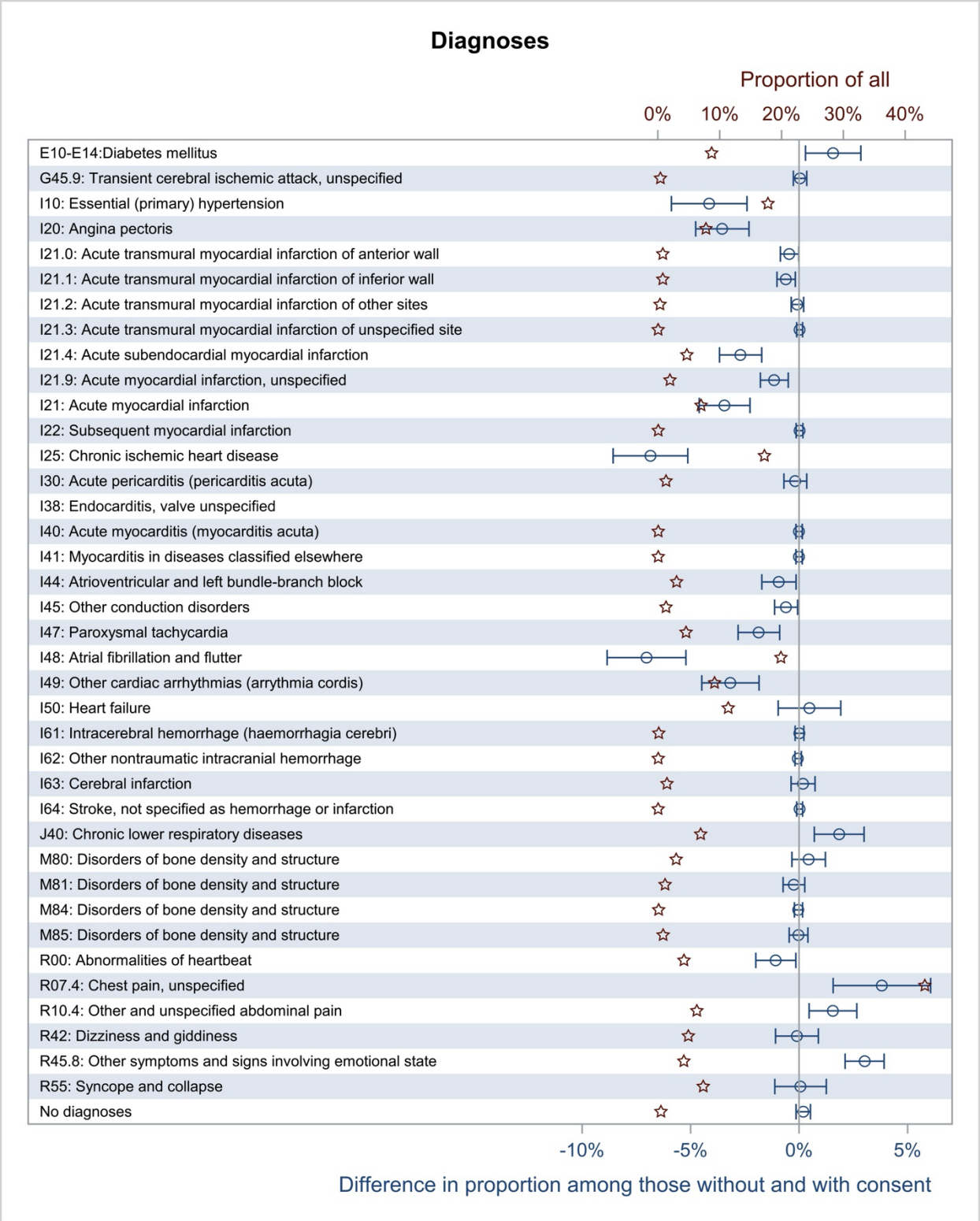


*Figure 4: Diagnostic groups independent of gender and age.*
*In red stars: percentage of the total number of patients*
*In blue: difference between non-respondents and respondents in percentage with a 95% CI. Positive differences mean more non-responders, negative differences mean more respondents.*

### Death

6851 patients were still alive when data was extracted, 3356 of these responded, 3495 did not respond. 626 patients were deceased at the time of extraction, 201 had responded, 425 had not. The difference between respondents and non-respondents in the living and deceased populations is 5,2% (95% CI = 4,0-6,4). This means that even though most of both groups did not respond, a larger part of the living population responded as compared to the deceased.

## Discussion

Most of the ischemic, hypertension and arrythmia diagnostic groups were more common amongst the responders than non-responders. There were more non-responders with the diagnostic groups J40-J47, R10.4, R45.8 and R07.4. The other 15 differential diagnoses showed no significant difference between non-respondents and respondents. Of the relevant comorbidities only E10-E14: *Diabetes mellitus* had a difference, more of the non-respondents than respondents had diabetes.

As for the gender differences, men and women responded very similarly per age group, but a larger percentage of the men responded. There were also more male patients in the study population. The patients aged 20-50 had more non-respondents than respondents, while the patients aged 60-80 had more respondents. Others have shown that survey response rates tend to be negatively correlated with age [(6)], and this seems to be the case also for this study up until the age of 80.

The same study found that “respondents to postal surveys have shown to be more likely to be younger”. This suggest that the age differences found in the BIOMAK data may vary from other research, even though this study was conducted over 35 years ago.

The five diagnostic groups (J40-J47, R10.4, R45.8, R07.4, E10-E14) that had a low response rate all have a difference under 4%. These are what can be seen as non-cardiac diagnoses, but their relevance to the diagnostic algorithm of NSTEMI is important as these diagnoses often present with what can resemble chest pain or heart disease (except diabetes). It is positive that the differences were relatively small, as this indicates that there is not much difference between the population that responded to BIOMAK, and the general population of patients admitted to hospital with suspicion of ischemic heart disease. Still, the largest diagnostic group R07.4 *Chest pain, unspecified*, was given to 43% of BIOMAK’s patients (n=3229). The difference between non-respondents and respondents among patients recieving this diagnosis was 3,8%, which is not a large difference, but 1465 patients did not respond. With that many patients, one can argue that 3,8% is a more important difference than for smaller diagnostic groups, where differences under 5% hardly does have any significance for the external validity of BIOMAK’s results.

On the other hand, most cardiac diagnostic groups (ischemia, hypertension, arrythmia) had high response rates. It is possible that these patients responded to heart disease research because they have a personal interest in this kind of research as they have diseases with an important symptomatic burden, and they have frequent hospital check-ups and doctor appointments [(6)]. Also, most of the ones given a diagnosis of acute myocardial infarction responded. The diagnosis I21.4: *Acute subendocardial myocardial infarction* was given to 4,6% of the patients, which is few, given that this is a study on diagnostic accuracy of troponins, which again are used to diagnose NSTEMI. When including patients to BIOMAK it has been observed that patients admitted with type 2 AMI because of e.g. severe arrythmias, are discharged with arrythmia diagnoses and not AMI. Why is it that doctors do not discharge patients with heart attack diagnoses, when the patients fill the diagnostic criteria of a “rise-and-fall" pattern in cTnt? All the arrythmia diagnoses (I44, I45, I47, I48, I49, R00) had more respondents than non-respondents, and I48: *Atrial fibrillation and flutter* had a difference of 7,0%, which should be considered as important (>5%). The diagnosis was given to 1488 patients. In addition to I48: *Atrial fibrillation and flutter*, one more diagnosis had a difference over 5%; I25: *Chronic ischemic heart disease* had a difference of 6,9%. The diagnosis was given to 1289 patients. These are both very relevant diagnostic groups, with many patients and important differences between non-respondents and respondents, and it is positive that so many responded to the study.

The patients who did not get a conclusive cardiological diagnosis, such as the 43% with unspecified chest pain, responded less. A considerable number of patients reached out via phone or e-mail to BIOMAK’s administration because they were unsure if their participation was indeed wanted, given that they did not have a heart attack. It is desirable to question the wording of the information letter the patients were sent. The information letter was called “Request for participation in research project - *Biomarkers in patients admitted with suspicion of acute heart attack*” and in the beginning of the letter *(appendix 1* (in Norwegian)*)* it was written *“This is a question for you to participate in*

*a research project of how the presence of various substances in the blood can be used to detect or rule out that patients have an acute heart attack, or a possible higher risk of getting a heart attack or other severe cardiovascular diseases. The project is important to improve the diagnostics and treatment for patients where these diseases are suspected*." This wording and focus on heart attack can be root for misunderstanding, as so many did not understand if they were wanted in the research. It is also possible that not all who were in doubt reached out to verify whether their participation was wanted or not. This is a weakness in BIOMAK, and the project may have lost several consents due to this.

BIOMAK has a relatively low response rate. 47,5% is according to Borg and Gall "unacceptable" [6]. The Helseundersøkelsen i Nord-Trøndelag (HUNT) studies are similar studies in that they use postal questionnaires sent to the same demographic population as BIOMAK (Trøndelag). In HUNT4[7] the response rate was 51,9% for women and 40,1% for men, 46% for both. This differs from BIOMAK, where men responded more than women. Still, HUNT4 has a similar response rate as BIOMAK. Central studies within the same discipline, such as APACE [8,9] and High STEACS [10] do not include their response rates in their reports, as they should do according to the STARD 2015 guidelines [11]. This makes it difficult to conclude on whether the studies resemble in response rates. It has been suggested [6] that deceased non-respondents should not take part when calculating the response rate. In this case, the response rate for BIOMAK increases to 50,4% (total number of patients minus deceased non-respondents equals a new n; 7477-425=7052). On the other hand, it has been shown that response rates decreased during the Covid-19 pandemic [12], and the inclusion for BIOMAK started early 2020 and lasted until late fall 2022. Another study [13], though old (1998), have shown that non-respondents showed more psychological diseases than respondents. A Danish study [14] on response rates in postal questionnaires showed a response rate of 58,7% in 2017. This study also found that people with lower sociodemographic status had a low rate of response. All this together can explain the low response rate in BIOMAK.

One issue with a low response rate is that this is said to increases the risk of non-response bias. The purpose of this study was to see if there was a difference in the health of BIOMAK's study population and the general population of patients admitted to hospital with suspicion of ischemic heart disease. If the non-respondents have a better or poorer health status, the findings of BIOMAK do not represent the population, because this population appears to be healthier or sicker than it truly is. Research from 2019[5] suggests that the response rate of survey studies do not correspond to non-response bias. Also, the differences between non-respondents and respondents for most of the diagnostic groups in this study are so small, that they are not likely to affect the external validity of BIOMAKS findings in a significant manner. The largest absolute differences were for diagnostic groups with more respondents than non-respondents, which is only beneficial as this strengthens the validity of the findings in BIOMAK.

A weakness with this study, is that we were not allowed to use detailed data about the non-responders. It was therefore not possible to study the differences within diagnostic groups or age groups. To enhance the strength of this study, it would be favourable to do a comparison of the diagnoses based on age groups, to see if there are differences between age groups in prevalence of disease. With an increasing number of patients with increasing age, one can think that the older the population gets, the more diagnoses they have, but to conclude on this, one would have to conduct a more thorough study. Comparing diagnoses and gender could also enlighten more on the differences between men and women.

# Conclusion:

In conclusion, there are differences between the non-responding and responding populations in BIOMAK, concerning both gender, age and diagnoses. The responding population had more chronic and cardiological diagnoses such as arrythmias, angina pectoris and acute myocardial infarction, whilst the non-responding population had more diagnoses like unspecified chest pain and symptoms involving an emotional state. The young and very old responded less, and men responded more than women. For further research, comparing the diagnoses with age and gender would be favourable.

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# Appendix:

## Appendix 1:

The information letters.

## Appendix 2:

The confidence intervals are all calculated with 95% confidence, thus 1,96 is used as the z value to calculate them. To calculate the confidence intervals, we first calculated these three properties for both the consenting and non-consenting populations.

$A = 2r + z^2$ ; $B = z * \sqrt{(z^2 + 4rq)}$ ; $C = 2(n + z^2)$

Where

- r is the number of observed cases, i.e. how many had diabetes mellitus
  p is the proportion (r/the total of observed cases, i.e. diabetics/non-consenting population)
  q is 1-p
  z is 1,96

The lower limit of the confidence interval is then calculated as such

$$l = (A - B) / C$$

And the upper limit as follows:

$$u = (A + B) / C$$

To calculate the differences in proportion with a 95% CI, the same chapter of the same book gives another recommended method under the paragraph *Two samples: unpaired case;*

Lower limit = $D - \sqrt{(p_1 - l_1)^2 + (u_2 - p_2)^2}$ ; Upper limit = $D + \sqrt{(p_2 - l_2)^2 + (u_1 - p_1)^2}$

Where

D is the difference in proportions $p_1 - p_2$
$p_1$ is the non-consenting proportion
$p_2$ is the consenting proportion
$l_1$ and $u_1$ are the lower and upper limits of the confidence intervals of $p_1$
$l_2$ and $u_2$ are the lower and upper limits of the confidence interval of $p_2$

## Appendix 3:

Alternative figures

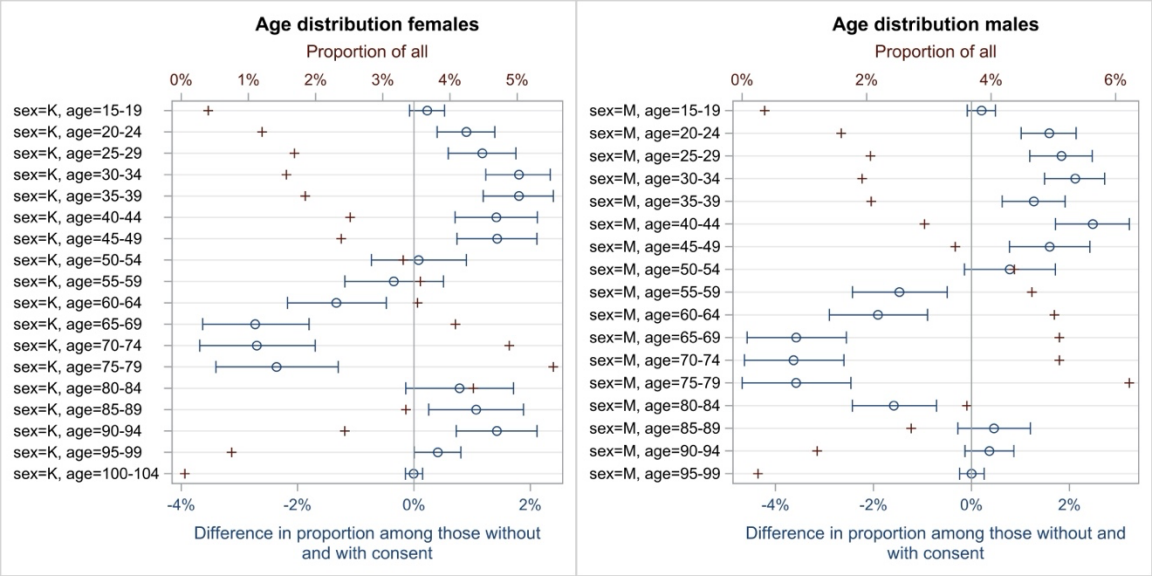


*Figure $X_1$: Age groups in the male and female population*
*In red: percentage of BIOMAK's total number of patients per age group*
*In blue: difference between non-respondents and respondents in percentage with 95% CI.*

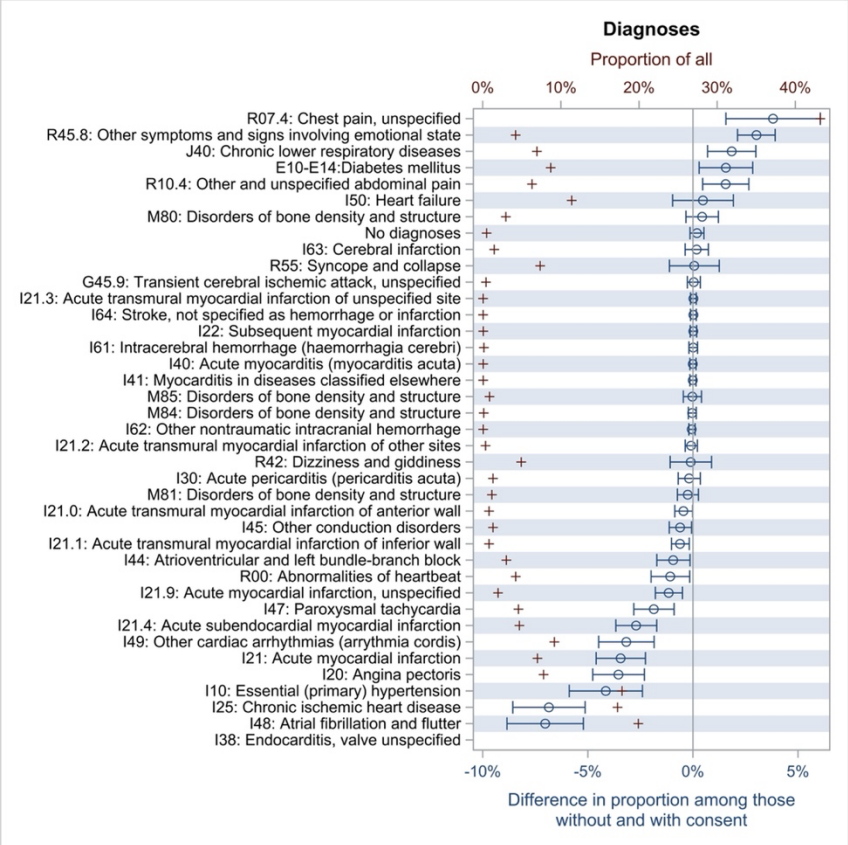


*Figure $X_2$: Diagnostic groups independent of gender and age.*
*In red: percentage of the total number of patients*
*In blue: difference between non-respondents and respondents in percentage with a 95% CI.*